INFORMATION TO USERS

This reproduction was made from a copy of a document sent to us for microfilming. While the most advanced technology has been used to photograph and reproduce this document, the quality of the reproduction is heavily dependent upon the quality of the material submitted.

The following explanation of techniques is provided to help clarify markings or notations which may appear on this reproduction.

1. The sign or "target" for pages apparently lacking from the document photographed is "Missing Page(s)". If it was possible to obtain the missing page(s) or section, they are spliced into the film along with adjacent pages. This may have necessitated cutting through an image and duplicating adjacent pages to assure complete continuity.

2. When an image on the film is obliterated with a round black mark, it is an indication of either blurred copy because of movement during exposure, duplicate copy, or copyrighted materials that should not have been filmed. For blurred pages, a good image of the page can be found in the adjacent frame. If copyrighted materials were deleted, a target note will appear listing the pages in the adjacent frame.

3. When a map, drawing or chart, etc., is part of the material being photographed, a definite method of "sectioning" the material has been followed. It is customary to begin filming at the upper left hand corner of a large sheet and to continue from left to right in equal sections with small overlaps. If necessary, sectioning is continued again—beginning below the first row and continuing on until complete.

4. For illustrations that cannot be satisfactorily reproduced by xerographic means, photographic prints can be purchased at additional cost and inserted into your xerographic copy. These prints are available upon request from the Dissertations Customer Services Department.

5. Some pages in any document may have indistinct print. In all cases the best available copy has been filmed.

University
Microfilms
International

300 N. Zeeb Road
Ann Arbor, MI 48106

Allen, Evelyn B.

AB-INITIO MOLECULAR ORBITAL STUDIES OF CERTAIN NITROSOUREAS AND CERTAIN DIAZOHYDROXIDES AND THE RESPECTIVE INFLUENCE OF CATIONS (HYDROGEN, LITHIUM) AND COUNTER IONS (LITHIUM, SODIUM, AMMONIA) ON THEIR ANTITUMOR ACTIVITY

City University of New York PH.D. 1985

University
Microfilms
International 300 N. Zeeb Road, Ann Arbor, MI 48106

"*AB-INITIO* MOLECULAR ORBITAL STUDIES OF CERTAIN NITROSOUREAS AND CERTAIN DIAZOHYDROXIDES AND THE RESPECTIVE INFLUENCE OF CATIONS (H^+, Li^+) AND COUNTER IONS (Li^+, Na^+, NH_4^+) ON THEIR ANTITUMOR ACTIVITY."

"*Ab-Initio* Molecular Orbital Studies of Certain Alkyldiazohydroxides and the Influence of Counter Ions (Li^+, Na^+, NH_4^+) on the Biological Properties of the Alkyldiazohydroxides as Related to Their Antitumor Activity."

"*Ab-Initio* Molecular Orbital Studies of Certain Nitrosoureas and the Influence of Cations (H^+, Li^+) on the Mechanism of Activation of the Nitrosoureas as Carcinostatic Agents."

by

Evelyn B. Allen

A dissertation submitted to the Graduate Faculty in Chemistry
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy, The City University of New York.

1985

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

Dec 18, 1984
date

Chairman of Examining Committee

Dec 18, 1984
date

Executive Officer

Charlotte S Russell

Supervisory Committee

The City University of New York

ABSTRACT

AB-INITIO MOLECULAR ORBITAL STUDIES OF CERTAIN NITROSOUREAS AND CERTAIN DIAZOHYDROXIDES AND THE RESPECTIVE INFLUENCE OF CATIONS (H^+, Li^+) AND COUNTER IONS (Li^+, Na^+, NH_4^+) ON THEIR ANTITUMOR ACTIVITY.

by

Evelyn B. Allen

Advisor: Professor Anne-Marie Sapse

Ab-initio molecular orbital studies of alkyldiazohydroxides, alkyldiazotates, and nitrosoureas are performed. The Hartree-Fock calculations clarify the electronic properties that effect the alkylation of DNA by the alkyldiazohydroxides, R-N=N-OH. The lithium, sodium, and ammonium salts of the alkyldiazohydroxides exhibit substantial charge transfer which perturbs the electron density and modifies the geometric parameters. The effect of cations on the geometries, net atomic charges, and activation energy of the nitrosoureas is markedly evident.

ACKNOWLEDGEMENT

FAMILY AND FRIENDS, YOUR CONSTANT PRAYERS
AND UNWAVERING FAITH HAVE SUPPORTED ME.

PAX DOMINI SIT SEMPER VOBISCUM

TABLE OF CONTENTS

LIST OF TABLES

Table Page

LIST OF TABLES IN THE APPENDIX

Tables Page

1-A to 6-A

7-A

8-A to 13A

14-A to 19A

20-A

21-A

22-A

23-A to 26A

27-A to 29-A

List of Tables in the Appendix Continued

LIST OF ILLUSTRATIONS

Figures Page

Schemes

LIST OF ILLUSTRATIONS IN THE APPENDIX

INTRODUCTION

The nitrosoureas, potent antitumor drugs, have been investigated extensively by the scientific community in order to understand their chemical, biological, and pharmacological properties. Yet, theoretical studies which could help to rationalize the observed effects have just recently been considered. Therefore, more extended *ab-initio* calculations have been undertaken to elucidate the structure-activity relationships of the nitrosoureas.

Historical Background

When the National Cancer Institute's Chemotherapy Program was organized in 1955, the primary screening process of numerous materials was based on the substances' activities in three transplantable mouse tumors - Sarcoma 180, Carcinoma 755, and murine Leukemia L1210 (1). In 1959, routine screening of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) indicated weak activity against Leukemia L1210 (2). This finding stimulated experimental investigations of compounds structurally related to MNNG. Among those submitted, 1-methyl-1-nitrosourea (MNU) not only demonstrated more effective antitumor activity, but more importantly was active against intracerebrally inoculated Leukemia L1210 cells (3). Since both MNNG and MNU were used as chemical precursors in the preparation of diazomethane, this mode of alkylation of DNA was investigated. The experimetal use of deuterated dimethylnitrosoamine (4) and MNNG (5) showed that the "CD_3" methyl group was transferred intact. If diazomethane had contributed significantly to the alkylation process, then the alkylated adducts would have contained the "CD_2H" methyl group. Further verification of intact transmethylation was evidenced by the simultaneous reaction of DNA with ^3H-methyl-labeled and ^{14}C-methyl-labeled MNU. In each of the various products that were isolated, the original ratio of the two isotopes was maintained (6).

The ability of MNU to penetrate the blood-brain barrier prompted Southern Research Institute to initiate a synthesis program to produce more active nitrosoureas. Systematic modifications of the MNU molecule and the evaluation of numerous congeners established structural relationships that enhanced antitumor efficacy: (a) the lack of antitumor activity of methylurea and other ureas clearly indicated the necessity of the nitroso group (7), (b) the biological inactivity of a disubstituted amino group showed the necessity of a proton for spontaneous decomposition in aqueous media (8), and (c) superior activity was obtained when the substituent on N-4 of a nitrosourea was the 2-chloroethyl group (9). Thereafter, most of the nitrosoureas that were prepared for clinical trials contained the 2-chloroethyl moiety on N-4 with various monosubstituents on N-3 such as 2-chloroethyl (BCNU) (9), cyclohexyl (CCNU) and trans-4-methylcyclohexyl (MeCCNU) (10). (See Figure 1 for the numbering system.)

Among the most active compounds tested at Southern Research Institute, MeCCNU and its carboxy and acetic acid congeners exhibited highly effective activity against a variety of solid tumors as well as systemic leukemias. The sodium salts of these analogues, which are

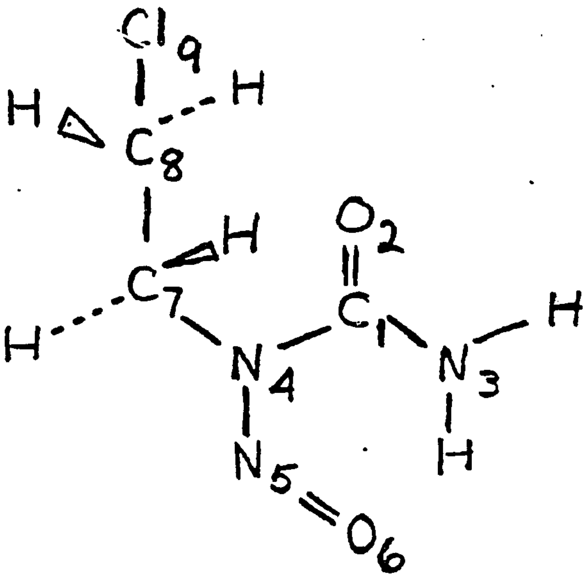


Figure 1. Chloroethylnitrosourea (CENU)

readily soluble in water and more easily formulated for injection, are equivalent in activity, if not better than, MeCCNU (11). The nitrosoureas have shown a broader spectrum of activity against experimental neoplasms than any other class of agents reported in the scientific literature, and since the inception of the screening process, begun almost thirty years ago, six nitrosourea compounds have been clinically accepted in the United States (12). The antitumor spectra of the more widely tested nitrosoureas, as single agents, are compared in Table 1 (13).

Congener synthesis of nitrosoureas continues along with the concomitant development of combination chemotherapy. This approach to improving therapeutic effectiveness serves to (a) lessen drug

TABLE 1

Comparative Antitumor Spectra of Nitrosoureas

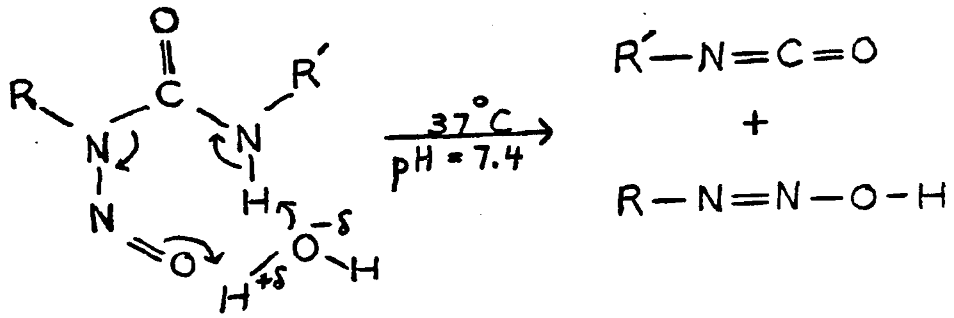
Neoplasm	BCNU	CCNU	MeCCNU
Brain	+	+	±
Colon	+	±	+
Stomach	±	±	+
Hodgkin's	+	+	+
Lung	±	+	±
Melanoma	+	±	+

toxicity for vital normal cells, (b) obtain synergistic cell kill of drug-resistant cells, and/or (c) control overgrowth of drug-resistant cells. The therapeutic synergism of the nitrosoureas (BCNU, CCNU, and MeCCNU) is well-established (14).

The extensive evaluative studies of the nitrosoureas have focused on structure-activity relationships, physiological conditions, and plausible mechanisms for the observed biologic effects. The future rational design and delivery of new nitrosoureas require further molecular understanding of their chemical and electronic properties as well as the biological interactions of these potent antitumor drugs with their target DNA molecule.

Chemical and Electronic Properties of Nitrosourea

The antitumor and cytotoxic activity of nitrosoureas is related to the ability of the drugs to alkylate DNA (15). The decomposition of chloroethylnitrosoureas proceeds spontaneously under physiological conditions to produce alkylating moieties and isocyanates that may function as carbamoylating agents (7). Urea precursors of the N-nitroso compounds are not biologically active (7); however, introduction of the N-nitroso group labilizes the bond between the nitrosated nitrogen and the adjacent carbon atom of the carbonyl so that decomposition occurs spontaneously in aqueous media. The stability of chloroethylnitrosoureas with a disubstituted amino group in aqueous media (8) suggested that the decomposition reaction may require the loss of a proton from the amino group. The following mechanism has been proposed (16):

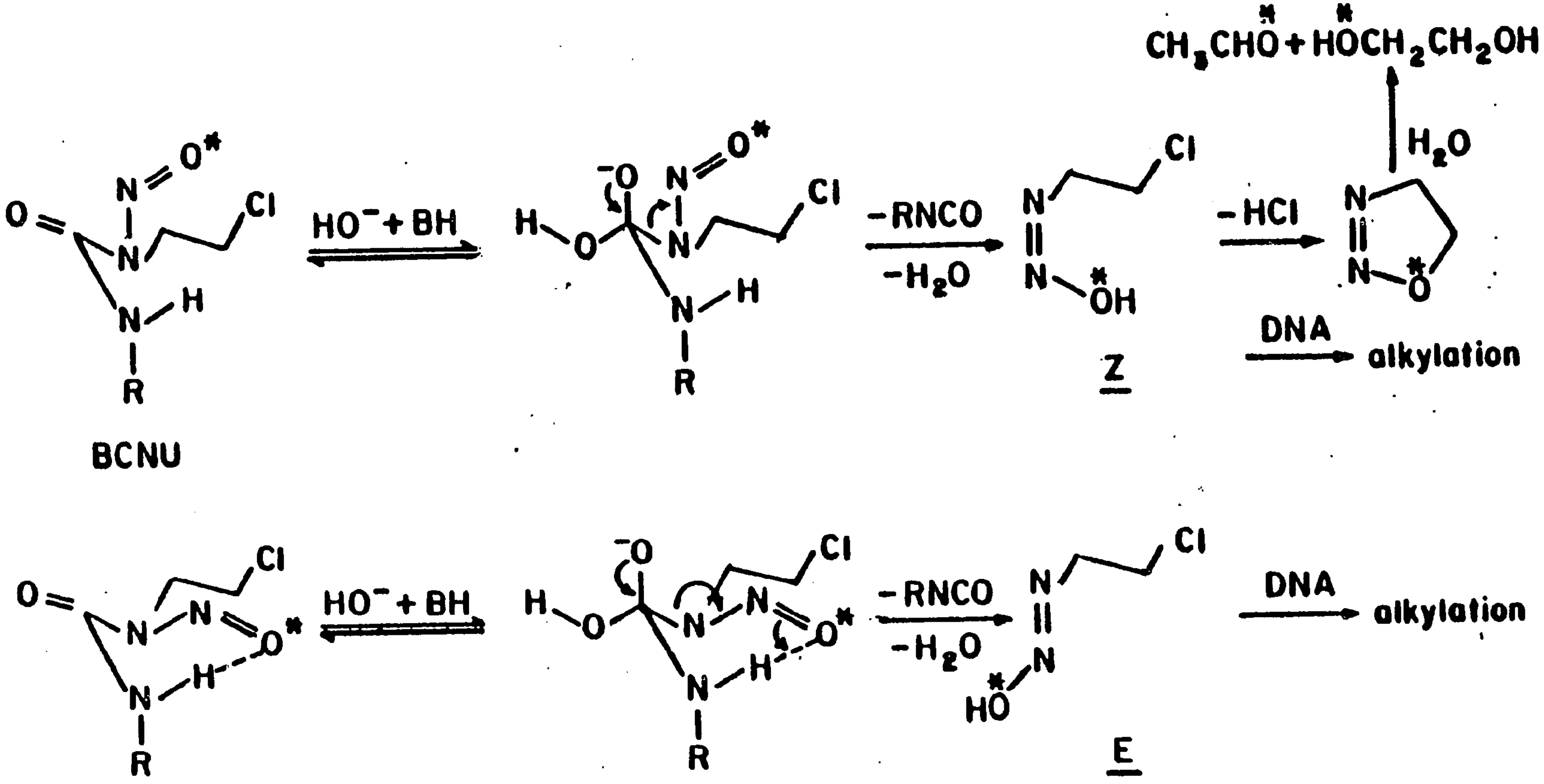


Scheme 1. Aqueous Decomposition of N-Alkyl-N-Nitrosoureas

Conformational studies of the aqueous decompostion of specifically labeled 2-haloethylnitrosoureas suggest the existence of tetrahedral intermediates which lead to the formation of *E* and *Z* haloethyldiazonium hydroxides as diagramed in Scheme 2 (17). Additional experimental evidence on the aqueous decomposition of specifically labeled *bis*-(2-chloroethyl)nitrosourea (BCNU) indicates a relative contribution of approximately 80 to 20 for the competing pathways that form the *E* and *Z* diazohydroxide configurational isomers, respectively. The studies also show that the isomers do not readily interconvert, but rather are discrete entities that essentially react independently (18). The computed estimate of the energy barrier for configurational inversion of the *Z* to *E* methyldiazohydroxides is 49.35 Kcal. per mole (19). Stereochemical studies of methyl substituted BCNU indicate that the alkylations seem to occur by a predominantly Sn2 attack on the electrophilic species, chloroethyldiazonium hydroxide, rather than through a free carbonium ion. It was postulated that the alkylating agent, R-N=N-OH, probably existed with a short, but finite life-time, inside the target cell (20). Although alternative pathways have been proposed for the decomposition of nitrosoureas (8,16,17,21), each implies the formation of the electrophilic species, R-N=N-OH, as the putative alkylating agent.

Subsequent studies of the reaction of nucleic acids with various N-nitroso alkylating agents not only substantiated the predominance of a bimolecular pathway involving an alkyldiazohydroxide, but also indicated that adduct rearrangement occurred at the O^6 position of guanine and not at the N-7 nucleophilic site (22). Furthermore, ethylating agents reacted more extensively with all the oxygens in

FORMATION OF TETRAHEDRAL INTERMEDIATES



Scheme 2

nucleic acids, relative to the nitrogen centers, than did the methylating agents (23). These distinctions between the alkylating agents and the site of attack are significant since attack at 0^6 - guanine can lead to interstrand cross-linking which is a lethal event for the tumor cell (24). But, alkylation at 0^6 is also considered to have possible mutagenic/carcinogenic consequences (25), while alkylation at the N-7 position of guanine is deemed to be relatively innocuous (26). These suppositions, however, are still a matter of controversy and of continuing investigation.

Such observation of situ-selectivity and differences in the biological interactions of DNA alkylation suggest the importance of investigating the molecular basis of alkylation and correlating it to the activity of nitrosoureas in order to elucidate their carcinostatic and/or carcinogenic properties.

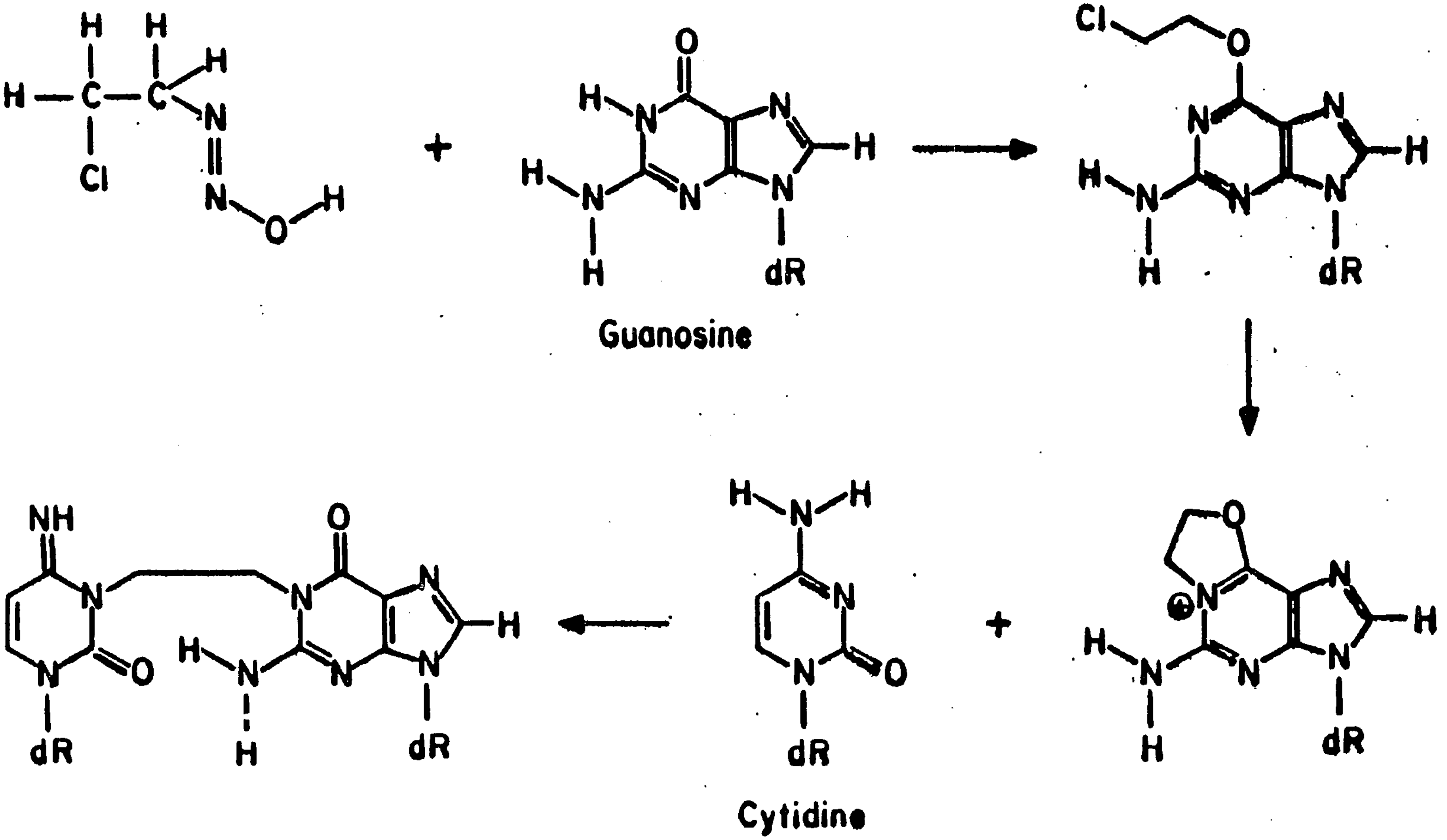
Biological Interactions with DNA

DNA - Alkylation

Classical alkylating agents such as nitrogen mustards require bifunctional groups to form covalent cross-links between nucleophilic sites on opposite strands of DNA, thereby producing cytotoxic lesions (27). These classes of agents, particularly the methyl analogues, react primarily at the N-7 position of guanine (28) which is not considered to lead to carcinogenesis or mutagenesis (26). The structure of nitrosoureas, however, incorporates only a single alkylating functionality, yet methyl nitrosourea is strongly mutagenic (29) and chloroethylnitrosoureas produce lethal interstrand cross-links (24,30). The proposed sequence in the formation of DNA cross-links by chloroethylnitrosoureas begins with the generation of the reactive intermediate, chloroethyldiazohydroxide, which transfers the chloroethyl moiety to a nucleophilic site on one DNA strand. This monoadduct then reacts with a second nucleophilic site on the opposite DNA strand through the displacement of the labile chloride resulting in an ethylene bridge between the two alkylated strands (31). The helical nature of DNA suggested that a two-carbon bridge between the base pairs, guanine and cytosine, would be the more probable link (24,30). Since experimental evidence had demonstrated that the 0^6 position of guanine could be ethylated (23a,32), it was proposed that this was the site of initial chloroethylation, which then led to the subsequent formation of the interstrand cross-links (24). The dinucleoside 1-[N^3-deoxycytidyl],2-[N^1-deoxyguanosinyl]-ethane was isolated from DNA treated with bis-(2-chloroethyl)nitrosourea (BCNU) (33). Scheme 3 illustrates its proposed formation from an initial attack at the 0^6 position of guanine.

It was hypothesized that the decisive factor in carcinogenesis was not the absolute extent of modification of nucleic acids, but rather the relative amount of 0^6 guanine adduct that was formed (32a,b). This hypothesis was supported by the findings that the alkylation of the 0^6 position of guanine could cause mispairing or misincorporation during transcription (34). The persistence of 0^6 alkylation (32a,b;35) as well as the slowness of the second alkylation (24,30) prompted further investigations of the repair mechanism of DNA.

FORMATION OF INTERSTRAND CROSS-LINK BY 2-CHLOROETHYLDIAZOHYDROXIDE



Scheme 3

DNA - Repair Mechanism

The repair mechanism in normal human cells would be capable of removing the initial chloroethyl lesion at the 0^6 position of guanine before the slow conversion to lethal interstrand cross-links was completed. This natural defensive process spares vital normal cells during the regimen of chemotherapy with alkylating agents (31). The selective cytotoxicity of nitrosoureas is also apparent among tumor cells which show varying susceptibility to alkylation chemotherapy (36). Such experimental findings suggest that tumor cells which exhibited sensitivity toward alkylating agents are deficient in removing the monoadduct from the 0^6 position of guanine. Extensive studies of normal human cells and various tumor cell strains identified two groups of cells that did indeed differ in their proficiency to remove 0^6 - methylguanine. Tumor cell strains that are deficient in DNA methylation repair are designated as phenotype "Mer^-" (37). The experimental studies were extended to show that the effective or defective repair system which was operational for 0^6 - methylguanine removal was also functional for 0^6 - chloroethylguanine monoadducts (38). It has been proposed that normal human cells (Mer^+) remove the monoadduct from 0^6-guanine by the action of an alkyltransferase protein and not by excision (39).

In adddition to cross-links chloroethylnitrosoureas induce DNA single-strand breaks (40) which are normally repaired by an excision and rejoining process (41), which is illustrated in Figure 2.

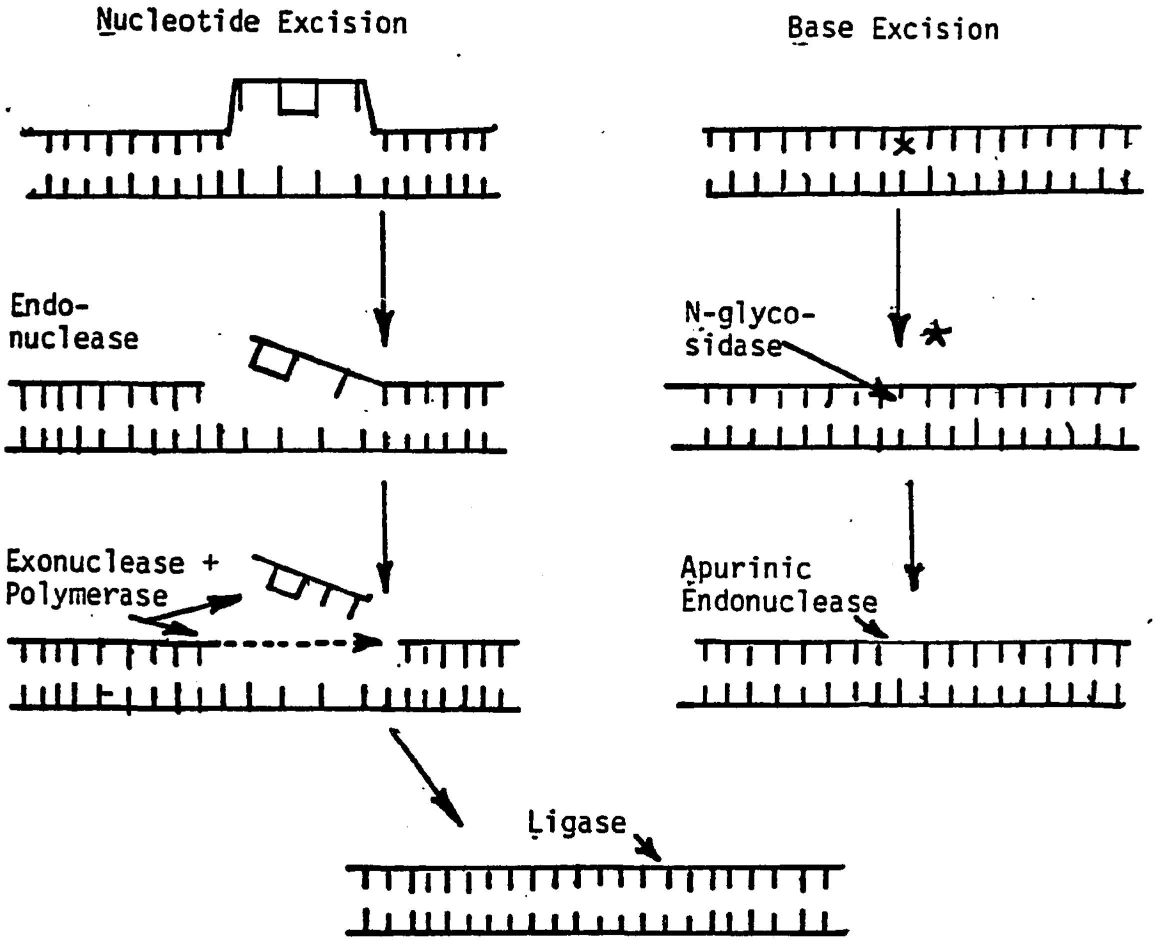


Figure 2. Excision Repair Mechanism

Inhibition of DNA repair for this type of damage has been related to the carbamoylating activity of the nitrosoureas (42) which occurs as a result of the formation of isocyanates during decomposition (7). The effect on tumor cells treated with selected nitrosoureas that exhibited strong and weak carbamoylating activity indicated that a delay in the repair of single-strand breaks was associated with strongly carbamoylating nitrosoureas (43). A study of DNA cross-linking and cytotoxicity in normal (Mer^+) and transformed human cells (Mer^-) treated with various nitrosoureas shows that the nitrosoureas which could generate alkylisocyanates produced smaller differences in cytotoxicity between the cell types, whereas the noncarbamoylating nitrosoureas demonstrated substantially greater differences between the two cell types (44). The decrease in DNA repair in normal human cells indicates that these cells are more sensitive to strongly carbamoylating chloroethylnitrosoureas, possibly due to the inhibition of the strand-rejoining step in DNA repair (45).

Chemotherapeutic value of an antitumor drug depends not only upon its selective cytotoxicity, but also upon the absence of deleterious effects on vital normal cells. While experimental studies such as those described above help to identify the inherent chemical-biological properties of the nitrosoureas, pharmacologic effects are crucial to the selection and development of rational approaches to clinical trials.

Pharmacologic Aspects

Nitrosoureas are prodrugs whose cytotoxicity is related to their ability to generate the reactive alkylating species, R-N=N-OH, at the intracellular target site (8,24a). While the nitrosoureas share common modes of activation, many factors contribute to the rate of activation and the extent of biodistribution, so that individual pharmacokinetics of the nitrosoureas can differ significantly (46). Most chloroethylnitrosoureas are rapidly cleared ($t_{\frac{1}{2}} \sim$ 15-30 min.) from plasma, in which the more lipophilic nitrosoureas distribute more extensively than the less lipophilic ones (47). The amount of alkylating species in the tumor cell determines cell kill and is dependent on the intracellular half-life of the parent nitrosoureas as well as the exposure of the tumor cell to the drug (48). Among the options available to oncologists to maximize drug exposure without increasing systemic toxicity would be to reduce myelotoxicity (bone marrow destruction) and to increase membrane fluidity as well as tumor capillary permeability. Osmotic agents that could passively open capillaries would increase tumor drug levels and the cell kill of sensitive tumors (46).

Intraarterial administration of hypertonic solutions such as lithium chloride are shown to open, reversibly, the blood-brain barrier independent of any specific chemical or drug action (49). The lithium cation has been found to stimulate the transport of the amino acid, proline, in whole cells of *Escherichia coli* (50). Several clinical studies report that the administration of lithium chloride or lithium carbonate to patients who are undergoing treatment with chemotherapeutic drugs reduces the incidence of infection (51). This beneficial effect in those patients treated with lithium is attributed to the elevated white blood count due to the stimulatory effect of the lithium cation on stem cells in the bone marrow (52). The combined treatment of lithium chloride with the chemotherapeutic agents, bleomycin and vinblastine, produces a significant decrease in tumor size and prolongs the survival of the melanoma-bearing mice. These effects seem to demonstrate that the lithium may produce changes in membrane fluidity and permeability which would increase the penetration of cytotoxic agents into the tumor cell (53).

Lithium cation affinities of nitrogen bases have been calculated and found to be linearly related to the proton affinity of the bases (54). Recently, lithium and sodium cation affinities of aziridine were calculated (55), and although smaller than the proton affinity, the possibility remains that the activity of the antitumor antibiotic, mitomycin C, which contains the aziridine ring, might be enhanced if used in conjunction with salts. Similar findings for the nitrosoureas would support dosage regimens of combination chemotherapy with salts for possible improved therapeutic effectiveness.

Knowledge of the effects of the nitrosoureas upon cell survival along with the knowledge of cell kinetics in the target tumor cells allows for designing clinical trials and combinations that produce synergistic results (56).

Summary

Nitrosoureas have been established as effective antitumor agents against a variety of human carcinomas (12). The decomposition of chloroethylnitrosoureas proceeds spontaneously under physiological conditions to produce alkylating moieties and carbamoylating isocyanates (7). The antitumor and cytotoxic activity of the nitrosoureas is related to the formation of the reactive electrophilic species, R-N=N-OH, which alkylates DNA (15), thus producing interstrand cross-links which are lethal to tumor cells (24).

Chloroethylation of O^6- guanine may initiate the formation of the lethal interstrand cross-links so that attack at this position is strongly related to the antitumor activity of nitrosoureas and the cytotoxic selectivity among cell strains (31). However, carcinogenic potency of the alkylating agents also correlates with their affinity to alkylate the 0^6 position of guanine, but there is no correlation between the extent of N-7 alkylation and carcinogenesis (23b,26).

DNA repair mechanism in normal human cells (Mer^+) can effectively remove 0^6- alkyladducts before lethal interstrand cross-links are formed, whereas sensitive tumor cell strains designated (Mer^-) are deficient in this repair process which results in their selective susceptibility to cytotoxic agents (37). Mutagenicity is associated with lesions that produce DNA single-strand breaks (57). The carbamoylating activity of the nitrosoureas inhibit the DNA repair mechanism which rejoins single-strand breaks (43). The differential cytotoxicity between Mer^+ and Mer^- cells is less with carbamoylating congeners of nitrosoureas than with noncarbamoylating ones (44).

Biological interactions of the nitrosoureas are also a function of pharmacokinetics. Delayed and cumulative myelosuppression limits both the frequency and total dosage of the nitrosoureas (13), yet little attention has been given to the use of intravenous hyperosmotic agents, such as lithium chloride, in combination with the nitrosoureas (46).

The evident complexity of the nitrosoureas with regard to their chemical and electronic nature, their biological interactions, and their pharmacokinetics emphasizes the importance of a fuller understanding on a molecular basis of those structure-activity relationships that determine selective cytotoxicity, carcinostatic properties, and carcinogenic/mutagenic possibilities.

It is acknowledged that ab-initio molecular orbital studies obtain calculations for a gas-phase environment, which may differ from the physiological environment of the cell. Regardless of the actual cell's surroundings, theoretical calculations permit an extensive study of the reactive intermediates. Detailed information concerning relative energies, electron distribution, and reaction pathways, which is not always obtainable through experimental endeavors, is provided by theoretical investigations. Theoretical studies are accorded deserved recognition for their value in the elucidation of chemical and biological phenomena.

PURPOSE

A fuller understanding on a molecular basis of those structure-activity relationships that influence the observed biologic effects of the nitrosoureas might be attainable by ab-initio molecular orbital studies. Hartree-Fock calculations that obtain optimized geometries, energies, LUMO composition, and charge distribution could determine the essential electronic properties that differentiate the alkylating activity of the electrophilic alkyldiazohydroxides, R-N=N-OH.

The spontaneous decomposition of the parent nitrosoureas in aqueous media is fundamental to the generation of this reactive alkylating species. In one postulated mechanism, the loss of a proton from the amino group and the addition of a proton to the nitroso group initiates this decomposition (16). The source of the proton has not been unequivocally determined since the decomposition occurs at physiological pH which is slightly alkaline; however, alkali cations might also function as initiators of the reaction. Among the many roles of alkali metals in biological systems is metal ion catalysis, which is possible in pH ranges where proton catalysis, would be ineffective (58). Thus, the determination of the effect of alkali metal cations on the activity of the nitrosoureas and the alkyldiazohydroxides is informative.

Therefore, the two principal objectives of this work were (1) the elucidation of the mechanism of DNA alkylation by the electrophilic species, R-N=N-OH, which is produced by the decomposition of nitrosourea, and (2) the investigation of the possible effects of alkali metal cations on the activity of the nitrosoureas and the alkyldiazohydroxides which result from their decomposition.

The first objective was accomplished by performing ab-initio Hartree-Fock calculations as implemented by the Gauss-80 computer program with Gaussian basis sets (59) on representative diazohydroxide compounds with different alkyl substituents on the nitrogen in order to compare the LUMO compositions and charge distributions among the configurational isomers. If the alkylation of DNA proceeds through a soft nucleophile, the LUMO composition of the electrophile is of great importance; however, if the reaction occurs via a hard nucleophile, then net atomic charges become significant, for the interaction with DNA is then electrostatically controlled. This approach is referred throughout the discussion as the Hard-Soft, Acid-Base concept (HSAB) (60).

The second objective was accomplished by also performing ab-initio Hartree-Fock level calculations on nitrosourea and methylnitrosourea to determine (a) if the nucleophilic sites on the drugs exhibit significant affinity for alkali cations, and (b) the influence of such cations on the process of decomposition. Furthermore, in order to investigate salt effects on R-N=N-OH, the product of decomposition of nitrosourea, calculations were performed on representative diazotates with different counter ions to determine (a) if a significant affinity for such counter ions exists, and (b) the influence of such counter ions on the geometries, energies, LUMO composition, and charge distribution of the diazotates.

METHOD

Ab-initio self-consistent field (Hartree-Fock) calculations of the geometries, energies, net atomic charges, and composition of the molecular orbitals were obtained by solving Roothaan equations (61) using Gaussian basis sets as implemented by the Gauss-80 computer program (59). The program incorporates the Berny optimization method (62) for obtaining energetically optimized molecular geometries. In ab-initio SCF-MO calculations, a set of orbitals is selected to obtain an initial operator and an initial energy. The set of orbitals that is selected constitutes the basis set. The initial operator is used to construct a new set of orbitals which in turn proceeds to generate another operator and another energy. This iterative process continues until convergence occurs and a self-consistency is achieved, that is, the set of orbitals produced by the operator is the same set of orbitals that produced the energy terms in the operator (63).

The Gaussian basis set chosen for the calculations depended on the specific system that was investigated. Larger systems such as the nitrosoureas were studied with minimal basis sets, namely STO-6G (64) and the small extended basis set 3-21G (65). Smaller systems were investigated with larger basis sets such as 6-31G* (66) as well as the 3-21G basis set. A minimal basis set such as STO-6G approximates a Slater-type orbital as a linear combination of six gaussian functions. The exponent in a Slater-type calculation is "e^{-ar}" which requires considerable time to evaluate the integrals; therefore, by replacing such an exponent with a linear combination, $b_1e^{-a_1r^2} + b_2e^{-a_2r^2} + \ldots$

$b_n e^{-a_n r^2}$, the integrals are readily calculated. The extended basis set 3-21G incorporates a linear combination of three gaussian functions to each inner shell Slater-type orbital (STO). Additionally, each valence shell STO is split into inner and outer parts with hydrogen atoms having 1s + 1s' orbitals and the other atoms having 1s, 2s + 2s', 2p + 2p' orbitals. The inner 1s, 2s, and 2p orbitals are described by two gaussian functions, while the outer 1s', 2s', and 2p' orbitals are described by one gaussian function. The larger 6-31G* split-valence basis set not only extends the number of gaussian functions to the STOs, but also adds "d" functions to the nonhydrogen "s" and "p" orbitals. The addition of new functions increases the capability of the basis set; however, the resulting continuous decrease in energy approaches a limiting value as the basis set approaches mathematical completeness. This limiting energy value is the lowest that can be achieved for a single determinantal wavefunction. It is called the Hartree-Fock energy (63).

Alkyldiazohydroxides and Alkyldiazotates

The calculations for the _E_ and _Z_ isomers of methyldiazohydroxide, their respective anions and diazotate salts, were performed with both 3-21G and 6-31G* basis sets. The calculations for the _E_ and _Z_ isomers of ethyldiazohydroxide, their respective anions and diazotate salts, were performed only with the 3-21G basis set. The results obtained using the smaller extended basis set are essentially representative of those that would have been obtained from the larger basis set. The only discrepancy observed in all the calculations when both the 3-21G and 6-31G* basis sets were used is that the LUMO participation of the carbon in the E isomers of methyldiazohydroxide is set-dependent. The 3-21G calculations show participation, while at both the 6-31G* and 6-31G levels there is virtually no contribution. The larger basis sets are considered more reliable and depict LUMO composition with more exactness; therefore, the participation of the carbon in the E isomer of methyldiazohydroxide is reported as minimal. The results presented correspond to completely optimized geometric parameters for the E and Z isomers of methyl- and ethyldiazohydroxides, their respective anions and lithium diazotates.

Calculations on the substituted ethyldiazohydroxides (2-fluoro, 2-chloro, 2-hydroxy) and the n-propyldiazohydroxide conformers as well as the 1,2,3-oxadiazoline intermediate were performed with the 3-21G basis set. The results presented correspond to partial geometrical optimization of the total energy. To optimize every bond distance and every bond angle for all the conformers of the molecules investigated in this study would require a prohibitive amount of computer time, money and resources. A pragmatic and theoretically justifiable alternative is to focus on selected geometric optimizations that still produce relevant calculations in those areas that are pertinent to the objectives.

The net atomic charge calculated for the chlorine atom is sensitive to complete optimization and is basis set-dependent, so when partial optimization is performed and the 3-21G basis set is used, the charge on the chlorine atom becomes almost neutral. Additionally, the C-Cl bond length that was obtained with the 3-21G basis set is too long. Bond distances associated with the minimum in the Hartree-Fock energy surface tend to be slightly longer than experimental results indicate. However, qualitative changes induced in the geometry of one part of a molecule by geometrical changes elsewhere in the molecule are well-represented.

Single-point calculations for the sodium and ammonium diazotate of ethyldiazohydroxides and for the lithium diazotate of 2-chloroethyldiazohydroxides were performed. The single-point geometries were chosen as follows: the diazotate entity was assigned the geometry obtained from the complete optimizations of the lithium diazotates. The O-Na and O-NH_4 distances were given the respective values of 2.25 Å as found for the O-Na length in sodium oxirane (55), and 1.50 Å for O-NH_4 which was point-by-point optimized to within 0.02 Å. The C-Cl distance was set at 1.85 Å and previously optimized angles were used.

All split-valence basis sets exaggerate the charge separation for the C-H bonds; therefore, group net atomic charges for CH_2, CH_3, CH_2F, CH_2Cl and CH_2OH, which are more indicative of the spacial charge concentration, are used for comparative purposes and for defining the observed trends in charge distribution.

Nitrosoureas

The STO-6G basis set was used to calculate the binding energies of lithium to the oxygen of the nitroso group (-N=O) and the carbonyl group (-C=O) of methylnitrosourea. The geometry of the lithiated methylnitrosoureas was optimized with the exception of the CH_3 and NH_2 groups whose parameters were kept at experimental values to conform and compare with the previously optimized methylnitrosoureas (67). The values of the lithium affinities are higher compared to values obtained for lithiated $H_2C=O$ and HN=O with the 6-31G* basis set (54). This result is due to the effect of the basis set superposition error which should be large when a minimal basis set is used, especially when a small entity such as a lithium cation is attached to a large molecule. The error results from the fact that the basis set for the lithium complex (AB) comprises the basis sets for both lithium cation (A) and methylnitrosourea (B). Hence, when calculating the energy of AB the basis set of B improves the energy of A and vice versa. The total energy E_{AB} is thus the sum of the improved energies of A and B and of the energy of their interaction (68). Cationic affinities are calculated using the formula:

$$\Delta E = E_{\text{complex(AB)}} - (E_{\text{cation(A)}} + E_{\text{entity (B)}})$$

Since the superposition error is intrinsic to the STO-6G basis set, further calculations of the binding energy of lithium and other cations to the nitroso group of nitrosoureas were performed with the 3-21G basis set. Completely optimized geometries were obtained for <u>syn</u> N-nitrosourea as well as for the lithiated and protonated nitrosoureas.

The energy associated with C-N bond breaking in nitrosourea was determined by incremental lengthening of the C-N bond and optimization of the other geometric parameters. When the transition state had been approximately determined in this manner, then the second derivative eigenvalues were examined to locate the saddle point according to the Berny optimization method (62), thus fixing the exact transition state, geometric parameters, charge distribution, and energy. Calculations were performed for *syn* N-nitrosourea, the lithiated and protonated nitrosoureas to compare the changes in energy from the ground state to the transition state.

RESULTS AND DISCUSSION

Alkyldiazohydroxides

Complete tabulation of the data obtained by the described methods as well as graphic representations of the structures of the investigated conformers of the alkyldiazohydroxide compounds and the 1,2,3-oxadiazoline intermediate are presented in the Appendix. Composite tabulations of the more pertinent aspects of the accumulated data are incorporated within the discussion of results.

The selected configurations of ethyldiazohydroxide, ethyldiazohydroxide derivatives (2-fluoro, 2-chloro, and 2-hydroxy), and n-propyldiazohydroxide are representative of the principal conformers for each group of the investigated compounds. The E isomers consist of the A and B conformers, while the Z isomers consist of the C and D conformers. The optimized geometric parameters for these conformers as well as their energies are given in Tables 1-A through 6-A in the Appendix. Concomitantly, Figures 1-A through 6-A illustrate their structural configurations. As seen in Table 1-A a very small difference in energy exists between conformers A-Ie and A-IIe due to the position of the hydrogen on the oxygen atom. In subsequent calculations the position of the hydrogen in the E isomers (A and B conformers) is syn to N-1, while in the Z isomers (C and D conformers) it is anti to N-1 (Figure 2-A). An examination of Tables 1-A and 2-A shows that significantly lower energies are calculated with the larger extended basis set (6-31G*), but comparative energies among the conformers are strikingly similar. Therefore, for pragmatic and economic reasons calculations on the other investigated compounds are performed with the smaller 3-21G basis set.

Table 2 compares the energies of the various alkyldiazohydroxide compounds as well as the relative differences in energy among each group's conformers. Except for the consistently higher relative energies of the Z (D-I) conformers, the differences in the calculated energies among the other representative conformers of the various alkyldiazohydroxides are not large. While these results might imply possible energetically favored interconversions among some of the conformers, this is unlikely since the energy barrier for configurational inversion of Z to E methyldiazohydroxides is 49.35 Kcal/mole (19). The lack of interconversion is supported by the formation of discrete E and Z 2-haloethyldiazohydroxides from tetrahedral intermediates (17). Preformed E 2-chloroethyl and E 2-fluoroethyl diazotates, generated in situ at 1 mM, cross-link λ-DNA, 25% within 15 min. and 24% within 75 min., respectively. In contrast, the Z isomers of 2-chloroethyl at 40 mM give slow interstrand cross-linking of 45% in 20 hours. These results are attributed to the preferred cyclization pathway (69) of the Z (D-I) conformer (Scheme 2), which effectively removes a significant fraction of the Z isomer.

Table 7-A and Figure 7-A present the optimize geometric parameters, energy, LUMO composition, and net atomic charges of the proposed cyclization species. Figures 3-A, 4-A, and 5-A (the structural configurations of 2-fluoro, 2-chloro, and 2-hydroxyethyldiazohydroxides) graphically present the close alignment between oxygen and the CH_2Y

TABLE 2

Energies (au) of Alkyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

Alkyl		Conformers		
Group	A-I	B-I	C-I	D-I
CH_2CH_3				
E	-261.3948	-261.3853	- 61.3832	-261.2251
ΔE^a	0.00	5.96	7.28	106.49
CH_2CH_2F				
E	-359.7161	-359.7176	-359.7180	-359.5894
ΔE	1.19	0.25	0.00	80.70
CH_2CH_2Cl				
E	-718.1160	-718.1211	-718.1199	-717.8699
ΔE	3.20	0.00	0.75	157.63
CH_2CH_2OH				
E	-335.8256	-335.8208	-335.8274	-335.6387
ΔE	1.13	4.14	0.00	118.41
$CH_2CH_2CH_3$				
E	-300.2190	-300.2130	-300.2198	-300.0129
ΔE	0.50	4.27	0.00	129.83

---

a. Kcal/mole

group, in the _Z_ (D-I) conformers. The interatomic distances between oxygen and carbon-6 in 2-fluoro, 2-chloro, and 2-hydroxy entities are 1.82 Å, 1.90 Å, and 1.98 Å, respectively, which allows for possible interaction, so that the displacement of a labile group by the lone pair electrons of oxygen is feasible. Since the _Z_ (C-I) conformer is less susceptible to cyclization, both _Z_ and _E_ isomers are considered viable alkylating agents of DNA.

To help clarify the process of DNA alkylation, consideration of the electronic properties of the alkyldiazohydroxide conformers such as their LUMO composition and net atomic charges becomes essential. Tables 8-A through 13-A present LUMO energies and atom contributions of ethyldiazohydroxide and its derivatives. Tables 14-A through 20-A present their net atomic and group atomic charges.

Hartree-Fock calculations with 6-31G* basis set show that the carbon atom of the _Z_ isomer of methyldiazohydroxide contributes strongly to the LUMO composition (0.387), while the carbon atom of the _E_ isomer has minimal contribution (0.075) (Table 34-A). In contrast, similar calculations for ethyldiazohydroxide show that the nitrogen-bonded carbon of the _E_ isomer contributes strongly to the LUMO composition (0.358), while the comparable carbon of the _Z_ isomer contributes 0.203 (Table 8-A). Moreover, calculations obtained with the 3-21G basis set show that the carbon-5 atoms of the _E_ (A-I) isomers of substituted derivatives of ethyldiazohydroxide also participate strongly in the LUMO composition. Table 3 is a compilation of pertinent data from Tables 9-A to 13-A that compares the contribution of the nitrogen-bonded carbon-5 atoms to the LUMO of representative alkyldiazo-

TABLE 3

Substituent Effects on the LUMO Energies[a] and Carbon-5 Contribution[b] of Alkyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

Alkyl	Conformers			
Group	A-I	B-I	C-I	D-I
CH_2CH_3				
C-5	0.039	0.002	-0.002	-0.010
	0.310	0.181	-0.296	+0.223
E	0.14548	0.15544	0.16357	0.15031
CH_2CH_2F				
C-5	-0.032	0.012	-0.004	+0.004
	-0.278	0.206	-0.257	-0.233
E	0.12147	0.15359	0.13677	0.13624
CH_2CH_2Cl				
C-5	0.026	-0.003	-0.007	-0.007
	0.305	+0.167	-0.261	+0.218
E	0.11956	0.14149	0.13219	0.12765
CH_2CH_2OH				
C-5	0.031	-0.001	0.003	-0.009
	0.307	+0.184	0.243	+0.184
E	0.13257	0.14055	0.14353	0.12574
$CH_2CH_2CH_3$				
C-5	-0.029	-0.003	0.001	+0.013
	-0.305	+0.188	0.238	-0.172
E	0.14360	0.15392	0.15616	0.13608

---

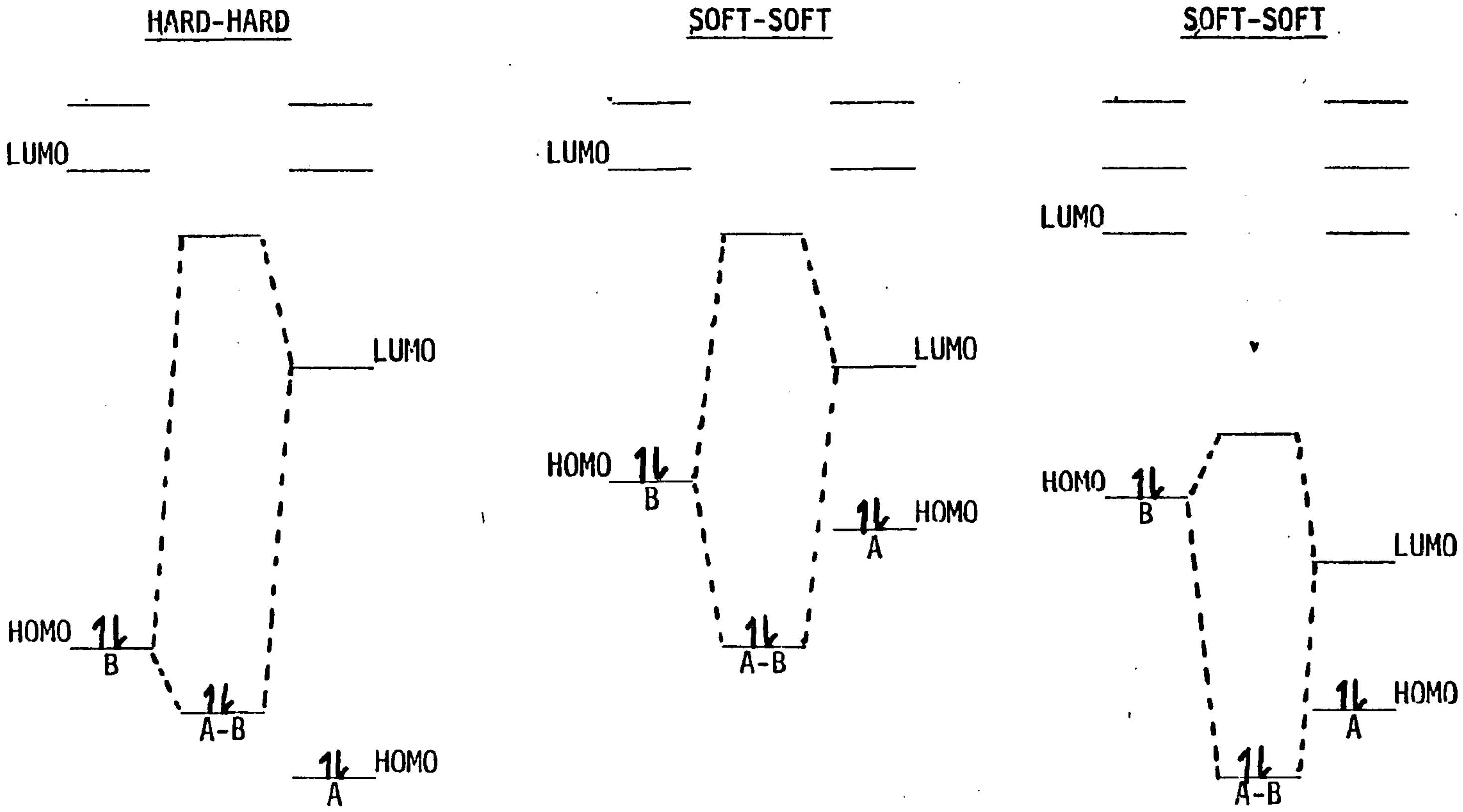
a. Atomic units; b. 2 Py orbital

hydroxides.

Such findings of disparity in the LUMO composition between the Z and E isomers of methyldiazohydroxide, and the contrast between the E isomers of methyl- and ethyldiazohydroxide could account for the situ-selectivity of DNA alkylation.

The Hard-Soft, Acid-Base (HSAB) approach (60) predicts interaction between hard-hard and soft-soft species as illustrated in Figure 3. The interaction of frontier orbitals, that is, the HOMO (highest occupied molecular orbital) of one molecule with the LUMO (lowest unoccupied molecular orbital) of another molecule leads to the largest decrease in energy when the interacting orbitals are close in energy (70). In hard-hard interaction there is a large energy difference between the donor HOMO and the acceptor LUMO. The bonding orbital formed resembles that of the donor. The electron pair continues to reside mainly on the donor and the bond that is formed has more ionic character. In soft-soft interactions donor and acceptor frontier orbitals are closer in energy and more interaction occurs. The electrons are shared and the bonding is covalent (60,70).

The electron contribution which an atomic orbital makes to the molecular orbital is quantified by its coefficient value. The squares of the coefficient values are a measure of the electron population or density, thus in each orbital the sum of the squares of all the coefficient values must equal one. If all molecular orbitals are filled, then the sum of squares of all the coefficient values on any one atom in all the molecular orbitals must equal one. This is



Fiqure 3. Idealized Hard-Hard and Soft-Soft Interactions

expressed as $c_1^2 + c_2^2 + c_3^2 + \ldots\ldots c_n^2 = 1$ for normalized functions (70a).

The contribution of the reactive sites to the composition of the frontier orbitals classifies the degree of softness or hardness of the reaction. The larger the contribution of the reactive site to the HOMO or LUMO, the softer is that site according to the concepts of HSAB (60) and Frontier Orbital Theory (FOT) (70). In the present study the carbon of the Z isomer of methyldiazohydroxide is the softer site since its LUMO coefficient (0.387) is larger than the coefficient (0.075) of the carbon in the E isomer. The contributions of the 0^6 and N-7 atoms of guanine to its HOMO are 0.362 and 0.189, respectively (71), which indicate that the 0^6 position of guanine is the softer site. Since soft-soft and hard-hard interactions are predicted (60), the carbon of the Z isomer would be expected to react with the 0^6 position of guanine, while the carbon of the E isomer would alkylate the N-7 nucleophilic site in an electrostatically controlled reaction (70b). The E isomer of methyldiazohydroxide is the thermodynamically more stable isomer by 12.80 Kcal/mole, and predictably, methylation of guanine occurs predominatly at the N-7 position (23b). Conversely, Table 3 indicates that the carbons-5 of the E (A-I) isomers of ethyldiazohydroxide regardless of alkyl substituent have the highest LUMO coefficients which classify these carbon-5 atoms as the softest electrophiles among the investigated conformers. Consequently, predominant alkylation at the 0^6 position of guanine, its softer nucleophilic site, by the carbons-5 of the E isomers of ethylating agents would be predicted, which supports the experimental evidence (23).

Frontier orbitals can be used as a criterion for determining the type of controlling effect that occurs when two reactants approach each other (70). A simplified quantitative expression for the change in energy when the orbitals of one reactant overlap with that of another is given by the following equation:

$$\Delta E = \frac{Q_n Q_e}{R_{ne}} + \frac{2(c_n^{HOMO} c_e^{LUMO} \beta_{ne})^2}{E_{(HOMO)_n} - E_{(LUMO)_e}}$$

Q_n and Q_e are total charges on atoms n and e.

R_{ne} is the distance between atoms n and e.

β_{ne} is the resonance integral (sharing of electrons).

E_n and E_e are the energies of the frontier orbitals for n and e.

c_n and c_e are the coefficients in the frontier orbitals for the atoms at the reaction center.

n and e are subscripts that define nucleophile and electrophile.

The first term is the Coulombic attraction or repulsion between the nucleophile (base) and electrophile (acid). It is designated the "charge control term" and measures the effect of hard-hard interaction. The second term represents the interaction of the filled HOMO (base) with the unfilled LUMO (acid) when the energies of the HOMO and LUMO are not degenerate. It is designated the "orbital control term" and measures the effect of soft-soft interaction (70b).

The numerical value of the second term for the *E* isomers of both methyl-and ethyldiazohydroxide was calculated using the HOMO and LUMO compositions determined with the 6-31G* basis set. These values quantitatively compare their ability to alkylate the O^6 position of guanine which is its softer site. The value for the carbon-5 atom of E (A-I) ethyldiazohydroxide is $0.094\beta^2$, while the value for the carbon-5 atom of E methyldiazohydroxide is $0.004\beta^2$.

Thus, the ethylation of the O^6 position of guanine by the dominant E isomer is considered to be "orbitally controlled" with the LUMO of the electrophile (alkylating agent) and the HOMO of the nucleophile (O^6- guanine) overlapping to form covalent bonds, while the methylation of N-7 is considered to be "charge controlled" (60,70). These fundamental electronic properties determined by ab-initio calculations are pertinent to a better understanding of the in-vivo activity of the nitrosoureas.

Examination of Table 3 shows that the LUMO energies and carbon-5 contributions of the E propyldiazohydroxide conformers are similar to the corresponding E ethyldiazohydroxide conformers. The Z propyl conformers have smaller carbon-5 contributions than the corresponding Z ethyl conformers, but their LUMO energies are more accessible. Table 20-A which lists the group net atomic charges of the investigated conformers shows substantially equal positiveness for the $C_5H_7H_8$ entity among the (A-I), (B-I), and (C-I) propyl isomers. These data indicate that the "orbitally controlled" attack at the O^6 position of guanine is as feasible for propyldiazohydroxides as it is for ethyldiazohydroxides. The results of propylation of the N-7 position of guanosine in-vitro by n-propylnitrosourea or of RNA guanine *in-vivo* by di-*n*-propylnitrosamine yields 7-*n*-propyl guanine derivatives; however, the principal adduct of O^6 alkylation is isopropyl guanine (22).

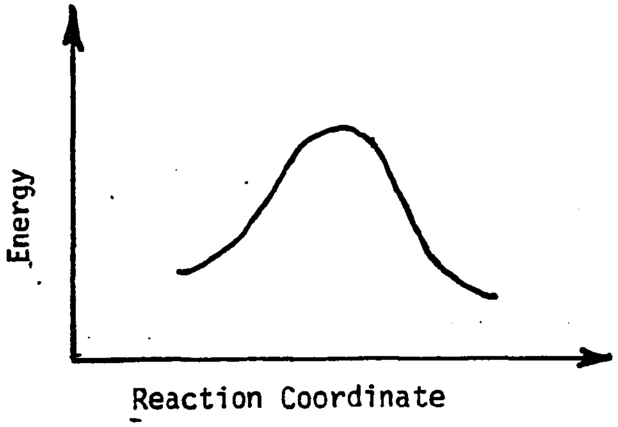
The alkylation of DNA occurs by a predominantly Sn2 attack on the electrophile, R-N=N-OH, rather than through a free carbonium ion (20,22). Bimolecular reactions are affected more by the nature of the nucleophile than the lability of the leaving group. As a nucleophile approaches the reaction site, its electron pair begins to form a partial bond to carbon, while the existing bond to the leaving group begins to break. With a good nucleophile, there is an early "tight" transition state with both entering nucleophile and leaving group close to the attacked carbon. If an Sn2 reaction occurs with a poor nucleophile, the transition state is "looser", both partial bonds are broken, and more Sn1 character can develop, particularly if the formation of a carbonium ion is energetically favorable (72). The bonding in the transition state of an Sn2 reaction may vary as follows:

Nu...C...X   Nu.....C.....X   Nu....C....X   Nu..C....X   Nu....C..X
tight   *loose*   *symmetrical*   *unsymmetrical*

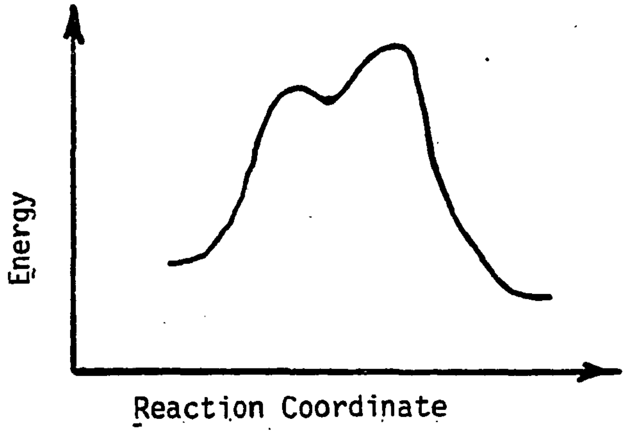
A recent theoretical study (73) reveals the presence of shallow energy minima in Sn2 reaction profiles of the alkylation reaction of simple oxygen and nitrogen nucleophiles characteristic of those in nucleic acid bases. Such reaction profiles involve ion-pair complexes preceding the transition state which are indicative of Sn1 character in bimolecular reactions. Figure 4 illustrates the reaction profiles of the principal nucleophilic processes. The calculations reflect "looser" transition states for nucleophiles whose lone electron pair is less available.

Since O^6- guanine is a weaker nucleophile than N-7, the transition state during its nucleophilic attack on the electrophile, _n_-propyldiazohydroxide, is looser. This means that the C-N bond of the leaving group is nearly broken, while the C-O bond of the nucleophile is only starting to form. Such an occurrence contributes Sn1 character to the reaction which permits rearrangement of the _n_-propyl group as some partial charge develops on the carbon (72). The "later and looser" bond formation to an _n_-propyl conformer could energetically favor isomerization to 2-propyl in the ion-pair complex.

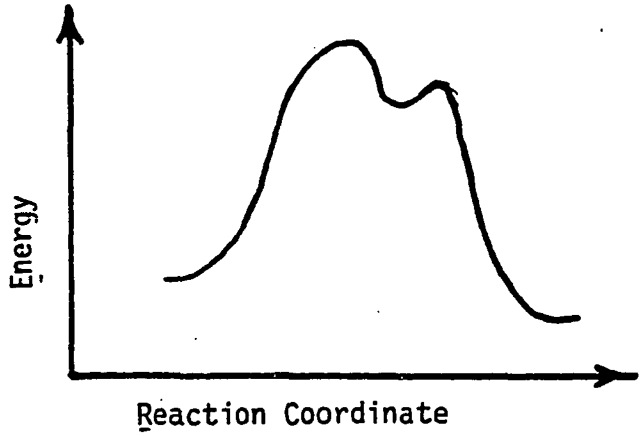
The propyl system has been investigated to ascertain the mechanism of carbon and hydrogen equilibration and cyclopropane formation in the reactions of the _n_-propyl cation (74). Scheme 4 illustrates the equilibration of corner-protonated and edge-protonated cyclopropanes. The labeled 1-propanol products formed in the deamination of 1-aminopropane-1-^{14}C were considered to arise via rearrangements involving 1,3-hydride shifts, 1,2-methyl shifts, or edge- and face-protonated cyclopropanes (74,75). Recent _ab-initio_ calculations (76) with the 6-31G*/MP4(SDQ) basis set show the relative energies in Kcal/mole for 2-propyl, 1-propyl, corner-protonated cyclopropane, and edge-protonated cyclopropane to be 0.0, 20.0, 8.2, and 10.5, respectively. The 1-propyl cation does not have a local minimum at the 6-31G* level and is converted without activation to



Sn2

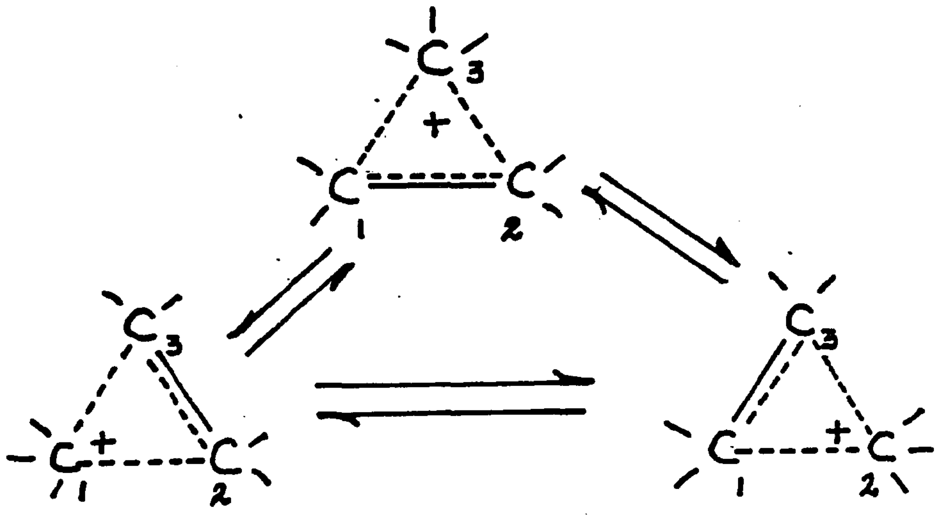


Ion Pair Sn2

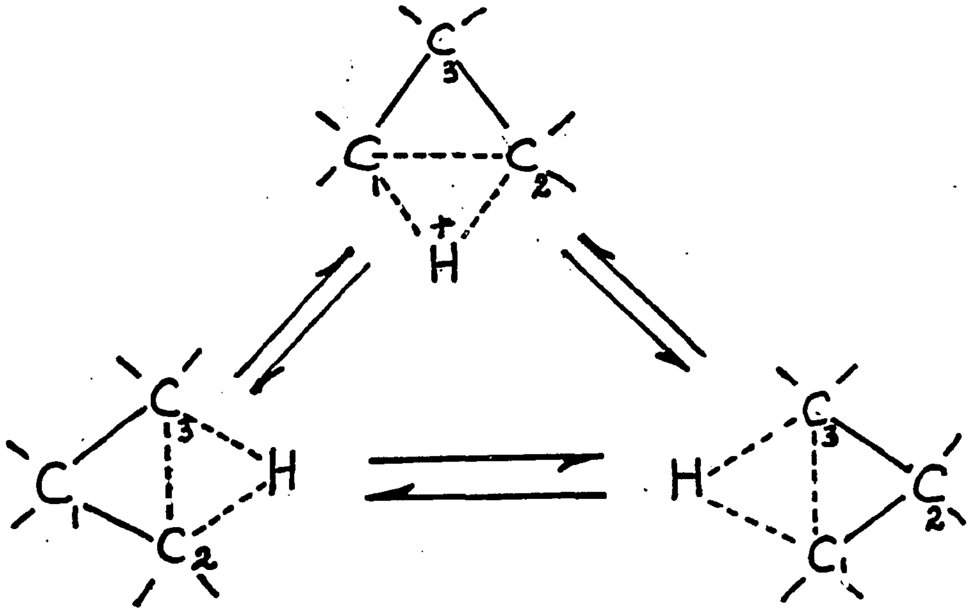


Sn1

Figure 4. Nucleophilic Reaction Profiles



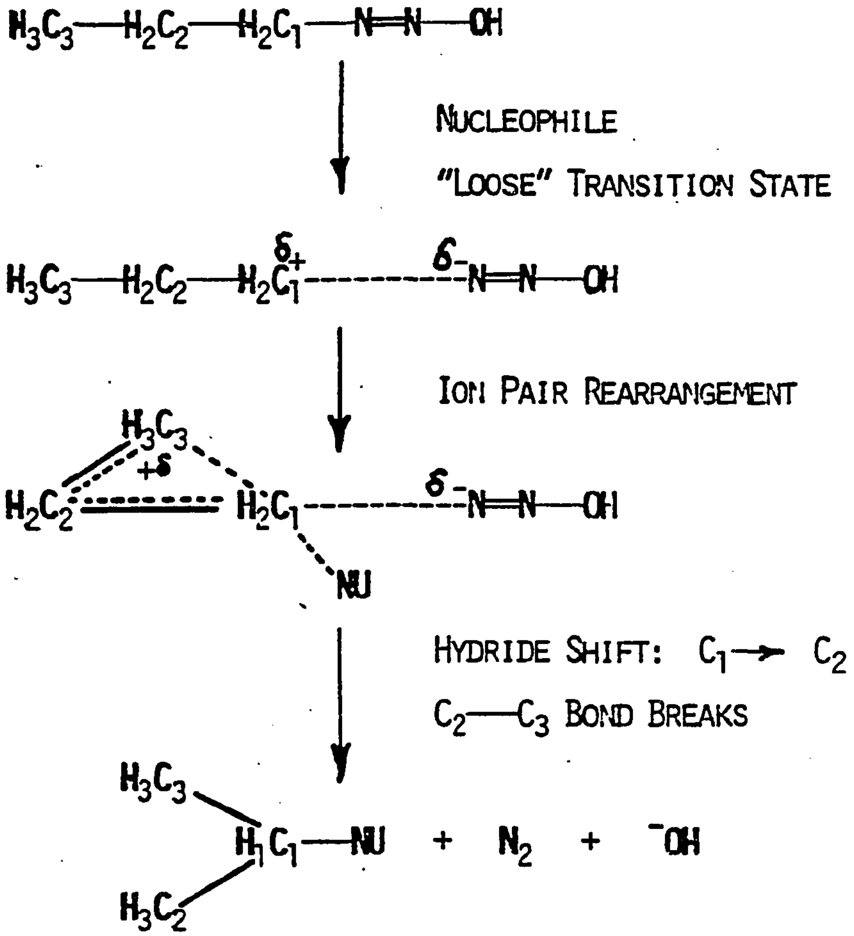
CORNER-PROTONATED



EDGE-PROTONATED

Scheme 4. Equilibration of Corner-Protonated and Edge-Protonated Cyclopropanes the corner-protonated cyclopropane upon optimization. The calculations indicate two local minima with an energy difference of 8.2 Kcal/mole, the 2-propyl cation and the corner-protonated cyclopropane. This is in good agreement with experimental studies of $C_3H_7^+$ species (77) which suggest that the most stable form is the 2-propyl and that protonated cyclopropane either isomerizes to the 2-propyl cation or is a second isomer higher in energy by _ca._ 7 Kcal/mole. In gas-phase studies (78) the 1-propyl cations formed from _n_-butane rearrange within 10^{-10} sec. to the 2-propyl cation. The above studies concern the free carbonium ion in the propyl system, but may be used analogously to explain the favorable circumstances that permit the rearrangement of _n_-propyldiazohydroxide to the isopropyl entity at the 0^6 position of guanine, as depicted in Scheme 5.

In summary, the Hartree-Fock _ab-initio_ calculations performed on the alkyldiazohydroxides clarify the electronic properties that effect the alkylation of DNA. Ethylation of 0^6- guanine is a soft-soft interaction (60) which is "orbitally controlled" (70). The Sn2 reaction at 0^6- guanine proceeds through a "loose" transition state (72) imparting some Sn1 character, which allows the rearrangement of _n_-propyldiazohydroxide to an isopropyl entity.



Scheme 5. Rearrangement of n-Propyldiazohydroxide

Alkyldiazotates

The process of DNA alkylation by the electrophilic alkyldiazohydroxides is rationalized by the preceding ab-initio molecular orbital studies. The investigation of the effects of alkali metal counter ions on the properties of the alkyldiazohydroxides is now presented. Calculations were performed on the E and Z isomers of methyl- and ethyldiazohydroxides, their respective anions and diazotate salts. Complete tabulation of the data obtained by the described methods as well as graphic representations of the considered structures are presented in the Appendix.

The methyl compounds whose geometries were calculated with both the 3-21G and 6-31G* basis sets do not exhibit any significant differences relative to the basis set used (Tables 27-A to 29-A). The placement of oxygen-bonded hydrogen was varied for the Z isomer of methyldiazohydroxide. The expected more stable configuration has hydrogen anti to nitrogen-1. Pertinent geometric parameters obtained with the 6-31G* basis set include:

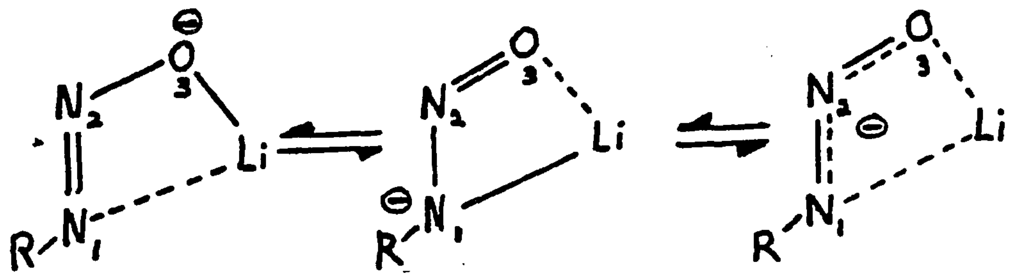
	H-4 anti N-1	H-4 syn N-1
H_4-O_3-N_2 angle	104.4°	112.5°
O_3-H_4 bond length	0.948 Å	0.950 Å
H_4---N_2 distance	1.852 Å	1.933 Å

Although the distance and angle between hydrogen and nitrogen-2 are reduced in the anti configuration, the hydrogen remains closely associated with the oxygen. Examination of the H-4 anti N-1 configuration of Z lithium methyldiazotate (Figure 13-A) shows that the Li_4---N_2 distance (1.899 Å) is not too much longer than the Li_4-O_3 bond length (1.748 Å). As depicted in Figures 12-A to 17-A, the position of the lithium ion is between N-1 and O-3 for the E species and between N-2 and O-3 for the Z species (both closer to the more electronegative oxygen). This bridging position exposes the lithium counter ion to the lone electron pairs on the respective nitrogens. There are no significant differences between methyl and ethyl substituted compounds as far as the positioning of the lithium counter ion is concerned, nor do the chloroethyl compounds exhibit geometric differences. The out-of-plane position of the lithium counter ion increases the energy of the diazotate.

When the diazohydroxides are compared to the lithium diazotates (Tables 27-A to 32-A and Figures 12-A to 17-A), the Li-O-N angle closes to almost 90 degrees in the E isomer and to about 73 degrees in the Z isomer relative to the H-O-N angle of ca. 106 degrees. This is attributable to the larger positive charge on the lithium which is attracted to the lone electron pairs of the nitrogens. These results are consistent with those determined in previous studies (54) for H_2NOH in which the Li-O-N angle for the Z hydroxylamine structure was 76.0 degrees with the lithium ion close to a bridging position. A lengthening of the N_1-N_2 bond concomitant with a shortening of the N_2-O_3 bond is also observed. This is due to the ionic nature of lithium diazotate which imparts to the diazotate moiety a stronger anionic character. Therefore, the geometry resembles that of the anion which features almost equal N_1-N_2 and N_2-O_3 bond lengths (Tables 27-A and 28-A). X-Ray studies (79) of Z potassium methyldiazotate indicate that the negative charge of the anion is delocalized, and both the N_1-N_2 and N_2-O_3 linkages are intermediate between single and double bonds. When salts of the diazotates are viewed by NMR methods, the spectra indicate that for the Z diazotate the potassium counter ion is located on average between the nitrogen and oxygen atoms. The NMR results for the E diazotate indicate two discrete species. The sufficiently slow interconversion rate permits the potassium ion to move in position across the $\mathrm{N}\underset{\cdots\cdots}{\text{———}}\mathrm{N}\underset{\cdots\cdots}{\text{———}}\mathrm{O}$ system so that two discrete signals are observed (19).

Changes in electron density also attest to the structures of the diazotates. Table 4 lists the net atomic charges on some of the atoms as well as the group atomic charges for methyl and halomethyl groups. Complete Mulliken population results are given in Tables 39-A to 43-A.

The N-1 and N-2 atoms in the E isomer of methyldiazohydroxide have net atomic charges of -0.314 and +0.114, respectively. The comparable lithium diazotate shows a greater charge separation between N-1 and N-2 of -0.474 for N-1 and +0.173 for the N-2 atom. The electron density of O-3 is increased, but the change is less than that of N-1. N-1 becomes decidedly more negative from -0.314 to -0.474 since the charge on the anion is delocalized. This allows the lithium to assume bridging positions as depicted in the following structures:



Scheme 6. Bridging Positions of E Lithium Alkyldiazotate

Bridging of hydrogen between oxygen and the respective nitrogens in the methyl- and ethyldiazohydroxides does not occur. In the Z isomer of the diazotate, the lithium counter ion bridges the N-2 and O-3 atoms so the changes in electron density are greatest for N-2. Its net atomic charge in methyldiazohydroxide is +0.149, while in the diazotate it is -0.031. Similar changes in electron density also occur for the E and Z isomers of ethyl- and 2-chloroethyldiazotates.

In Table 4, the net atomic charges for lithium in E methyl- and E ethyldiazotate are +0.570 and +0.568, respectively. The calculations indicate substantial transfer of charge from the lithium to the diazotate moiety, approximately 0.430 for the E isomer and 0.385 for the Z isomer. The charge transfer decreases for the sodium and ammonium salts to an average of 0.330 and 0.215, respectively, for the E and Z isomers. The binding energies of both proton and counter

TABLE 4

Net Atomic Charges[a] and Group Atomic Charges[a] of the H^+, Li^+, Na^+, and NH_4^+-Diazotates

	E-Ethyl				Z-Ethyl			
Atom(s)	H^+	Li^+	Na^+	NH_4^+	H^+	Li^+	Na^+	NH_4^+
N_1	-0.311	-0.471	-0.426	-0.465	-0.250	-0.284	-0.321	-0.334
N_2	+0.144	+0.168	+0.122	+0.092	+0.093	-0.029	+0.004	-0.030
O_3	-0.514	-0.562	-0.578	-0.603	-0.566	-0.567	-0.607	-0.633
CH_2	+0.266	+0.257	+0.229	+0.204	+0.266	+0.252	+0.229	+0.211
CH_3	+0.050	+0.041	+0.017	+0.004	+0.050	+0.015	-0.011	-0.013
X^b	+0.393	+0.568	+0.637	+0.769	+0.409	+0.613	+0.704	+0.801

a = electron units obtained by SCF 3-21G

b = H^+, Li^+, Na^+, NH_4^+

Table 4 Continued

	Methyl				2-Chloroethyl			
	E		Z		E		Z	
Atoms(s)	H^+	Li^+	H^+	Li^+	H^+	Li^+	H^+	Li^+
N_1	-0.314	-0.474	-0.268	-0.284	-0.299	-0.461	-0.251	-0.284
N_2	+0.114	+0.173	+0.149	-0.031	+0.108	+0.155	+0.105	-0.023
O_3	-0.513	-0.562	-0.548	-0.569	-0.504	-0.551	-0.562	-0.562
CH_3	+0.319	+0.294	+0.269	+0.268	—	—	—	—
CH_2	—	—	—	—	+0.343	+0.336	+0.337	+0.320
CH_2Cl	—	—	—	—	-0.048	-0.066	-0.044	-0.079
X^b	+0.394	+0.570	+0.397	+0.615	+0.400	+0.587	+0.416	+0.628

b = H^+, Li^+, Na^+, NH_4^+

ions, as shown in Tables 23-A to 26-A, decrease from the E to the Z species and do not exhibit significant substituent effects. The calculations indicate that the diazotates have strong cation affinities.

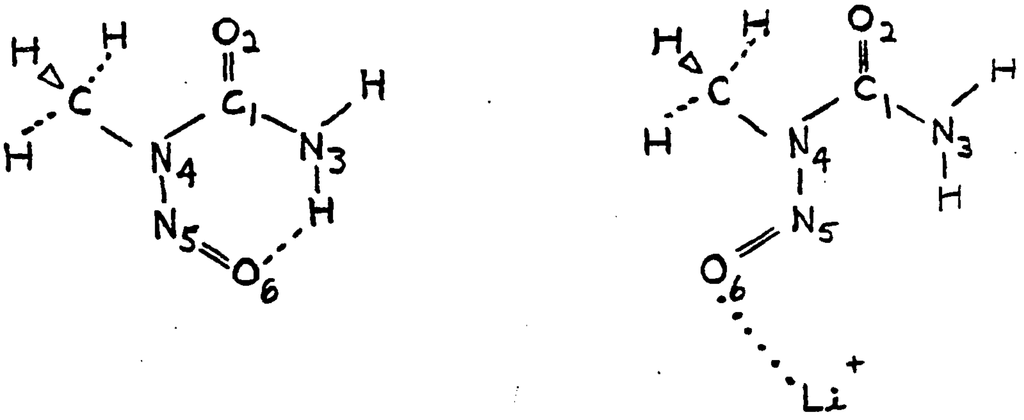
Complete tabulation of the LUMO composition, energies, and atom contributions are given in Tables 34-A to 38-A. The calculations show that the LUMO resides on the counter ions. The LUMO contribution of carbon-5, strongly present for ethyldiazohydroxides, is minimal for both the E and Z isomers. The same results are determined for the methyl and chloroethyl substituents.

In summary, Hartree-Fock ab-initio calculations performed on the alkyldiazotates established that the alkyldiazo anions have a significant affinity for alkali metal counter ions. The diazotate salts incur substantial charge transfer which perturbs the electron density and modifies the geometric parameters. The LUMO of the diazotate salts resides on the counter ion, thus soft "orbitally controlled" alkylation is not feasible by the diazotate until solubilized to the diazohydroxide (69).

Nitrosoureas

The influence of cations on the electron density and geometric parameters of the diazotate moiety is markedly evident. The effect of such cations on the process of decomposition of the nitrosoureas was also determined by ab-initio calculations and is now presented.

Previous theoretical calculations of methylnitrosoureas (67) determined that the syn isomer is more stable by 3.82 Kcal/mole; however, the presence of a positive charge attached to the nitroso group (-N=O) reverses the stability. This is understandable since the additional positive charge will be repulsed by the positively charged hydrogens from the amino group (NH_2). Figure 5 shows both isomers of methyldiazohydroxide.



Syn

Anti

Figure 5. Isomers of Methyldiazohydroxide

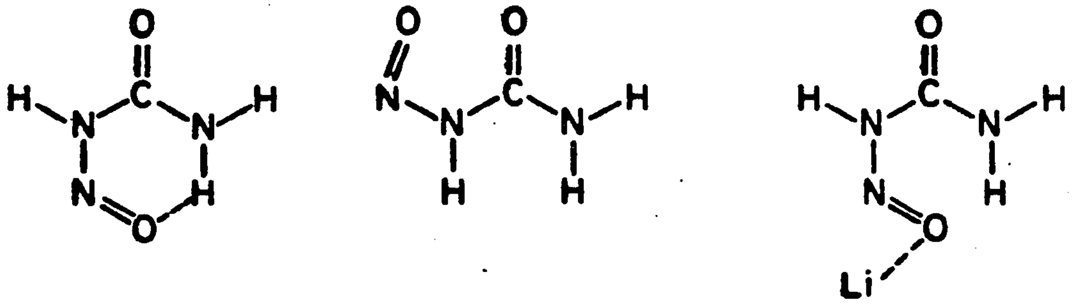
The position of the lithium cation on the nitroso oxygen and the carbonyl oxygen was varied. In-plane placement of lithium, both linear and angular, is more stable than out-of-plane positioning as determined with the STO-6G basis set. The linear (180 degree) alignment of the Li-O-N angle is slightly more stable (ca. 4 Kcal/mole) than the one obtained with an Li-O-N angle of about 110 degrees. The best geometry obtained for the lithiated carbonyl group (-C=O) is in-plane and linear which corresponds to previous studies (54) of lithiated $H_2C=O$. Table 21-A presents the binding energies of lithium positioned at the nucleophilic sites of methylnitrosourea. The greater lithium affinity obtained for the carbonyl group relative to that for the nitroso group is consistent with results determined in prior studies (54) for lithiated $H_2C=O$ and HN=O. The relative affinities are explainable by the much higher negative charge present on the carbonyl oxygen (-0.303) than that on the nitroso oxygen (-0.149) (67). The lithium and proton affinities of the nitroso group are larger for anti methylnitrosourea which is consistent with the above mentioned reversed stability in the presence of a positive charge (67).

The values of the lithium affinities are higher than the values obtained with the 6-31G* basis set for lithiated $H_2C=O$ and HN=O (54), which is attributable to the superposition error (68). Since the superposition error is intrinsic to the STO-6G basis set, continued calculations of the binding energy of lithium and other cations to the nitroso group of syn N-nitrosourea were performed with the 3-21G basis set. The values of the lithium affinities, shown in Table 22-A, although expectedly smaller than those of proton affinity, are considered to be significant. The results of the calculations establish the existence of cation affinity for the nitroso group of nitrosourea.

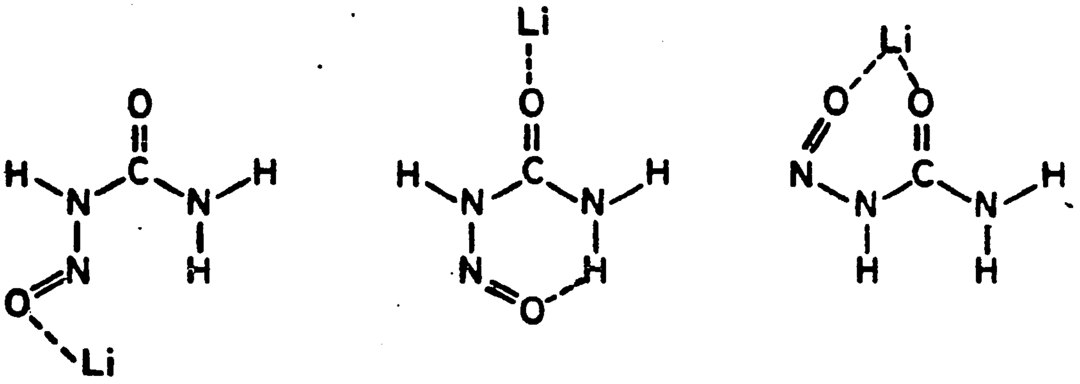
Several lithiated N-nitrosourea conformers are possible (Figure 6). The lithium cation can be positioned on the oxygen of either the nitroso or carbonyl group as well as on both groups. Figure 6-F shows the in-plane positioning of the lithium cation in the proximity of both the nitroso and carbonyl groups. The distribution of the various lithiated conformers can be approximated by the difference in their ground state energies and by the energy of rotation around the C_1-N_4 bond. The rotational barrier is the energy difference between the more stable conformer and the conformer in which the N_4-N_5 bond is perpendicular to the plane of the molecule. Pertinent energies obtained for the various conformers are as follows:

Conformer	Energy(GS)	Rot. E.	ΔE(Kcal)	K
A - *syn* NU	350.6240	350.5950	18.2	2.2×10^{13}
B - dual NU	350.6048	350.5950	8.5	1.8×10^{6}
C - *syn* LION	357.8853	357.8668	11.6	3.3×10^{8}
D - *anti* LION	357.8913	357.8712	12.6	1.8×10^{9}
E - *linear* LIOC	357.9102	357.8809	18.4	1.9×10^{13}
F - dual Li	357.9135	357.8712	26.5	2.9×10^{19}
G - dilithium	365.0724	365.0464	16.3	9.2×10^{11}

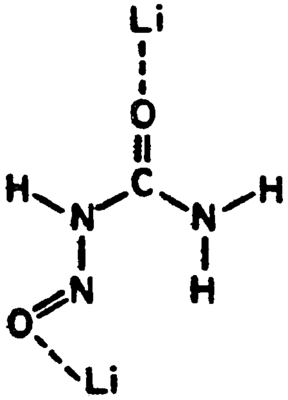
The equilibrium constant, K, was calculated using the formula: $\ln K = -\Delta E/RT$. Examination of the above calculations indicates that



A-<u>syn</u> NU B-dual NU C-<u>syn</u> LION



D-<u>anti</u> LION E-<u>linear</u> LIOC F-dual Li



G-dilithium

Figure 6. Lithiated Conformers of N-Nitrosourea

the lithiated conformer illustrated in Figure 6-F has the lowest ground state energy. The position of the lithium cation on the carbonyl oxygen of _syn_ N-nitrosourea (Figure 6-E) results in a slightly higher energy of 2.07 Kcal/mole. However, the difference in energy between similar, but nonlithiated conformers (Figure 6-A and 6-B), indicates that _syn_ N-nitrosourea (Figure 6-A) is more stable by _ca_. 9.7 Kcal/mole and the rotational barrier equals 18.2 Kcal/mole.

Similar conformations of N-nitrosourea, lithiated and protonated nitrosourea are chosen to obtain a more valid comparison of the process of decomposition and the activation energy associated with the C_1-N_4 bond breaking.

Completely optimized geometries were obtained for _syn_ N-nitrosourea as well as for the lithiated and protonated _syn_ N-nitrosoureas. The presence of the proton or lithium cation positioned on the nitroso group during the process of decomposition has a substantial effect. The cations on the nitroso group perturb the electronic distribution in such a manner that even the ground state geometry of the nitrosourea begins to change significantly. The C_1=O_2 carbonyl bond length of 1.213 Å in the ground state of _syn_ N-nitrosourea decreases to 1.179 Å in the ground state of protonated nitrosourea. Similarly, the C_1-N_3 bond length of the amino group shortens, but the C_1-N_4 bond of the nitrosated nitrogen lengthens considerably from 1.420 Å in _syn_ N-nitrosourea to 1.617 Å in protonated nitrosourea. As the course of the C_1-N_4 bond breaking continues by incremental lengthening of the C_1-N_4 distance, the geometrical changes elsewhere in the molecule resemble the parameters of the decomposition products, R-N=N-OH and R-N=C=O. Table 5 presents a comparison of the geometries in the ground state, transition state, and near product state which shows the marked effect of the cations on the bond lengths and angles of syn N-nitrosourea.

Of particular interest: (a) the carbonyl bond $C_1=0_2$ shortens as the bond between the carbonyl group and the amino group assumes more double bond character; (b) concomitantly, the angle between the carbonyl and amino groups becomes more linear; (c) the N_4-N_5 single bond attains more double bond character, while the nitroso bond $N_5=0_6$ lengthens; (d) the distance between the nitroso oxygen and the amino hydrogen closes to within bonding range. Changes in the lithiated nitrosourea from the ground state to the near product state illustrate the above generalizations: (a) the C_1-N_3 bond length of 1.325 Å decreases to 1.256 Å, as more π bonding develops; (b) the $N_3-C_1-0_2$ angle of 130.5 degrees increases to 172.1 degrees as the linearity of the isocyanate is almost achieved; (c) the N_4-N_5 single bond length of 1.277 Å decreases to 1.225 Å as more π bonding develops; (d) the $N_5=0_6$ bond length of 1.285 Å increases to 1.385 Å as the π bonding lessens. Similar changes are evident for syn N-nitrosourea and the protonated nitrosourea.

Table 6 presents a comparison of the net atomic charges of the atoms in the ground state, transition state, and near product state of syn N-nitrosourea, together with the lithiated and protonated nitrosoureas.

Of particular interest: (a) as the bond between the carbonyl

TABLE 5

SCF 3-21G Optimized Geometric Parameters for syn N-nitrosourea, Lithiated and Protonated Nitrosourea

Parameters	Ground State			Transition State			Product State		
A°;		Li^+	H^+		Li^+	H^+		Li^+	H^+
$C_1=O_2$	1.213	1.916	1.179	1.177	1.126	1.150	1.142	1.130	1.128
C_1-N_3	1.337	1.325	1.308	1.317	1.261	1.285	1.249	1.256	1.251
C_1-N_4	1.420	1.487	1.617	2.548	2.512	1.904	2.900	2.900	2.900
N_4-N_5	1.361	1.277	1.229	1.335	1.240	1.222	1.260	1.225	1.213
$N_5=O_6$	1.225	1.285	1.370	1.232	1.355	1.403	1.328	1.385	1.452
N_5-H	0.998	1.008	1.017	1.005	1.011	1.017	1.009	1.012	1.016
N_3-H	0.996	0.996	1.001	1.001	1.025	1.008	1.080	1.038	1.033
O_6-X	——	1.757	0.978	——	1.729	0.974	——	1.704	0.970
$C_1N_4N_5$	132.3	134.8	136.6	127.5	124.4	137.2	118.9	123.1	121.0
$N_4N_5O_6$	117.0	118.0	112.6	116.6	114.0	110.4	114.0	109.3	107.7
C_1N_5H	115.0	112.1	109.4	115.6	117.2	110.2	132.3	124.6	129.1
$O_2C_1H_3$	126.5	130.5	136.6	149.5	158.5	149.9	169.2	172.1	179.3
$O_2C_1N_4$	117.9	114.6	110.5	124.3	117.8	106.2	118.2	109.3	95.9

$X = Li^+, H^+$

Table 5 Continued

Parameters	Ground State			Transition State			Product State		
Å;		Li^+	H^+		Li^+	H^+		Li^+	H^+
O_2N_3H	117.7	117.4	117.7	117.5	117.6	118.9	117.9	119.2	120.7
HN_3H	120.9	122.4	123.1	120.2	116.7	120.7	124.9	122.7	119.6
N_5O_6X	——	130.6	107.4	——	126.9	107.0	——	121.5	107.5
O_6---H_9	1.930	2.028	1.977	1.392	1.513	1.867	1.454	1.594	1.580

$X = Li^+, H^+$.

TABLE 6

Net Atomic Charges (au) for *syn* N-nitrosourea, Lithiated and Protonated Nitrosourea Obtained by SCF 3-21G

	syn-N-nitrosourea			Lithiated			Protonated		
Atom	G.S.	T.S.	P.S.	G.S.	T.S.	P.S.	G.S.	T.S.	P.S.
C-1	+1.194	+1.088	+1.151	+1.174	+1.150	+1.200	+1.180	+1.174	+1.203
O-2	-0.638	-0.450	-0.450	-0.567	-0.390	-0.370	-0.516	-0.462	-0.363
N-3	-0.970	-0.929	-0.940	-0.980	-0.972	-0.942	-0.950	-0.944	-0.947
N-4	-0.726	-0.618	-0.554	-0.604	-0.464	-0.436	-0.470	-0.407	-0.349
N-5	+0.347	+0.219	+0.314	+0.411	+0.198	+0.146	+0.340	+0.261	+0.150
O-6	-0.407	-0.584	-0.594	-0.599	-0.647	-0.636	-0.482	-0.513	-0.558
H-7	+0.417	+0.317	+0.300	+0.482	+0.387	+0.359	+0.499	+0.460	+0.402
H-8	+0.376	+0.406	+0.430	+0.395	+0.442	+0.470	+0.439	+0.453	+0.482
H-9	+0.407	+0.550	+0.524	+0.471	+0.550	+0.512	+0.446	+0.481	+0.515
$N_3H_8H_9$	-0.187	+0.027	+0.014	-0.114	+0.020	+0.040	-0.065	-0.010	+0.050
H^+	—	—	—	—	—	—	+0.516	+0.498	+0.465
Li^+	—	—	—	+0.816	+0.739	+0.698	—	—	—

G. S. = Ground State; T. S. = Transition State; P. S. = Product State.

group $C_1=O_2$ and the amino group $N_3H_8H_9$ assumes more double bond character, the electrons on nitrogen-3 are delocalized toward carbon-1. In the ground state the net atomic charge on the amino group in syn N-nitrosourea is -0.187, while in the transition state it is +0.027; (b) concomitantly, the electrons of the carbonyl oxygen are also delocalized as evidence by the change in net atomic charge from -0.638 in the ground state to -0.450 in the transition state; (c) as the N_4-N_5 single bond attains more double bond character, the electrons of N-4 are delocalized toward N-5. In the ground state the net atomic charges for N-4 and N-5 are -0.726 and +0.347, respectively, while in the transition state they are -0.618 and +0.219, respectively; (d) concomitantly, the nitroso bond $N_5=O_6$ lengthens and the electrons on the nitroso oxygen become more localized. In the ground state the atomic charge on O-6 is -0.407, while in the transition state it is -0.584. Similar changes in electron density occur for the lithiated and protonated nitrosoureas.

Figures 8-A to 10-A show the geometries of the ground state and transition state of the nitrosoureas and the respective energies in hartrees. The energy difference from the ground state to the transition state for syn N-nitrosourea in the absence of cations is calculated to be 82.08 Kcal/mole. In the presence of the lithium cation, the energy difference is reduced to 27.42 Kcal/mole and with a proton the energy profile indicates spontaneity. Figure 11-A graphically presents the energy in Kcal/mole associated with the various C_1-N_4 bond lengths for nitrosourea together with lithiated and protonated nitrosoureas. The reaction profiles illustrate the Hammond Postulate (80), which states that in an endothermic reaction the transition state resembles the product, whereas in an exothermic reaction the transition state resembles the reactant. Table 5 shows that for protonated nitrosourea, which has an activation energy of only 1.13 Kcal/mole, the geometric parameters in the transition state are more like those of the ground state than those of the product state. Conversely, for lithiated nitrosourea the geometric parameters in the transition state are more like those of the product state. In support of the noted geometric changes, the net atomic charges (Table 6) show less change for protonated nitrosourea from the ground state to the transition state than from the transition state to the product state. In contrast, the changes in net atomic charges for syn N-nitrosourea and lithiated nitrosourea are greater from the ground state to the transition state than are the changes that occur from the transition state to the product state.

In summary, the effect of cations on the geometric parameters, net atomic charges, and activation energy of nitrosoureas is markedly evident. The presence of cations quickens the transformation of the parent nitrosourea to the products of decomposition, the isocyanates and the alkyldiazohydroxides.

REFERENCES

1. Gellhorn, A.; Hirschberg, E. Cancer Res. Suppl. 1955, 3, 1-25.

2. Skinner, W. A.; Gram, H. F.; Greene, M. O.; Greenberg, J.; Baker, B. R. J. Med. Pharm. Chem. 1960, 2, 299-333.

3. Skipper, H. E.; Schabel, F. M., Jr.; Trader, M. W.; Thomson, J. R. Cancer Res. 1961, 21, 1154-1164.

4. Lijinski, W.; Loo, I.; Ross, A. E. Nature (London) 1968, 218, 1174-1175.

5. Sussmuth, R.; Haerlin, R.; Lingens, F. Biochim. Biophys. Acta. 1972, 269, 276-286.

6. Lawley, P. D.; Shah, S. A. Chem-Biol. Interact. 1973, 7, 115-120.

7. Montgomery, J. A.; James, R.; McCaleb, G. S.; Johnston, T. P. J. Med. Chem. 1967, 10, 668-674.

8. Colvin, M.; Brundrett, R. B.; Cowens, J. W.; Jardine, I.; Ludlum, D. B. Biochem. Pharmacol. 1976, 25, 695-699.

9. (a) Johnston, T. P.; McCaleb, G. S.; Montgomery, J. A. J. Med. Chem. 1963, 6, 669-681.
   (b) Johnston, T. P.; McCaleb, G. S.; Opliger, P. S.; Montgomery, J. A. J. Med. Chem. 1966, 9, 892-911.

10. Johnston, T. P.; McCaleb, G. S.; Opliger, P. S.; Laster, W. R., Jr.; Montgomery, J. A. J. Med. Chem. 1971, 14, 600-614.

11. (a) Johnston, T. P.; McCaleb, G. S.; Clayton, S. D.; Frye, J. L.; Krauth, C. A.; Montgomery, J. A. J. Med. Chem. 1977, 20, 279-290.
    (b) Montgomery, J. A.; McCaleb, G. S.; Johnston, T. P.; Mayo, J. G.; Laster, W. R., Jr. J. Med. Chem. 1977, 20, 291-295.

12. Prestayko, A. W.; Crooke, S. T.; Baker, L. H.; Cater, S. K.; Schein, P. S. (eds.), Nitrosoureas: current status and new developments. Academic Press: New York, 1981.

13. Carter, S. K. in "Nitrosoureas: current status and new developments." Prestayko, A. W.; Crooke, S. T.; Baker, L. H.; Carter, S. K.; Schein, P. S. (eds), Academic Press: New York, 1981; Chapter 35.

14. Schabel, F. M., Jr.; Laster, W. R., Jr.; Trader, M. W.; Corbett, T. H.; Griswold, D. P., Jr. in "Nitrosoureas: current status and new developments." Prestayko, A. W.; Crooke, S. T.: Baker, L. H.; Carter, S. K.; Schein, P. S. (eds.), Academic Press: New York, 1981; Chapter 2.

15. Montgomery, J. A. *Cancer Treat. Rep.* 1976, *60*, 651-654.

16. Montgomery, J. A. in "Structure-Activity Relationships of Anti-Tumor Agents." Reinhoudt, D. N.; Connors, T. A.; Pinedo, H. M.; van de Poll, K. W. (eds.), Martimus Nijhoff Publishers: The Hague, 1983; 219-238.

17. Lown, J. W.; Chauhan, S. M. S. *J. Org. Chem.* 1981, *46*, 5309-5321.

18. Lown, J. W.; Chauhan, S. M. S. *J. Org. Chem.* 1982, *47*, 851-856.

19. Lown, J. W.; Chauhan, S. M. S.; Koganty, R. R.; Sapse, A. M.; *J. Amer. Chem. Soc.* 1984, *106*, 6401-6408.

20. Brundrett, R. B; Colvin, M. *J. Org. Chem.* 1977, *42*, 3538-3541.

21. (a) Chatterjii, D. C.; Greene, R. F.; Gallelli, J. F. *J, Pharm. Sci.* 1978, *67*, 1527-1532.
    (b) Brundrett, R. B. *J. Med. Chem.* 1980, *23*, 1245-1247.
    (c) Lown, J. W.; Chauhan, S. M. S. *J. Med. Chem.* 1981, *24*, 270-279.
    (d) Lown, J. W.; Chauhan, S. M. S. *J. Org. Chem.* 1981, *46*, 2479-2489.
    (e) Weinkam, R. J.; Lin, H-S. *J. Med. Chem.* 1979, *22*, 1193-1198.

22. (a) Scribner, J. D.; Ford, G. P. *Cancer Lett.* 1982, *16*, 51-56.
    (b) Park, K. K.; Archer, M. C.; Wishnok, J. S. *Chem.-Biol. Interact.* 1980, *2*, 139-144.

23. (a) Singer, B. *Nature (London)* 1976, *264*, 333-339.
    (b) Singer, B. *J. Nat'l. Cancer Inst.* 1979, *62*, 1329-1339.

24. Kohn, K. W. *Cancer Res.* 1977, *37*, 1450-1454.

25. (a) Loveless, A. *Nature (London)* 1969, *223*, 206-207.
    (b) Loveless, A.; Hampton, C. L. *Mutat. Res.* 1969, *7*, 1-12.

26. (a) Singer, B. *J. Toxicol. Environ. Health* 1977, *2*, 1279-1295.
    (b) Lawley, P. D. *Brit. Med. Bull.* 1980, *36*, 19-24.
    (c) Singer, B. J.; Kusmierek, J. T. *Ann. Rev. Biochem.* 1982, *52*, 655-693.

27. Stacey, K. A.; Cobb, M.; Cousens, S. F.; Alexander, P. *Ann. N. Y. Acad. Sci.* 1958, *68*, 682-701.

28. Singer, B. *Prog. Nucl. Acid Res. Mol. Biol.* 1975, *15*, 219-284, 303-332.

29. Newbold, R. F.; Warren, W.; Medcalf, A. S. C.; Amos, J. *Nature (London)* 1980, *283*, 596-599.

30. Lown, J. W.; McLaughlin, L. W.; Chang, Y-M. *Bioorg. Chem.* 1978, *7*, 97-110.

31. Kohn, K. W.; Erickson, L. C.; Laurent, G.; Ducore, J.; Sharkey, N.; Ewig, R. A. in "Nitrosoureas: current status and new developments." Prestayko, A. W.; Crooke, S. T.; Baker, L. H.; Carter, S. K.; Schein, P. S. (eds), Academic Press: New York, 1981; Chapter 6.

32. (a) Goth, R.; Rajewsky, M. F. *Z. Krebsforsch* 1974, *2*, 37-64.
    (b) Goth, R.; Rajewsky, M. F. *Proc. Nat'l. Acad. Sci.* 1974, *71*, 639-643.
    (c) Lawley, P.D.; Warren, W. *Chem-Biol. Interact.* 1975, *11*, 55-57.
    (d) Sun, L.; Singer, B. *Biochemistry* 1975, *14*, 1795-1802.

33. Tong, W. P.; Kirk, M. C.; Ludlum, D. B. *Cancer Res.* *42* 3102-3105.

34. Gerchman, L. L.; Ludlum, D. *Biochim. Biophys. Acta.* 1973, *308*, 310-316.

35. Pegg, A. E. *Adv. Cancer Res.* 1977, *25*, 195-269.

36. (a) Day, R. S., III; Ziolkowski, C. H. J. *Nature (London)* 1979, *279*, 797-799.
    (b) Kornblith, P. L.; Szypko, P. E. *J. Neurosurg.* 1978, *48*, 580-586.
    (c) Salmon, S. E.; Hamburger, A. W.; Soehnlen, B.; Durie, B. G. M.; Alberts, D. S.; Moon, T. E. *New Eng. J. Med.* 1978, *298*, 1321-1327.

37. (a) Day, R. S., III; Ziolkowski, C. H. J.; Scudiero, D. A.; Meyer, S. A.; Mattern, M. R. *Carcinogenesis* 1980, *1*, 21-32.
    (b) Day, R. S., III; Ziolkowski, C. H. J.; Scudiero, D. A.; Meyer, S. A.; Lubiniecki, A.S.; Girardi, A.J.; Galloway, S.M.; Bynum, G.D. *Nature (London)* 1980, *288*, 724-727.

38. Erickson, L. C.; Laurent, G.; Sharkey, N. A.; Kohn, K. W. *Nature (London)* 1980, *288*, 727-729.

39. (a) Olson, M.; Lindahl, T. *J. Biol. Chem.* 1980, *255*, 10, 569-10, 571.
    (b) Foote, R. S.; Mitra, S.; Pal, B. C. *Biochem. Biophys. Res. Commun.* 1980, *97*, 654-659.

40. (a) Erickson, L. C.; Bradley, M. O.; Kohn, K. W. *Cancer Res.* *1977*, *37*, 3744-3750.
    (b) Erickson, L. C.; Osieka, R.; Kohn, K. W. *Cancer Res.* 1978, *38*, 802-808.
    (c) Ewig, R. A. G.; Kohn, K. W. *Cancer Res.* 1977, *37*, 2114-2122.

41. (a) Lindahl, T. *Annu. Rev. Biochem.* 1982, *51*, 61-87.
    (b) Lindahl, T.; Sedgwick, B. *J. Mol. Biol.* 1982, *154*, 169-175.

42. (a) Formace, A. J.; Kohn, K. W.; Kann, H. E., Jr. Cancer Res. 1978, 38, 1064-1069.
(b) Kann, H. E., Jr. Cancer Res. 1978, 38, 2363-2366.
(c) Kann, H. E., Jr.; Schott, M. A.; Petkas, A. Cancer Res. 1980, 40, 50-55.

43. (a) Kann, H. E., Jr.; Kohn, K. W.; Lyles, J. M. Cancer Res. 1974, 34, 398-402.
(b) Heal, J. M.; Fox, P. A.; Schein, P. S. Cancer Res. 1979, 39, 82-89.

44. Erickson, L. C.; Bradley, M. O.; Ducore, J. M.; Ewig, R. A. G.; Kohn, K. W. Proc. Nat'l Acad. Sci. U.S.A. 1980, 77, 467-471.

45. Sariban, E.; Erickson, L. C.; Kohn, K. W. Cancer Res. 1984, 44, 1352-1357.

46. Levin V. A. in "Nitrosoureas: current status and new developments." Prestayko, A. W.; Crooke, S. T.; Baker, L. H.; Carter, S. K.; Schein, P. S. (eds.) Academic Press: New York, 1981; Chapter 13.

47. Weinkam, R. J.; Liu, T-Y. J.; Lin, H-S. Chem.-Biol. Interact. 1980, 31, 167-178.

48. Weinkam, R. J.; Deen, D. F. Proc. Am. Assoc. Cancer Res. 1980, 21, 1 (abstract).

49. Rapoport, S. I.; Hori, M.; Klatzo, I. Science 1971, 173, 1026-1028.

50. Kayama, Y.; Kawaski, T. J, Bacteriol. 1976, 128, 157-164.

51. Rossof, A. H.; Robinson, W. A. (eds.) "Lithium Attenuation of Anti-Cancer Chemotherapy." Adv. Exper. Med. Biol. vol. 127 Plenum Press: New York, 1980; Section IV.

52. Levitt, L. J.; Quesenberry, P. J. N. Engl. J. Med. 1980, 303, 713-719.

53. Ballin, A.; Aladjem, M.; Banyash, M.; Boichis, H.; Barzilay, A.; Gal, R.; Witz, I. P. Br. J, Cancer 1983, 48, 83-87.

54. Del Bene, J. E.; Frisch, M. J.; Raghavachari, K.; Pople, J. A.; Schleyer, P. v. R. J. Phys. Chem. 1983, 87, 73-78.

55. Sapse, A. M.; Jain, D. C.; Bunce, J. D. J. Amer. Chem. Soc. 1984, 106, 6579-6581.

56. Wheeler, G. P. Biochem. Pharmac. Suppl. 1974, 2, 225-232.

57. Bradley, M. O.; Sharkey, N. A.; Kohn, K. W.; Layard, M. W. Cancer Res. 1980, 40, 2719-2725.

58. Hughes, M. N. "The Inorganic Chemistry of Biological Processes," 2nd ed.; John Wiley and Sons: New York, 1981.

59. Binkley, J. S.; Whiteside, R. A.; Kirshnan, R.; Sieger, R.; De Fries, D. J.; Schlegel, H. B. Topiol, S.; Kahn, L. R.; Pople, J. A. Gaussian-80 Dept. of Chem. Carnegie-Mellon Univ. Pittsburgh, Pa. 15213.

60. (a) Pearson, R.B.; Songstad, J. M. J. Amer. Chem. Soc. 1967, 89, 1827-1836.
    (b) Saville, B. Angew. Chem. Int. Ed. Engl. 1967, 6, 928-939.

61. Roothaan, C. C. J. Rev. Mod. Phys. 1951, 23, 69-89.

62. Schlegel, H. B. J. Comput. Chem. 1982, 3, 214-218.

63. Lowe, J. P. "Quantum Chemistry" (Student Edition) Academic Press: New York, 1978, pp. 309-346.

64. Hehre, W. J.; Stewart, R. F.; Pople, J. A. J. Chem. Phys. 1969, 51, 2657-2664.

65. Binkley, J. S.; Pople, J. A.; Hehre, W. J. J. Amer. Chem. Soc. 1980, 102, 939-947.

66. Hariharan, P. C.; Pople, J. A. Theor. Chim. Acta. 1973, 28, 213-222.

67. Sapse, A. M.; Snyder, G. Cancer Res. 1984, in press.

68. Liu, B.; McLean, A. D. J. Chem. Phys. 1973, 59, 4557-4558.

69. Lown, J. W.; Koganty, R. R.; Bhat, U. G.; Sapse, A. M.; Allen, E. B. Drugs Exptl. Clin. Res. in press.

70. (a) Fleming, I. "Frontier Orbitals and Organic Chemical Reactions" Wiley-Interscience: New York, 1976, pp. 23-47.
    (b) Klopman, G. J. Amer. Chem. Soc. 1968, 90, 223-234.

71. Del Bene, J. E. Private Communication.

72. (a) Thornton, E. R. J. Amer. Chem. Soc. 1967, 89, 2915-2927.
    (b) Frisone, G. J.; Thornton, E. R. J. Amer. Chem. Soc. 1968, 90, 1211-1215.

73. Ford, G. F.; Scribner, J. D. J. Amer. Chem. Soc. 1983, 105, 349-354.

74. (a) Lee, C. C.; Kruger, J. E.; Wong, E. W. C. *J. Amer. Chem. Soc.* 1965, *87*, 3985-3986.
    (b) Lee, C. C.; Kruger, J. E.; *J. Amer. Chem. Soc.* 1965, *87*, 3986-3987.
    (c) Lee, C. C.; Kruger, J. E. *Tetrahedron* 1967, *23*, 2539-2547.

75. (a) Roberts, J.D.; Halmann, M. *J. Amer. Chem. Soc.* 1953, *75*, 5759-5760.
    (b) Skell, R. S.; Starer, I. *J. Amer. Chem. Soc.* 1960, *82*, 2971.

76. Raghavachari, K.; Whiteside, R. A.; Pople, J. A.; Schleyer, P. v. R. *J. Amer. Chem. Soc.* 1981, *103*, 5649-5657.

77. (a) MaAdoo, D. J.; McLaffety, F. W.; Bente, P. F. *J. Amer. Chem. Soc.* 1972, *94*, 2027-2033.
    (b) Chong, S. L.; Franklin, J. L. *J. Amer. Chem. Soc.* 1972, *94*, 6347-6351.

78. Lias, S. G.; Rebbert, R. E.; Ausloos, P. *J. Amer. Chem. Soc.* 1970, *92*, 6430-6440.

79. Muller, E.; Hoppe, W.; Hagenmaier, H.; Haiss, H.; Huber, R.; Rundel, W.; Suhr, H. *Chem. Ber.* 1963, *96*, 1712-1716.

80. Hammond, G. S. *J. Amer. Chem. Soc.* 1955, *77*, 334-338.

TABLE 1-A

Optimized Geometric Parameters and Energies for Ethyldiazohydroxide Conformers Obtained by SCF 6-31G* Calculations

Parameters	Conformers			
A°	A-Ie	A-IIe	B-Ie	C-Ie
N-N	1.199	1.199	1.199	1.210
N-O	1.359	1.359	1.359	1.359
O-H	0.948	0.948	0.948	0.948
C-N	1.466	1.466	1.466	1.466
C-C	1.535	1.535	1.525	1.525
C-H	1.081	1.082	1.081	1.081
NNO	110.2	110.1	110.2	112.0
NOH	104.3	104.3	104.3	104.3
NNC	112.9	112.9	112.9	112.0
NCC	109.5	110.5	109.5	109.5
NCH	109.5	109.1	109.5	109.5
CCH	111.3	111.3	111.3	111.3
HCH	109.1	109.1	109.1	109.1
	-262.	-262.	-262.	-262.
Energy (au)	8906	8887	8809	8780
ΔE (Kcal)	0.00	1.19	6.09	7.91

TABLE 2-A

Optimized Geometric Parameters and Energies for Ethyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

Parameters	Conformers			
A°	A-Ie	B-Ie	C-Ie	D-Ie
N-N	1.199	1.199	1.2903	1.203
N-O	1.359	1.359	1.356	1.356
O-H	0.948	0.948	0.957	0.957
C-N	1.466	1.466	1.469	1.469
C-C	1.525	1.525	1.523	1.523
C-H	1.081	1.081	1.084	1.084
NNO	110.2	110.2	116.3	116.3
NOH	104.3	104.3	106.8	106.8
NNC	112.9	112.9	114.3	120.0
NCC	109.5	109.5	107.4	107.4
NCH	109.5	109.5	106.3	106.3
CCH	111.3	111.3	106.3	106.3
HCH	109.1	109.1	105.6	105.6
	-261.	-261.	-261.	-261.
Energy (au)	3948	3853	3832	3851
ΔE (Kcal)	0.00	5.96	7.68	106.49

TABLE 3-A

Optimized Geometric Parameters and Energies for 2-Fluoroethyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

Parameters	Conformers			
A°	A-If	B-If	C-If	D-If
N-N	1.218	1.217	1.215	1.199
N-O	1.434	1.425	1.443	1.359
O-H	0.975	0.977	0.966	0.948
C-N	1.487	1.486	1.486	1.466
C-C	1.079	1.079	1.079	1.081
C-H	1.399	1.404	1.406	1.397
NNO	111.5	110.7	113.3	110.2
NOH	106.4	105.8	105.5	104.3
NNC	114.2	115.9	119.6	120.0
NCC	110.7	105.8	108.3	109.5
NCH	107.8	105.8	108.9	109.5
CCH	109.5	110.2	109.98	111.3
HCH	107.7	108.96	107.3	109.1
CCF	110.8	108.96	108.4	99.5
FCH	107.7	108.96	107.3	109.1

Table 3-A Continued

	Conformers			
	A-If	B-If	C-If	D-If
	-359.	-359.	-359.	-359.
Energy (au)	7161	7176	7180	5894
ΔE (Kcal)	1.19	0.25	0.00	80.70

TABLE 4-A

Optimized Geometric Parameters and Energies for 2-Chloroethyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

Parameters	Conformers			
A°	A-Ic	B-Ic	C-Ic	D-Ic
NN	1.217	1.216	1.215	1.215
NO	1.429	1.423	1.425	1.425
OH	0.976	0.977	0.966	0.966
CN	1.488	1.489	1.486	1.486
CC	1.533	1.519	1.525	1.525
CH	1.077	1.077	1.079	1.079
CCl	1.880	1.879	1.850	1.850
NNO	110.0	111.6	113.3	115.0
NOH	106.2	106.0	105.8	105.8
NNC	114.1	116.1	119.6	119.6
NCC	109.7	115.5	108.3	108.3
NCH	108.9	105.3	108.9	108.9
CCH	111.1	111.4	110.0	110.2
HCH	106.4	105.6	106.5	105.0
CCCl	111.7	109.9	114.0	100.0
ClCH	106.4	105.6	106.5	105.0

Table 4-A Continued

	Conformers			
	A-Ic	B-Ic	C-Ic	D-Ic
	-718.	-718.	-718.	-717.
Energy (au)	1160	1211	1199	8699
ΔE (Kcal)	3.20	0.00	0.75	157.63

TABLE 5-A

Optimized Geometric Parameters and Energies for 2-Hydroxyethyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

Parameters		Conformers		
A°	A-Ih	B-Ih	C-Ih	D-Ih
NN	1.215	1.215	1.215	1.215
NO	1.425	1.425	1.425	1.425
OH	0.965	0.965	0.965	0.965
NC	1.485	1.485	1.485	1.485
CC	1.530	1.530	1.530	1.530
CH	1.080	1.080	1.080	1.080
CO	1.450	1.450	1.450	1.450
NNO	111.0	111.0	111.0	116.0
NOH	106.0	106.0	106.0	106.0
NNC	114.0	114.0	116.0	120.0
NCC	110.0	112.0	110.0	110.0
NCH	109.0	109.0	109.0	109.0
CCO	111.5	111.5	111.5	111.5
CCH	110.5	110.5	110.5	110.5
COH	110.5	110.5	110.5	110.5
OCH	110.5	110.5	110.5	110.5

Table 5-A Continued

	Conformers			
	A-Ih	B-Ih	C-Ih	D-Ih
Energy (au)	-335.8256	-335.8208	-335.8274	-335.6387
ΔE (Kcal)	1.13	4.14	0.00	118.41

TABLE 6-A

Optimized Geometric Parameters and Energies for n-Propyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

Parameters	Conformers			
A°	A-Ip	B-Ip	C-Ip	D-Ip
NN	1.205	1.205	1.205	1.205
NO	1.425	1.425	1.425	1.425
OH	0.965	0.965	0.965	0.965
CN	1.485	1.485	1.485	1.485
CC	1.540	1.540	1.540	1.540
CH	1.080	1.080	1.080	1.080
NNO	110.5	112.0	112.0	116.0
NOH	105.5	105.5	105.5	105.5
NNC	112.0	115.0	115.0	120.0
NCC	109.5	109.5	109.5	109.5
NCH	107.5	107.5	107.5	107.5
CCH	110.0	110.0	110.0	110.0
HCH	108.5	108.5	108.5	108.5
CCC	110.5	110.5	110.5	110.5

Table 6-A Continued

	Conformers			
	A-Ip	B-Ip	C-Ip	D-Ip
Energy (au)	-300.	-300.	-300.	-300.
	2190	2130	2198	0129
ΔE (Kcal)	0.50	4.27	0.00	129.83

TABLE 7-A

SCF 3-21G Completely Optimized Calculations for 1,2,3-Oxadiazoline Intermediate

LUMO Energy (au) and Atom Contributions			Net Atomic Charges (eu) Atom and Group	
E (au) + 0.14254			N_1	-0.236
N_1	+0.907	2 Py	N_2	+0.139
N_2	-0.993	"	O_3	-0.483
O_3	+0.258	"	C_4	-0.141
C_4	+0.100	"	C_5	-0.323
C_5	+0.215	"	H_6	+0.245
H_6	-0.145	1 s	H_7	+0.245
H_7	+0.145	"	H_8	+0.277
H_8	-0.379	"	H_9	+0.277
H_9	+0.379	"	$C_4H_6H_7$	+0.349
			$C_5H_8H_9$	+0.231

TABLE 8-A

LUMO Energies and Atom Contributions For Ethyldiazohydroxide Conformers Obtained by SCF 6-31G* Calculations

Atom [a]	Conformers			
	A-Ie	A-IIe	B-Ie	C-Ie
N_1	-0.370	0.376	-0.404	-0.389
	-0.525	0.520	-0.588	-0.551
N_2	0.438	-0.424	0.447	0.438
	0.591	-0.583	0.619	0.593
O_3	-0.153	0.153	-0.157	-0.181
	-0.200	0.195	-0.202	-0.221
C_5	-0.052	0.059	-0.012	-0.016
	-0.306	0.333	-0.146	-0.187
H_7	0.062	-0.064	-0.075	-0.079
	0.438	-0.456	-0.287	-0.351
H_8	-0.065	0.067	0.072	0.079
	-0.434	0.455	0.301	0.350
C_6	-0.023 x	0.025 x	-0.001 s	-0.017
	-0.157 x	0.166 x	-0.137 s	-0.143
H_9			-0.001	-0.014
			+0.145	-0.165
H_{10}	-0.013	0.013		0.014
	-0.145	0.155		0.152
H_{11}	-0.002	+0.001		
	+0.139	-0.137		

a. Orbital: 1s for H; 2Py for other atoms unless otherwise indicated.

Table 8-A Continued

	Conformers			
	A-Ie	A-IIe	B-Ie	C-Ie
E(au)	0.14342	0.14945	0.16399	0.15471

TABLE 9-A

LUMO Energies and Atom Contributions For Ethyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

Atom [a]	Conformers			
	A-Ie	B-Ie	C-Ie	D-Ie
N_1	0.314	0.338	-0.336	0.353
	0.530	0.582	-0.560	0.592
N_2	-0.367	-0.386	0.373	-0.375
	-0.599	-0.630	0.610	-0.611
O_3	0.133	0.136	-0.149	0.116
	0.202	0.208	-0.216	0.158
C_5	0.039	0.002	-0.002	-0.010
	0.310	0.181	-0.296	+0.223
H_7	-0.068	0.072	-0.069	-0.069
	-0.422	0.275	-0.347	-0.283
H_8	0.068	-0.072	0.072	0.073
	0.422	-0.273	0.351	0.291
C_6	0.016	+0.019	-0.014 x	-0.019
	0.111	-0.085	-0.134 x	-0.146
H_9				
H_{10}	-0.016			
	-0.142			
H_{11}	0.016		-0.003	-0.023
	0.142		-0.174	-0.217

a. Orbital: 1s for H; 2Py for other atoms unless otherwise indicated.

Table 9-A Continued

	Conformers			
	A-Ie	B-Ie	C-Ie	D-Ie
E(au)	0.14548	0.15544	0.16357	0.15031

TABLE 10-A

LUMO Energies and Atom Contributions for 2-Fluoroethyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

Atom [a]	Conformers			
	A-If	B-If	C-If	D-If
N_1	-0.318	0.330	-0.335	-0.346
	-0.524	0.565	-0.553	-0.579
N_2	0.370	-0.393	0.367	0.377
	0.590	-0.630	0.588	0.610
O_3	-0.123	0.139	-0.131	-0.119
	-0.178	0.210	-0.182	-0.172
C_5	-0.032	0.012	-0.004	+0.004
	-0.278	0.206	-0.257	-0.233
H_7	0.076	0.070	-0.082	0.076
	0.402	0.308	-0.342	0.300
H_8	-0.074	-0.072	0.081	-0.076
	-0.432	-0.589	0.375	-0.300
C_6	-0.014	-0.002 s	-0.023	0.041
	-0.056	-0.090 s	-0.086	0.200
F_9	0.012 x	0.004 s	-0.012	-0.022
	0.022 x	0.044 s	-0.021	-0.040
H_{10}	-0.012		0.010	-0.001
	-0.185		0.140	+0.130
H_{11}				+0.001
				-0.130

a. Orbital: 1s for H; 2Py for other atoms unless otherwise indicated.

Table 10-A Continued

	Conformers			
	A-If	B-If	C-If	D-If
E(au)	0.12147	0.15359	0.13677	0.13624

TABLE 11-A

LUMO Energies and Atom Contributions for 2-Chloroethyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

	Atom[a]	Conformers			
		A-Ic	B-Ic	C-Ic	D-Ic
	N_1	0.303	0.340	-0.322	0.344
		0.499	0.575	-0.531	0.564
	N_2	-0.345	-0.390	0.356	-0.371
		-0.553	-0.619	0.571	-0.592
	O_3	0.114	0.126	-0.132	0.115
		0.165	0.183	-0.184	0.157
	C_5	0.026	-0.003	-0.007	-0.007
		0.305	+0.167	-0.261	+0.218
	H_7	-0.082	0.066	-0.089	-0.064
		-0.435	0.261	-0.377	-0.277
	H_8	0.074	-0.068	0.085	0.068
		0.416	-0.239	0.377	0.241
	C_6	0.086	-0.007 s	-0.063	-0.068
		0.258	-0.092 s	-0.208	-0.295
2 Py	Cl_9	-0.042	+0.011	+0.030	0.012
3 Py		0.091	-0.025	-0.064	-0.022
3 Py		0.209	-0.060	-0.156	-0.120
	H_{10}	0.012		0.010	0.010
		0.110		0.118	0.137

[a] Orbital: 1s for H; 2Py for other atoms unless otherwise indicated.

Table 11-A Continued

	Conformers			
	A-Ic	B-Ic	C-Ic	D-Ic
E(au)	0.11956	0.14149	0.13219	0.12765

TABLE 12-A

LUMO Energies and Atom Contributions for 2-Hydroxyethyldiazohydroxide Conformers Obtained by SCF-312G Calculations

Atom [a]	Conformers			
	A-Ih	B-Ih	C-Ih	D-Ih
N_1	0.322	0.343	0.338	0.358
	0.533	0.576	0.559	0.591
N_2	-0.367	-0.384	-0.367	-0.374
	-0.589	-0.615	-0.590	-0.591
O_3	0.122	0.124	0.136	0.107
	0.177	0.181	0.191	0.155
C_5	0.031	-0.001	0.003	-0.009
	0.307	+0.184	0.243	+0.184
H_7	-0.069	0.070	0.080	-0.081
	-0.403	0.256	0.338	-0.283
H_8	0.069	-0.072	-0.080	0.081
	0.423	-0.269	-0.357	0.301
C_6	0.019	+0.009	0.016	+0.100
	0.089	-0.096	0.071	0.028
H_{10}	0.012		-0.008	
	0.130		-0.109	
O_9	-0.000 s	-0.000 s	-0.012 x	-0.011 z
	-0.045 s	-0.081 s	-0.025 x	-0.010 z
E(au)	0.13257	0.14055	0.14353	0.12574

a. Orbital: 1s for H; 2Py for other atoms unless otherwise indicated.

TABLE 13-A

LUMO Energies and Atom Contributions for n-Propyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

Atom [a]	Conformers			
	A-Ip	B-Ip	C-Ip	D-Ip
N_1	-0.325	0.345	0.340	-0.360
	-0.544	0.587	0.569	-0.603
N_2	0.366	-0.382	-0.366	0.372
	0.594	-0.619	-0.595	0.596
O_3	-0.120	0.123	0.135	-0.105
	-0.176	0.180	0.191	-0.152
C_5	-0.029	-0.003	0.001	+0.013
	-0.305	+0.188	0.238	-0.172
H_7	0.065	0.070	0.077	0.078
	0.389	0.264	0.324	0.265
H_8	-0.065	-0.070	-0.078	-0.079
	-0.411	-0.266	-0.345	-0.285
C_6	-0.011	+0.016	0.011	-0.007
	-0.108	-0.092	0.099	-0.041
H_{10}	-0.012		-0.007	
	-0.138		-0.122	
C_9	-0.004 s	-0.002 s	-0.005 s	+0.011 z
	+0.104 s	-0.161 s	+0.082 s	-0.047 z
E(au)	0.14360	0.15392	0.15616	0.13608

a. Orbital: 1s for H; 2Py for other atoms unless otherwise indicated.

TABLE 14-A

Net Atomic Charges (eu) for Ethyldiazohydroxide Conformers Obtained by SCF 6-31G* Calculations

Atom	Conformers			
	A-Ie	A-IIe	B-Ie	C-Ie
N_1	-0.307	-0.224	-0.195	-0.252
N_2	+0.173	+0.084	+0.056	+0.143
O_3	-0.573	-0.567	-0.565	-0.619
H_4	0.443	+0.458	+0.456	+0.470
C_5	-0.154	-0.152	-0.157	-0.177
H_7	+0.195	+0.186	+0.195	+0.208
H_8	+0.194	+0.185	+0.193	+0.209
C_6	-0.501	-0.492	-0.525	-0.506
H_9	+0.176	+0.169	+0.207	+0.167
H_{10}	+0.171	+0.163	+0.171	+0.165
H_{11}	+0.184	+0.189	+0.163	+0.192
$C_5H_7H_8$	+0.235	+0.219	+0.231	+0.240
$C_6H_9H_{10}H_{11}$	+0.030	+0.029	+0.016	+0.018

TABLE 15-A

Net Atomic Charges (eu) for Ethyldiazohydroxide Conformers

Obtained by SCF 3-21G* Calculations

Atom	Conformers			
	A-Ie	B-Ie	C-Ie	D-Ie
N_1	-0.333	-0.314	-0.266	-0.231
N_2	+0.145	+0.133	+0.120	+0.115
O_3	-0.525	-0.523	-0.565	-0.608
H_4	+0.397	+0.400	+0.428	+0.435
C_5	-0.236	-0.244	-0.276	-0.284
H_7	+0.252	+0.252	+0.258	+0.262
H_8	+0.252	+0.253	+0.257	+0.262
C_6	-0.615	-0.671	-0.601	-0.683
H_9	+0.234	+0.209	+0.207	+0.184
H_{10}	+0.214	+0.210	+0.205	+0.147
H_{11}	+0.214	+0.295	+0.234	+0.398
$C_5H_7H_8$	+0.268	+0.261	+0.239	+0.240
$C_6H_9H_{10}H_{11}$	+0.047	+0.043	+0.045	+0.046

TABLE 16-A

Net Atomic Charges (eu) for 2-Fluoroethyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

Atom	Conformers			
	A-If	B-If	C-If	D-If
N_1	-0.318	-0.324	-0.263	-0.236
N_2	+0.129	+0.161	+0.109	+0.127
O_3	-0.507	-0.520	-0.561	-0.619
H_4	+0.398	+0.400	+0.419	+0.443
C_5	-0.316	-0.281	-0.321	-0.317
H_7	+0.293	+0.252	+0.302	+0.278
H_8	+0.271	+0.270	+0.268	+0.278
C_6	-0.008	+0.007	+0.011	+0.026
F_9	-0.392	-0.398	-0.414	-0.460
H_{10}	+0.216	+0.228	+0.209	+0.239
H_{11}	+0.232	+0.206	+0.242	+0.239
$C_5 H_7 H_8$	+0.248	+0.241	+0.249	+0.239
$C_6 F_9 H_{10} H_{11}$	+0.048	+0.043	+0.048	+0.044

TABLE 17-A

Net Atomic Charges (eu) for 2-Chloroethyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

Atom	Conformers			
	A-Ic	B-Ic	C-Ic	D-Ic
N_1	-0.319	-0.310	-0.255	-0.221
N_2	+0.124	+0.135	+0.114	+0.127
O_3	-0.504	-0.504	-0.562	-0.621
H_4	+0.398	+0.397	+0.423	+0.436
C_5	-0.231	-0.221	-0.255	-0.250
H_7	+0.299	+0.273	+0.1300	+0.270
H_8	+0.273	+0.277	+0.279	+0.295
C_6	-0.561	-0.598	-0.579	-0.596
Cl_9	-0.068	-0.022	-0.052	-0.058
H_{10}	+0.284	+0.293	+0.277	+0.367
H_{11}	+0.306	+0.279	+0.309	+0.251
C_5 H_7H_8	+0.341	+0.329	+0.324	+0.315
C_6Cl_9 $H_{10}H_{11}$	-0.039	-0.048	-0.045	-0.036

TABLE 18-A

Net Atomic Charges (eu) for 2-Hydroxyethyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

Atom	Conformers			
	A-Ih	B-Ih	C-Ih	D-Ih
N_1	-0.318	-0.299	-0.251	-0.216
N_2	+0.123	+0.109	+0.107	+0.134
O_3	-0.513	-0.508	-0.565	-0.631
H_4	+0.397	+0.400	+0.419	+0.428
C_5	-0.275	-0.280	-0.299	-0.316
H_7	+0.269	+0.270	+0.278	+0.276
H_8	+0.253	+0.255	+0.262	+0.262
C_6	-0.099	-0.145	-0.102	-0.370
H_{10}	+0.200	+0.197	+0.194	+0.146
H_{11}	+0.259	+0.301	+0.258	+0.623
O_9	-0.670	-0.669	-0.673	-0.680
H_{12}	+0.374	+0.370	+0.371	+0.346
$C_5H_7H_8$	+0.247	+0.245	+0.241	+0.222
$C_6H_{10}H_{11}O_9H_{12}$	+0.064	+0.054	+0.048	+0.065

TABLE 19-A

Net Atomic Charges (eu) for n-Propyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

Atom	Conformers			
	A-Ip	B-Ip	C-Ip	D-Ip
N_1	-0.315	-0.302	-0.253	-0.216
N_2	+0.119	+0.108	+0.101	+0.130
O_3	-0.519	-0.513	-0.565	-0.629
H_4	+0.393	+0.395	+0.416	+0.418
C_5	-0.231	-0.233	-0.252	-0.267
H_7	+0.256	+0.257	+0.264	+0.262
H_8	+0.256	+0.257	+0.264	+0.265
C_6	-0.449	-0.500	-0.450	-0.734
H_{10}	+0.219	+0.244	+0.213	+0.169
H_{11}	+0.244	+0.296	+0.244	+0.636
C_9	-0.592	-0.586	-0.591	-0.563
H_{12}	+0.207	+0.203	+0.205	+0.168
H_{13}	+0.202	+0.196	+0.184	+0.178
H_{14}	+0.210	+0.210	+0.206	+0.183
$C_5H_7H_8$	+0.281	+0.281	+0.276	+0.260
$C_6H_{10}H_{11}$	+0.014	+0.040	+0.007	+0.071

Table 19-A Continued

	Conformers			
	A-Ip	B-Ip	C-Ip	D-Ip
C_9H_{12} $H_{13}H_{14}$	+0.027	+0.023	+0.004	-0.034

TABLE 20-A

Group Net Atomic Charges[a] of Alkyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations

	Ethyl		Propyl		
Conformers	$C_5H_7H_8$	C_6H_9[b] $H_{10}H_{11}$	$C_5H_7H_8$	$C_6H_{10}H_{11}$	C_9H_{12} $H_{13}H_{14}$
A-Ie	0.268	0.047			
B-Ie	0.261	0.043			
C-Ie	0.239	0.045			
D-Ie	0.240	0.046			
A-If	0.248	0.048			
B-If	0.241	0.043			
C-If	0.249	0.048			
D-If	0.239	0.044			
A-Ic	0.341	-0.039			
B-Ic	0.329	-0.048			
C-Ic	0.324	-0.045			
D-IC	0.315	-0.036			
A-Ih	0.247	0.064			
B-Ih	0.245	0.054			
C-Ih	0.241	0.048			
D-Ih	0.222	0.065			

Table 20-A Continued

	Ethyl		Propyl		
Conformers	$C_5H_7H_8$	C_6H_9[b] $H_{10}H_{11}$	$C_5H_7H_8$	$C_6H_{10}H_{11}$	C_9H_{12} $H_{13}H_{14}$
A-Ip			0.281	0.014	0.027
B-Ip			0.281	0.040	0.027
C-Ip			0.276	0.007	0.004
D-Ip			0.260	0.071	-0.034

a. atomic units

b. F_9 in 2-fluoroethyl

Cl_9 in 2-chloroethyl

O_9H_{12} in 2-hydroxyethyl

TABLE 21-A

Proton and Lithium Affinities of Methylnitrosourea

	Lithium Cation					Proton	
	$C_1 = O_2$	$N_5 = O_6$		$N_5 = O_6$		$N_5 = O_6$	
	linear	linear		angular		angular	
Energy (au)	syn[a]	syn	anti	syn	anti	syn	anti
Complex	-397.	-397.	-397.	-397	-397.	-390.	-390.
	6406	6054	6257	6122	6204	6812	6891
ΔE[b]	-0.1338	-0.0986	-0.1189	-0.1054	-0.1136	-0.3957	-0.4036
Kcal/mole[c]	-83.96	-61.87	-74.61	-66.14	-71.28	-248.30	-253.26
O-X[d]	1.701	1.701	1.639	1.702	1.701	0.997	0.998
C-O-X[d]	180.0	—	—	—	—	—	—
N-O-X[d]	—	180.0	180.0	110.1	111.4	105.0	105.1

a. Syn/Anti denotes position of Nitroso group relative to the Carbonyl group in MNU

b. $\Delta E = E_{complex} - (E_{MNU} + E_{cation})$

MNU = methylnitrosourea = -390.2855

Cation : Lithium = -7.2213; Proton = zero

c. Obtained by STO-6G;

d. $X = Li^+; H^+;$

TABLE 22-A

Proton and Lithium Affinities of the Nitroso Group (-N=O) of N-Nitrosourea

	Lithium Cation		Proton	
	syn	anti	syn	anti
Complex[a]	-357.8853	-357.8914	-350.9329	-350.9367
ΔE[b]	-0.0742	-0.0803	-0.3089	-0.3127
Kcal/mole	-46.56	-50.39	-193.83	-196.22
O-X[c]	1.757	1.759	0.978	0.979
N-O-X[c]	130.6	133.6	107.4	108.5

a. Energy (au) obtained by SCF 3-21G

b. $\Delta E = E_{complex} - (E_{NU} + E_{cation})$

NU = N-nitrosourea = -350.6240

Cation: Lithium = -7.1871; Proton = zero

c. $X = Li^+; H^+$

d. Syn/Anti denotes position of the Nitroso group relative to the Carbonyl group.

TABLE 23-A

Binding Energies (au) of the E and Z Complexes of Lithium Methyldiazotate

	Complexes			
	6-31G*		3-21G	
Energy (au)	E	Z	E	Z
Complex	-230.7873	-230.7710	-229.4864	-229.4732
Anion E	-223.2573		-221.9630	
Anion Z		-223.2630		-221.9776
Counter Ion	-7.2355	-7.2355	-7.1871	-7.1871
ΔE^a	-0.2945	-0.2725	-0.3363	-0.3085
Kcal/mole	-184.80	-170.99	-211.03	-193.58
ΔE	0.00	13.81	0.00	17.45

a. $\Delta E = E_{complex} - (E_{anion} + E_{counter\ ion})$

TABLE 24-A

Binding Energies (au) of the B and C Complexes of Lithium Ethyl- and Lithium 2-Chloroethyldiazotate

	Ethyl			2-Chloroethyl	
	B		C	B	C
Energy[a](au)	Gauche	Planar	Planar	Planar	Planar
Complex	-268.3064	-268.3009	-268.2911	-725.0162	-725.0073
Anion B	-260.7831	-260.7782		-717.5168	
Anion C			-260.7971		-717.5283
Counter Ion	-7.1871	-7.1871	-7.1871	-7.1871	-7.1871
ΔE[b]	-0.3362	0.3356	-0.3069	-0.3123	-0.2919
Kcal/mole	-210.96	-210.59	-192.58	-195.97	-183.17
ΔE	0.00	0.37	18.38	0.00	12.80

a. Obtained by SCF 3-21G

b. $\Delta E = E_{complex} - (E_{anion} + E_{counter\ ion})$

TABLE 25-A

Binding Energies[a] (au) of the B and C Complexes of Ethyldiazotate Counter Ions-Lithium, Sodium and Ammonium

	Counter Ions					
	Lithium		Sodium		Ammonium	
Entities	B	C	B	C	B	C
Complex	-268.3064	-268.2911	-421.7291	-421.7153	-317.2523	-317.2514
Anion B	-260.7831		-260.7782		-260.7782	
Anion C		-260.7971		-260.7971		-260.7971
Counter Ion	-7.1871	-7.1871	-160.6737	-160.6737	-56.2338	-56.2338
ΔE^b	-0.3362	-0.3069	-0.2772	-0.2445	-0.2403	-0.2205
Kcal/mole	-210.96	-192.58	-173.94	-153.42	-150.79	-138.36
ΔE	0.00	18.38	0.00	20.52	0.00	12.43

a. Obtained by SCF 3-21G

b. $\Delta E = E_{complex} - (E_{anion} + E_{counter\ ion})$

TABLE 26-A

Binding Energies[a] of H^+, Li^+, Na^+, and NH_4^+ to the Diazotates (Kcal/mole)

Anions	Counter Ions			
	H^+	Li^+	Na^+	NH_4^+
E-Methyl	389.86	211.03	——	——
Z-Methyl	370.79	193.58	——	——
E-Ethyl	392.12	210.96	173.94	150.79
Z-Ethyl	382.46	192.58	153.42	138.36
E-Cl-Ethyl	379.51	195.97	——	——
Z-Cl-Ethyl	371.92	183.17	——	——

a. Obtained by SCF 3-21G

TABLE 27-A

SCF 6-31G* Completely Optimized Geometric Parameters and Energies (au) for E and Z Conformers of Methyldiazohydroxide

Parameters	Conformers			
A°	E	Anion	Z	Anion
N-N	1.203	1.261	1.204	1.256
N-O	1.342	1.247	1.359	1.257
O-X[a]	0.957	1.000	0.950	1.000
N-C	1.454	1.444	1.459	1.453
C-H	1.083	1.094	1.084	1.090
NNO	112.9	116.6	119.9	119.3
NOX[a]	107.2	120.0	112.5	120.0
NNC	113.2	110.1	121.9	114.4
NCH	109.5	111.8	110.2	111.1
HCH	110.1	107.7	108.2	108.5
Energy (au)	-223.8596	-223.2573	-223.8392	-223.2630
ΔE (Kcal)	0.00	3.58	12.80	0.00

[a] H in methyl; - in anion

TABLE 28-A

SCF 3-21G Completely Optimized Geometric Parameters and Energies (au) for E and Z Conformers of Methyldiazohydroxide

Parameters	Conformers			
A°	E	Anion	Z	Anion
N-N	1.218	1.291	1.215	1.276
N-O	1.427	1.314	1.451	1.330
O-X[a]	0.977	1.000	0.969	1.000
N-C	1.490	1.477	1.486	1.487
C-H	1.079	1.091	1.081	1.086
NNO	111.0	115.6	118.8	117.7
NOX[a]	105.8	120.0	112.9	120.0
NNC	113.9	109.2	123.1	112.8
NCH	109.1	111.2	109.5	110.3
HCH	110.0	108.2	109.0	109.9
Energy (au)	-222.5843	-221.9630	-222.5685	-221.9776
ΔE (Kcal)	0.00	9.16	9.91	0.00

[a] H in methyl; - in anion

TABLE 29-A

Completely Optimized Geometric Parameters and Energies (au) for the E and Z Complexes of Lithium Methyldiazotate

Parameters	Complexes			
	6-31G*		3-21G	
A°	E	Z	E	Z
N-N	1.240	1.215	1.256	1.225
N-O	1.279	1.310	1.371	1.408
O-Li	1.813	1.748	1.772	1.712
N-C	1.447	1.457	1.472	1.490
C-H	1.085	1.083	1.082	1.079
NNO	113.8	121.2	111.7	119.8
NOLi	92.33	75.26	90.22	72.84
NNC	114.2	116.2	115.0	116.2
NCH	110.2	109.9	109.6	109.1
HCH	109.2	109.7	109.7	110.8
	-230.	-230.	-229.	-229.
Energy (au)	7873	7710	4864	4732
ΔE (Kcal)	0.00	10.23	0.00	8.28

TABLE 30-A

SCF 3-21G Completely Optimized Geometric Parameters and Energies (au) for the B and C Conformers of Ethyl- and 2-Chloroethyldiazohydroxide

Parameters	Conformers[b]							
	Ethyl				2-Chloroethyl			
A°	B	Anion	C	Anion	B	Anion	C	Anion
N-N	1.217	1.284	1.208	1.274	1.217	1.284	1.208	1.274
N-O	1.429	1.320	1.469	1.331	1.429	1.320	1.469	1.331
O-X[a]	0.976	1.000	0.967	1.000	0.976	1.000	0.967	1.000
C-N	1.487	1.487	1.493	1.488	1.487	1.487	1.493	1.488
C-C	1.532	1.544	1.538	1.549	1.532	1.544	1.538	1.549
C-H	1.082	1.086	1.081	1.085	1.082	1.086	1.081	1.085
C-Cl	——	——	——	——	1.85	1.85	1.85	1.85

Table 30-A Continued

NNO	110.0	115.6	112.0	117.4	110.0	115.6	112.0	117.4
NOX[a]	105.8	120.0	103.8	120.0	105.8	120.0	103.8	120.0
NNC	116.0	111.3	121.3	113.4	116.0	111.3	121.3	113.4
NCC	115.8	116.7	109.6	108.8	115.8	116.7	109.6	108.8
NCH	105.7	107.6	108.3	110.3	105.7	107.6	108.3	110.3
CCH	110.6	109.5	111.3	111.0	110.6	109.5	111.3	111.0
HCH	108.6	110.2	107.6	107.8	108.6	110.2	107.6	107.8
CCCl	——	——	——	——	110.5	110.5	110.5	110.5
Energy (au)	-261.	-260.	-261.	-260.	-718.	-717.	-718.	-717.
	4080	7831	4066	7971	1216	5168	1210	5283
ΔE (Kcal)	0.00	8.78	0.88	0.00	0.00	7.22	0.38	0.00

a. H in ethyl and 2-chloroethyl; - in anion

b. B is gauche; C is planar

TABLE 31-A

SCF 3-21G Completely Optimized Geometric Parameters and Energies (au) for B and C Conformers of Ethyldiazohydroxide

Parameters	Conformers					
	B				C	
A°	Gauche	Anion	Planar	Anion	Planar	Anion
N-N	1.217	1.284	1.214	1.278	1.208	1.274
N-O	1.429	1.320	1.430	1.323	1.469	1.331
O-X[a]	0.976	1.000	0.976	1.000	0.967	1.000
C-N	1.487	1.487	1.492	1.497	1.493	1.488
C-C	1.532	1.544	1.547	1.559	1.538	1.549
C-H	1.082	1.086	1.081	1.086	1.081	1.085
NNO	110.0	115.6	111.1	115.8	112.0	117.4
NOX[a]	105.8	120.0	105.8	120.0	103.8	120.0
NNC	116.0	111.3	117.3	112.8	121.3	113.4
NCC	115.8	116.7	117.2	117.9	109.6	108.8
NCH	105.7	107.6	104.8	106.8	108.3	110.3
CCH	110.6	109.5	110.9	109.7	111.3	111.0
HCH	108.6	110.2	108.0	109.1	107.6	107.8
Energy (au)	-261.4080	-260.7831	-261.4030	-260.7782	-261.4066	-260.7971
ΔE (Kcal)	0.00	8.78	3.14	11.86	0.88	0.00

a. H in ethyl; - in anion

TABLE 32-A

SCF 3-21G Completely Optimized Geometric Parameters and Energies (au) For the B and C Complexes of Lithium Ethyl- and Lithium 2-Chloroethyldiazotate

Parameters	Complexes					
	Ethyl			2-Chloroethyl		
	B		C	B		C
A°	Gauche	Planar	Planar	Gauche	Planar	Planar
N-N	1.252	1.248	1.224	1.252	1.248	1.224
N-O	1.377	1.380	1.410	1.377	1.380	1.410
O-Li	1.769	1.765	1.711	1.769	1.765	1.711
C-N	1.481	1.487	1.494	1.481	1.487	1.494
C-C	1.535	1.550	1.540	1.535	1.550	1.540
C-H	1.083	1.082	1.082	1.083	1.082	1.082
C-Cl	——	——	——	1.85	1.85	1.85
NNO	111.6	111.7	119.7	111.6	111.7	119.7
NOLi	90.23	90.21	72.86	90.23	90.21	72.86
NNC	116.9	118.2	116.7	116.9	118.2	116.7
NCC	114.8	116.3	109.5	114.8	116.3	109.5
NCH	106.8	105.9	108.7	106.8	105.9	108.7
CCH	110.3	110.6	111.2	110.3	110.6	111.2
HCH	108.4	108.3	107.6	108.4	108.3	107.6
CCCl	——	——	——	110.5	110.5	110.5

Table 32-A Continued

	Ethyl			2-Chloroethyl		
	B		C	B		C
	Gauche	Planar	Planar	Gauche	Planar	Planar
Energy (au)	-268.	-268.	-268.	-725.	-725.	-725.
	3064	3009	2911	0161	0162	0073
ΔE (Kcal)	0.00	3.45	9.60	0.06	0.00	5.58

TABLE 33-A

SCF 3-21G Optimized Geometric Parameters and Energies (au) for the B and C Complexes of Sodium and Ammonium Ethyldiazotate

Parameters	Complexes			
	Sodium		Ammonium	
A°	B	C	B	C
N-N	1.248	1.224	1.248	1.224
N-O	1.380	1.410	1.380	1.410
O-X[a]	2.250	2.250	1.500	1.500
C-N	1.487	1.494	1.487	1.494
C-C	1.550	1.540	1.550	1.540
C-H	1.082	1.082	1.082	1.082
N-H	——	——	1.028	1.028
NNO	111.7	119.7	111.7	119.7
NOX[a]	100.0	85.0	100.0	85.0
NNC	118.2	116.7	118.2	116.7
NCC	116.3	109.5	116.3	109.5
NCH	105.9	108.7	105.9	108.7
CCH	110.6	111.2	110.6	111.2
HCH	108.3	107.6	108.3	107.6
HNH	——	——	108.5	108.5

a. Na in sodium; H in ammonium

Table 33-A Continued

	Sodium		Ammonium	
	B	C	B	C
Energy (au)	-421.	-421.	-317.	-317.
	7291	7153	2523	2514
ΔE (Kcal)	0.00	8.66	0.00	0.56

TABLE 34-A

LUMO Energies and Atom Contributions for the Completely Optimized E and Z Conformers of Methyldiazohydroxide

	Conformers			
	6-31G*		3-21G	
Atom[a]	E	Z	E	Z
N_1	0.397	0.379	-0.330	-0.331
	0.602	0.509	-0.542	-0.531
N_2	-0.468	-0.448	0.372	0.376
	-0.638	-0.582	0.595	0.587
O_3	0.166	0.180	-0.122	-0.133
	0.220	0.212	-0.178	-0.181
C_5	0.015	0.043	-0.024	-0.022
	0.060	0.344	-0.305	-0.331
H_6	—	—	—	—
H_7	-0.064	0.082	0.066	0.078
	-0.222	0.470	0.393	0.412
H_8	0.064	-0.082	-0.066	-0.078
	0.222	-0.470	-0.392	-0.412
Energy (au)	0.15851	0.14908	0.13937	0.13749

a. Orbital: 1s for H; 2Py for other atoms unless otherwise indicated

TABLE 35-A

LUMO Energies and Atom Contributions for the Completely Optimized E and Z Complexes of Lithium Methyldiazotate

	Complexes			
	6-31G*		3-21G	
Atom[a]	E	Z	E	Z
N_1	-0.042 x	-0.011 x	0.037 x	-0.012 x
	-0.108 x	-0.072 x	0.048 x	-0.020 x
N_2	0.000 s	-0.045 z	-0.030 x	0.040 x
	-0.084 s	-0.123 z	-0.040 x	0.060 x
O_3	0.007 s	-0.010 s	0.028 x	-0.023 z
	0.089 s	-0.058 s	0.032 x	-0.026 z
C_5	-0.006 s	-0.003 s	-0.016 z	-0.002 s
	0.062 s	-0.041 s	-0.028 z	-0.034 s
H_6	———	0.002	———	0.002
		0.019		0.029
H_7	0.000	-0.001	———	-0.002
	-0.020	0.039		0.037
H_8	0.000	-0.001	———	-0.002
	-0.020	0.039		0.037
Li_4	0.449 s	-0.337 s	-0.147 s	-0.094 s
	-1.035 s	1.000 s	0.875 s	0.861 s
Energy (au)	0.01878	0.00777	0.01777	0.00941

a. Orbital: 1s for H; 2Py for other atoms unless otherwise indicated.

TABLE 36-A

LUMO Energies and Atom Contributions for the Completely Optimized B and C Conformers of Ethyl- and 2-Chloroethyldiazohydroxide

	Comformers					
	Ethyl				2-Chloroethyl	
	B		C		B	C
Atom[a]	Gauche	Planar	Planar		Planar	Planar
N_1	-0.344	0.346	-0.339		0.345	0.323
	-0.585	0.591	-0.564		-0.586	0.536
N_2	0.386	-0.386	0.364		-0.387	-0.353
	0.618	-0.619	0.587		-0.618	-0.566
O_3	0.124	0.123	-0.124		0.125	0.123
	0.180	0.179	-0.171		0.181	0.168
C_5	0.004	-0.008	-0.007		-0.008	0.007
	-0.155	0.145	-0.252		0.138	0.257
H_7	-0.070	0.070	-0.079		0.070	0.090
	-0.248	0.244	-0.355		0.232	0.377
H_8	0.072	-0.070	0.080		-0.072	-0.086
	0.264	-0.244	0.358		-0.250	-0.375
C_6	-0.021	0.016	-0.015		0.022	0.065
	0.017	-0.050	-0.087		-0.008	0.210
H_9	———	———	-0.009	2s	-0.004	-0.032
			-0.112	Cl_9 3s	0.010	0.068
				3s	0.002	0.170

Table 36-A Continued

Atom[a]	Gauche	Planar	Planar	Planar	Planar
H_{10}	———	———	0.009 0.110	———	-0.009 -0.104
Energy[b] (au)	0.15272	0.15409	0.15118	0.13204	0.13218

a. Orbital: 1s for H; 2Py for other atoms unless otherwise indicated.

B. Obtained by SCF 3-21G

TABLE 37-A

LUMO Energies and Atom Contributions for the Completely Optimized B and C Complexes of the Lithium Ethyl- and Lithium 2-Chloroethyldiazotate

	Complexes					
	Ethyl				2-Chloroethyl	
	B		C		B	C
Atom[a]	Gauche	Planar	Planar		Planar	Planar
N_1	-0.034 x	-0.034 x	0.011 x		-0.033 x	-0.010 x
	-0.043 x	-0.044 x	0.020 x		-0.043 x	-0.018 x
N_2	0.028 x	0.028 x	-0.040 x		0.027 x	0.040 x
	0.041 x	0.042 x	-0.060 x		0.042 x	0.060 x
O_3	-0.026 x	-0.026 x	0.023 z		-0.025 x	-0.022 z
	-0.030 x	-0.029 x	0.026 z		-0.028 x	-0.025 z
C_5	0.015 z	0.016 z	0.002 s		0.017 z	-0.002 s
	0.030 z	0.031 z	0.036 s		0.033 z	-0.038 s
H_7	———	———	0.002		———	-0.002
			-0.038			0.036
H_8	———	———	0.002		———	-0.002
			-0.038			0.036
C_6	0.003	0.004 z	-0.002 z		0.005 z	0.002 z
	-0.009 s	0.012 z	-0.018 z		0.015 z	0.017 z
H_9	———	———	———	2s	-0.001 s	0.001 y
				Cl_9 3s	-0.001 s	-0.003 y
				3s	0.012 s	-0.004 y
H_{10}	———	———	———		———	———

Table 37-A Continued

Atom[a]	Gauche	Planar	Planar	Planar	Planar
H_{11}	———	———	-0.000	———	0.000
			-0.022		0.022
Li_4	-0.149 s	-0.150 s	0.094 s	-0.139 s	-0.083 s
	0.857 s	0.877 s	-0.861 s	0.877 s	0.859 s
Energy[b] (au)	0.01826	0.01811	0.00948	0.01198	0.00392

a. Orbitals: 1s for H; other atoms as indicated.

b. Obtained by SCF 3-21G

TABLE 38-A

LUMO Energies and Atom Contributions for the Completely Optimized B and C Complexes of Sodium and Ammonium Ethyldiazotate

	Complexes				
	Sodium			Ammonium	
Atom^a	B	C		B	C
N_1	-0.032 x	-0.012 x		0.020 s	-0.003 s
	-0.035 x	-0.020 x		0.116 s	-0.040 s
N_2	0.025 x	0.028 x		-0.014 x	-0.027 x
	0.034 x	0.041 x		-0.031 x	-0.028 x
O_3	-0.030 x	-0.034 z		-0.028 z	0.032 z
	-0.032 x	-0.039 z		-0.032 z	0.028 z
C_5	0.013 z	-0.003 s		-0.024 z	0.004 s
	0.026 z	-0.032 s		-0.070 z	0.054 s
H_7	———	-0.002		-0.001	———
		0.022		-0.082	
H_8	———	-0.002		-0.001	———
		0.022		-0.082	
C_6	0.005 z	0.003 z		-0.008 z	-0.005 z
	0.013 z	0.017 z		-0.021 z	-0.027 z
Na_4	-0.147 s	-0.156 s	2s	———	———
	-0.146 s	-0.049 s	3s		
	0.933 s	0.882 s	3s		
N_{12}	———	———		0.051 s	0.055 s
				1.459 s	1.474 s

Table 38-A Continued

Atom[a]	B	C	B	C
H_{13}			-0.039	-0.049
			-0.861	-0.836
H_{14}			-0.056	-0.051
			-0.737	-0.749
H_{15}			-0.056	-0.051
			-0.737	-0.749
Energy[b] (au)	-0.00271	-0.01409	0.19522	0.17488

a. Orbital: 1s for hydrogen; other atoms as indicated.

b. Obtained by SCF 3-21G

TABLE 39-A

Net Atomic Charges[a] for the Completely Optimized E and Z Conformers of Methyldiazohydroxide

	Conformers			
	6-31G*		3-21G	
Atom	E	Z	E	Z
N_1	-0.279	-0.234	-0.314	-0.268
N_2	+0.157	+0.184	+0.114	+0.149
O_3	-0.569	-0.609	-0.513	-0.548
H_4	+0.444	+0.458	+0.394	+0.397
C_5	-0.324	-0.409	-0.414	-0.482
H_6	+0.190	+0.226	+0.241	+0.274
H_7	+0.190	+0.192	+0.246	+0.239
H_8	+0.190	+0.192	+0.246	+0.238
C_5H_6 H_7H_8	+0.246	+0.201	+0.319	+0.269

a. electron units.

TABLE 40-A

Net Atomic Charges[a] for the Completely Optimized E and Z Complexes of Lithium Methyldiazotate

	Complexes			
	6-31G*		3-21G	
Atom	E	Z	E	Z
N_1	-0.467	-0.323	-0.474	-0.284
N_2	+0.273	+0.126	+0.173	-0.031
O_3	-0.671	-0.683	-0.562	-0.569
Li_4	+0.654	+0.671	+0.570	+0.615
C_5	-0.298	-0.322	-0.375	-0.425
H_6	+0.183	+0.164	+0.231	+0.209
H_7	+0.163	+0.183	+0.219	+0.242
H_8	+0.163	+0.183	+0.219	+0.242
C_5H_6 H_7H_8	+0.211	+0.208	+0.294	+0.268

a. electron units

TABLE 41-A

SCF 3-21G Net Atomic Charges (eu) for the Completely Optimized B and C Conformers of Ethyl- and 2-Chloroethyldiazohydroxide

	Conformers[a]							
	Ethyl				2-Chloroethyl			
Atom	B	Anion	C	Anion	B	Anion	C	Anion
N_1	-0.311	-0.431	-0.250	-0.459	-0.299	-0.411	-0.251	-0.458
N_2	+0.144	+0.034	+0.093	+0.053	+0.108	+0.026	+0.105	+0.069
O_3	-0.514	-0.637	-0.566	-0.646	-0.504	-0.616	-0.562	-0.633
H_4	+0.393	———	+0.409	———	+0.400	———	+0.416	———
C_5	-0.238	-0.182	-0.264	-0.200	-0.216	-0.172	-0.249	-0.200
H_7	+0.252	+0.147	+0.265	+0.179	+0.279	+0.183	+0.305	+0.230
H_8	+0.252	+0.147	+0.265	+0.179	+0.280	+0.183	+0.281	+0.199
C_6	-0.619	-0.595	-0.616	-0.604	-0.597	-0.567	-0.580	-0.556
H_9	+0.209	+0.124	+0.211	+0.147	———	———	———	———
H_{10}	+0.230	+0.196	+0.212	+0.148	+0.294	+0.269	+0.279	+0.227
H_{11}	+0.230	+0.197	+0.243	+0.202	+0.294	+0.269	+0.308	+0.274
Cl_9	———	———	———	———	-0.039	-0.163	-0.051	-0.152

Table 41-A Continued

	Ethyl				2-Chloroethyl			
Atom	B	Anion	C	Anion	B	Anion	C	Anion
C_5 H_7H_8	+0.266	+0.112	+0.266	+0.158	+0.343	+0.194	+0.337	+0.229
$C_6H_9(Cl_9)$ $H_{10}H_{11}$	+0.050	-0.078	+0.050	-0.107	-0.048	-0.192	-0.044	-0.207

a. B is gauche; C is planar

TABLE 42-A

SCF 3-21G Net Atomic Charges (eu) for the Completely Optimized B and C Complexes of Lithium Ethyl- and Lithium 2-Chloroethyldiazotate

	Complexes					
	Ethyl			2-Chloroethyl		
	B		C	B		C
Atom	Gauche	Planar	Planar	Gauche	Planar	Planar
N_1	-0.471	-0.466	-0.284	-0.474	-0.461	-0.284
N_2	+0.168	+0.159	-0.029	+0.183	+0.155	-0.023
O_3	-0.562	-0.561	-0.567	-0.553	-0.551	-0.562
Li_4	+0.568	+0.572	+0.613	+0.583	+0.587	+0.628
C_5	-0.201	-0.204	-0.256	-0.182	-0.190	-0.245
H_7	+0.229	+0.233	+0.254	+0.257	+0.276	+0.293
H_8	+0.229	+0.233	+0.254	+0.247	+0.250	+0.272
C_6	-0.612	-0.651	-0.618	-0.586	-0.613	-0.583
H_9	+0.228	+0.207	+0.200	———	———	———
H_{10}	+0.196	+0.207	+0.200	+0.267	+0.275	+0.269
H_{11}	+0.229	+0.272	+0.233	+0.292	+0.332	+0.298
Cl_9	———	———	———	-0.033	-0.060	-0.063
$C_5H_7H_8$	+0.257	+0.262	+0.252	+0.322	+0.336	+0.320
$C_6H_9(Cl_9)H_{10}H_{11}$	+0.041	+0.035	+0.015	-0.060	-0.066	-0.079

TABLE 43-A

SCF 3-21G Net Atomic Charges[a] for the Optimized B and C Complexes of Sodium and Ammonium Ethyldiazotate

	Complexes			
	Sodium		Ammonium	
Atom	B	C	B	C
N_1	-0.426	-0.321	-0.465	-0.334
N_2	+0.122	+0.004	+0.092	-0.030
O_3	-0.578	-0.607	-0.603	-0.633
Na_4	+0.637	+0.704	———	———
H_4	———	———	+0.497	+0.520
C_5	-0.209	-0.245	-0.206	-0.243
H_7	+0.219	+0.237	+0.205	+0.227
H_8	+0.219	+0.237	+0.205	+0.227
C_6	-0.648	-0.614	-0.647	-0.613
H_9	+0.198	+0.190	+0.193	+0.188
H_{10}	+0.199	+0.190	+0.194	+0.188
H_{11}	+0.268	+0.223	+0.264	+0.224
N_{12}	———	———	-0.901	-0.926
H_{13}	———	———	+0.371	+0.393
H_{14}	———	———	+0.401	+0.407
H_{15}	———	———	+0.401	+0.407
C_5 H_7H_8	+0.229	+0.229	+0.204	+0.211

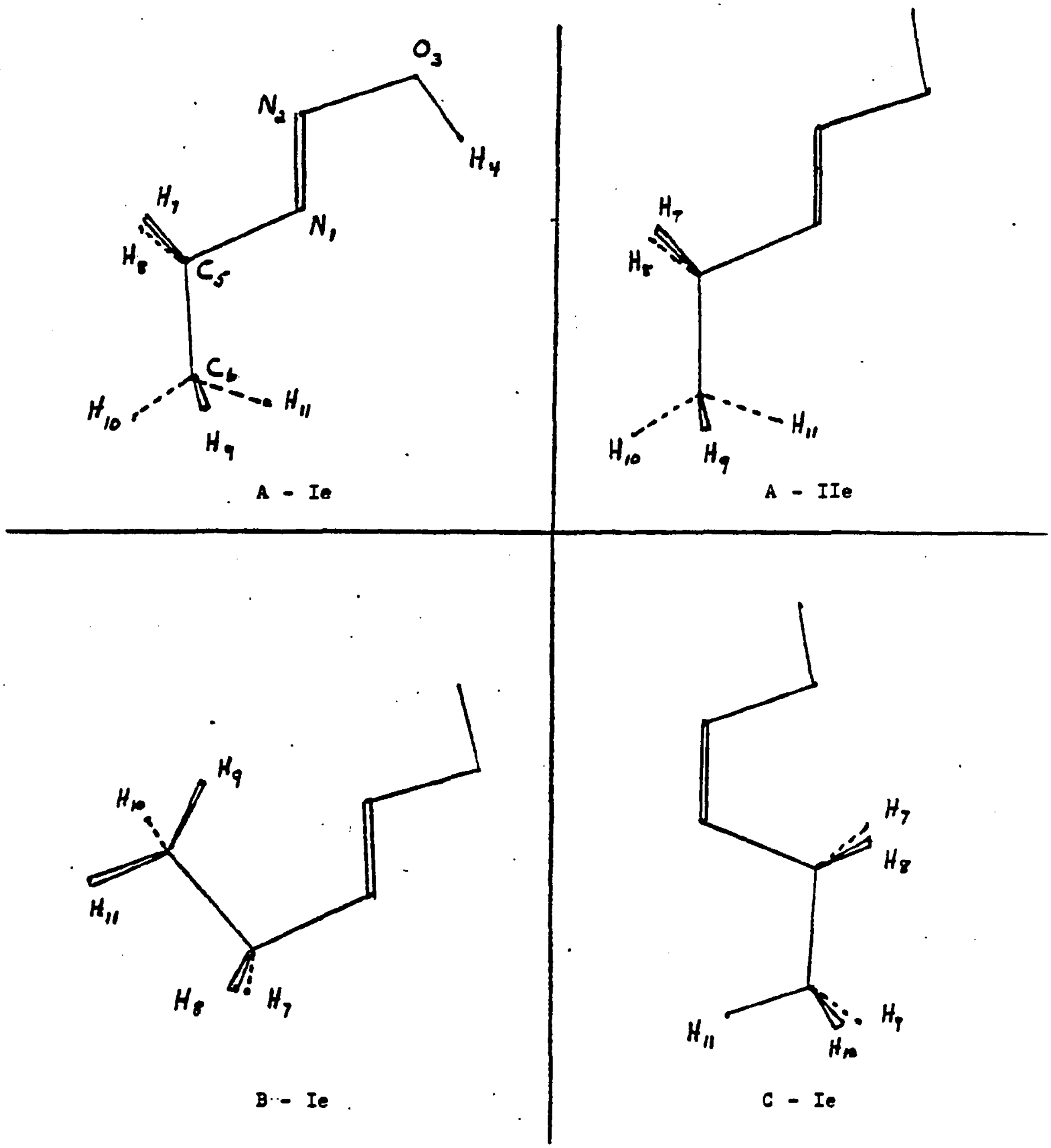
Table 43-A Continued

Atom	B	C	B	C
C_6H_9	+0.017	-0.011	+0.004	-0.013
$H_{10}H_{11}$				
$N_{12}H_4$	—	—	+0.769	+0.801
H_{13-15}				

a. electron units

FIGURE 1-A

Structural Configurations of Ethyldiazohydroxide Conformers Obtained by SCF 6-31G* Calculations



A - Ie

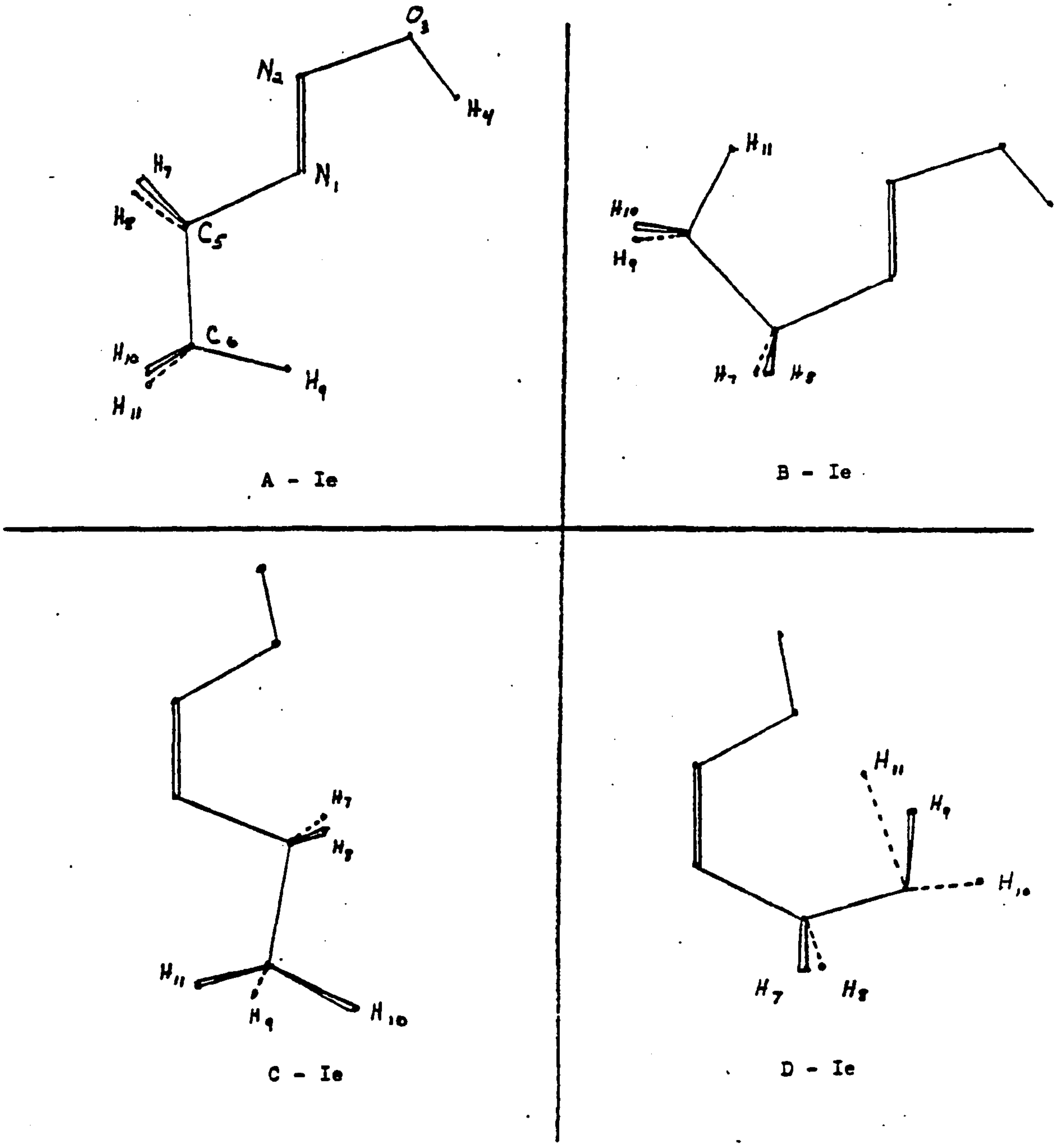
A - IIe

B - Ie

C - Ie

FIGURE 2-A

Structural Configurations of Ethyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations



A - Ie

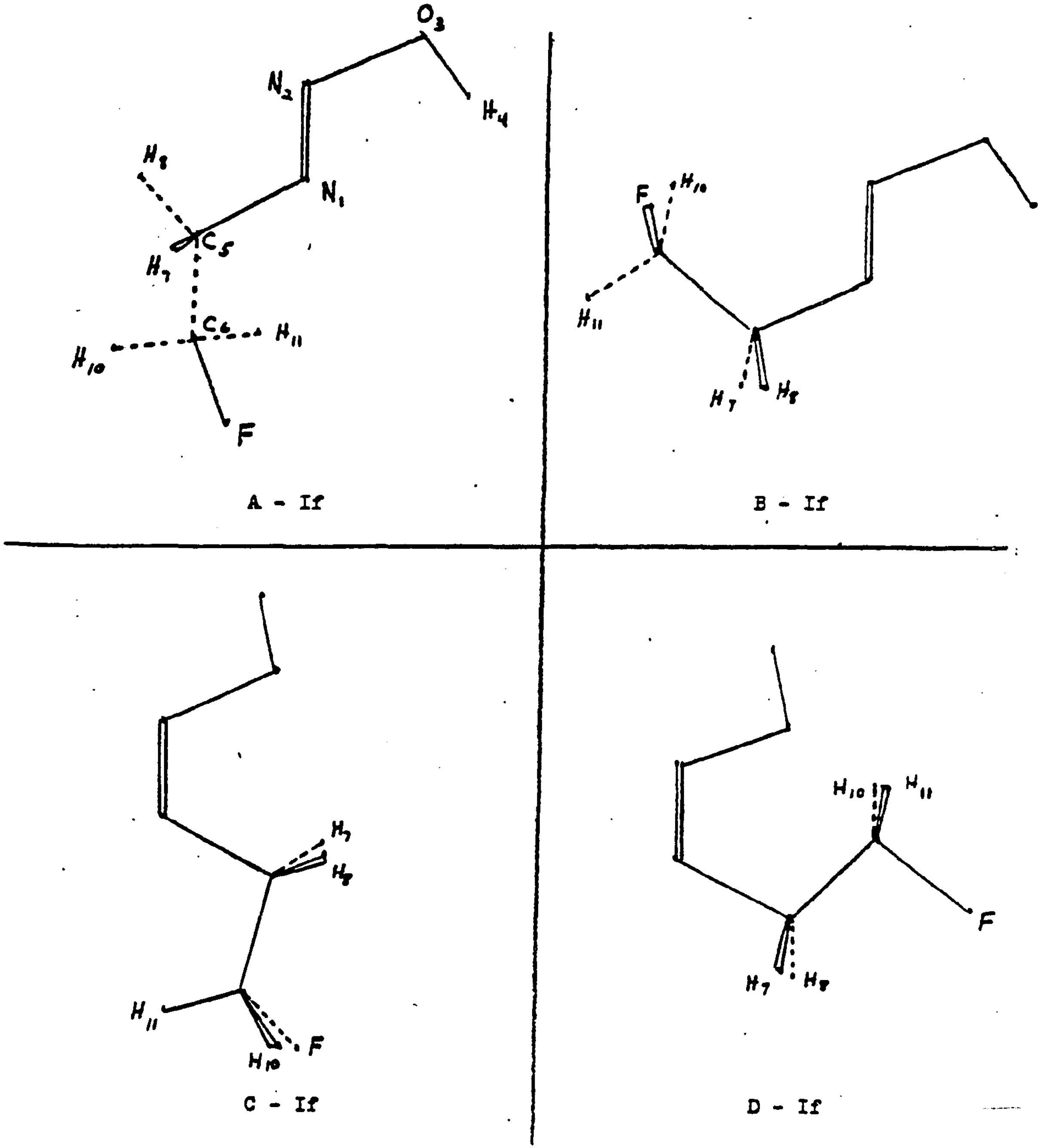
B - Ie

C - Ie

D - Ie

FIGURE 3-A

Structural Configurations of 2-Fluoroethyldiazohydroxide Conformers
Obtained by SCF 3-21G Calculations



A - If

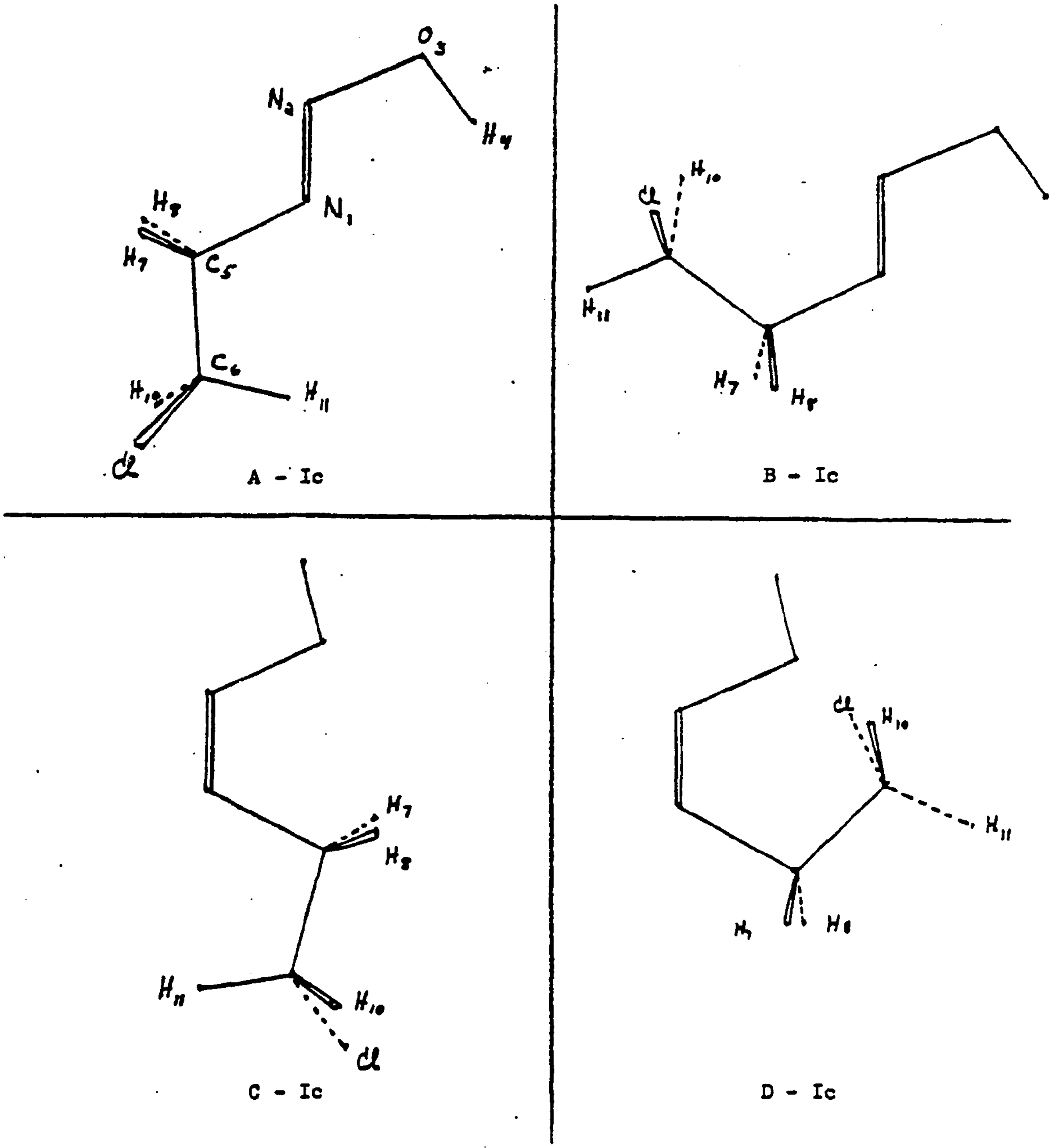
B - If

C - If

D - If

FIGURE 4-A

Structural Configurations of 2-Chloroethyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations



A - Ic

B - Ic

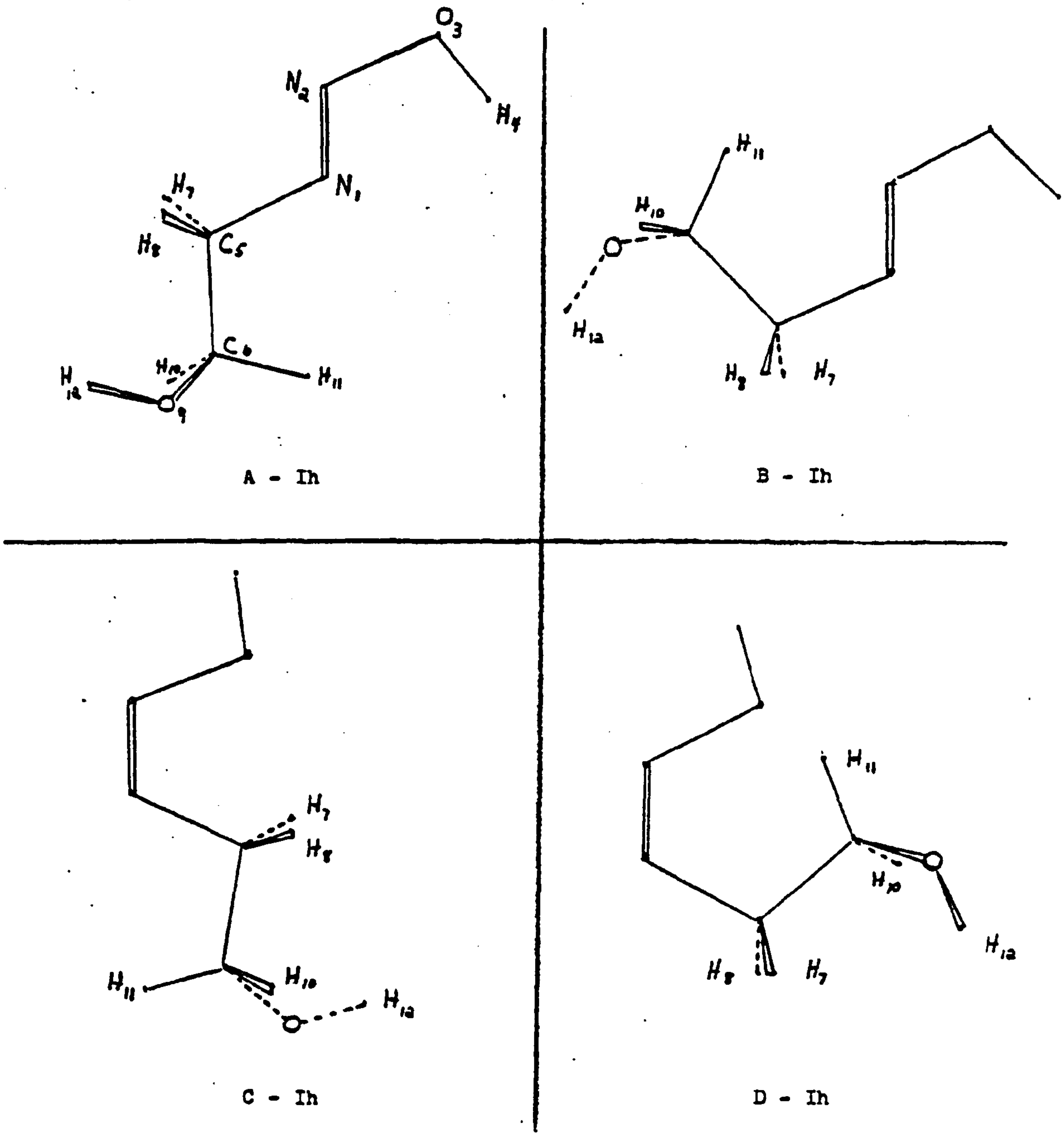
C - Ic

D - Ic

FIGURE 5-A

Structural Configurations of 2-Hydroxyethyldiazohydroxide Conformers

Obtained by SCF 3-21G Calculations



A - Ih

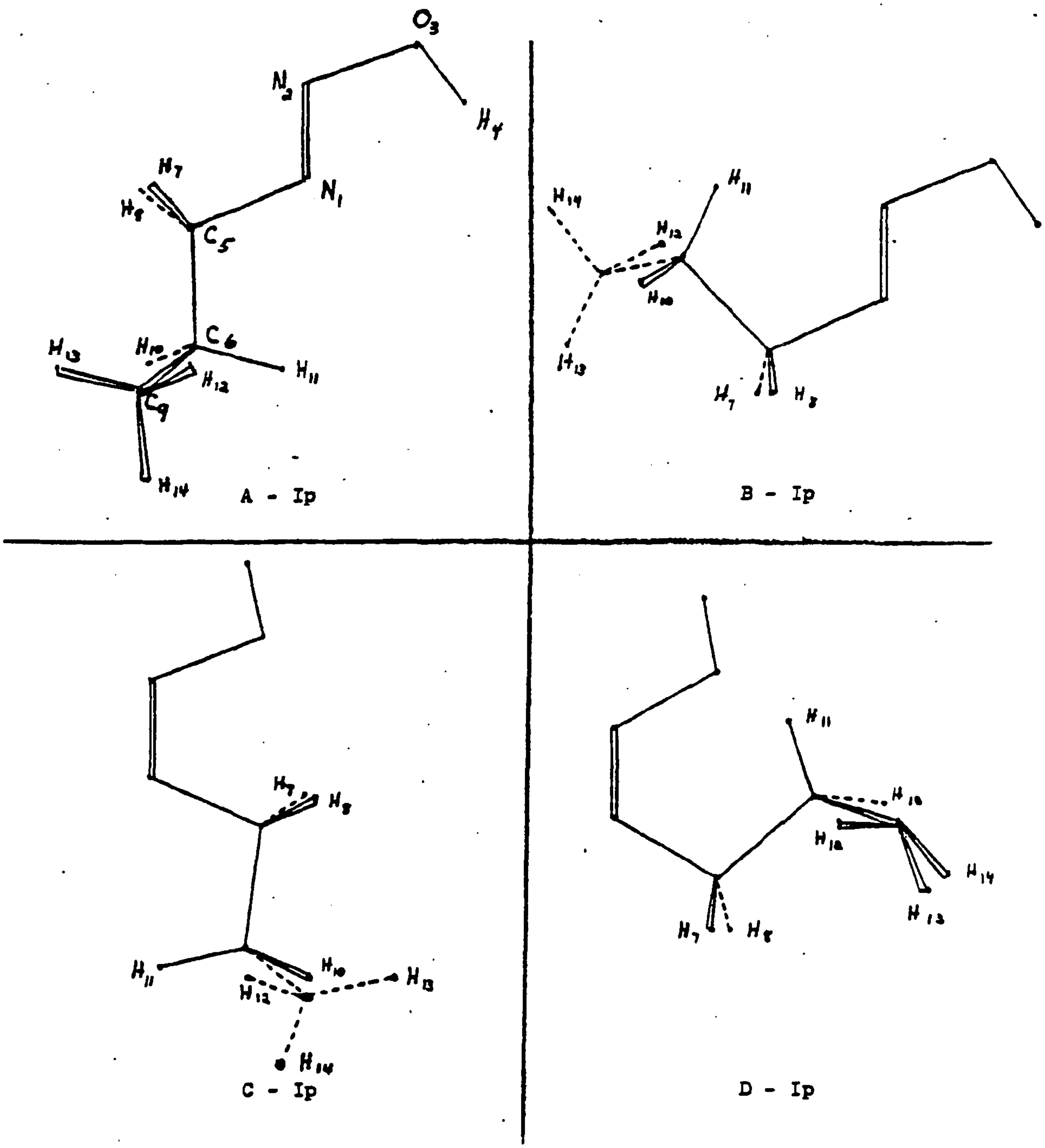
B - Ih

C - Ih

D - Ih

FIGURE 6-A

Structural Configurations of n-Propyldiazohydroxide Conformers Obtained by SCF 3-21G Calculations



A - Ip

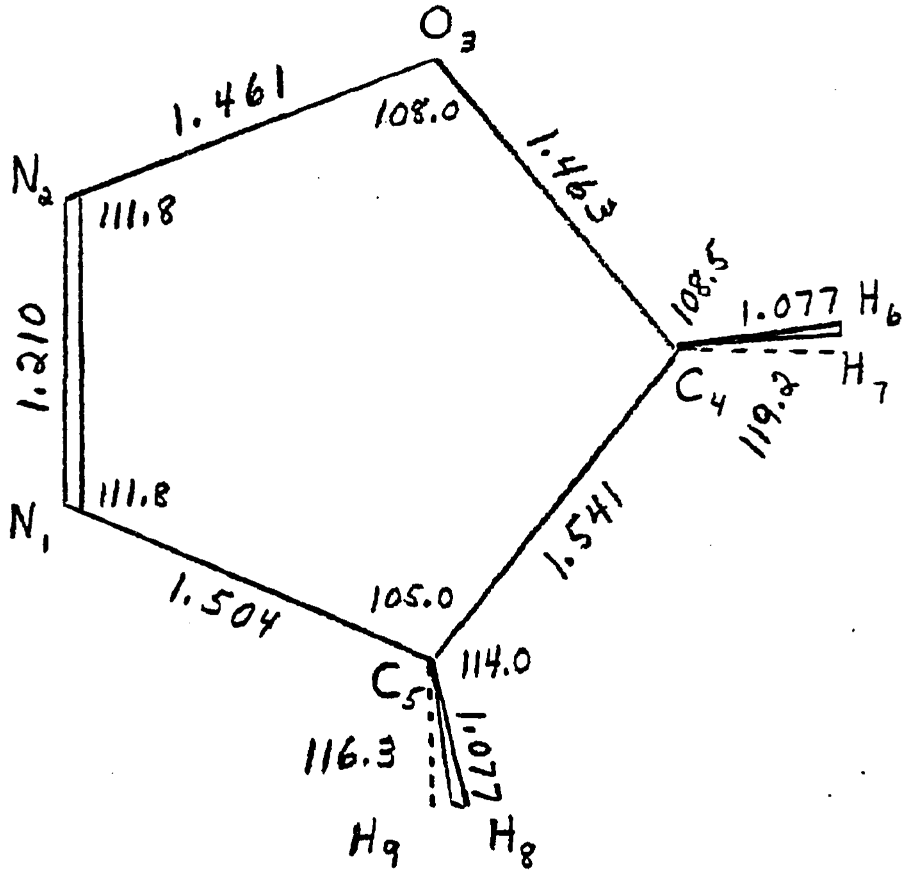
B - Ip

C - Ip

D - Ip

FIGURE 7-A

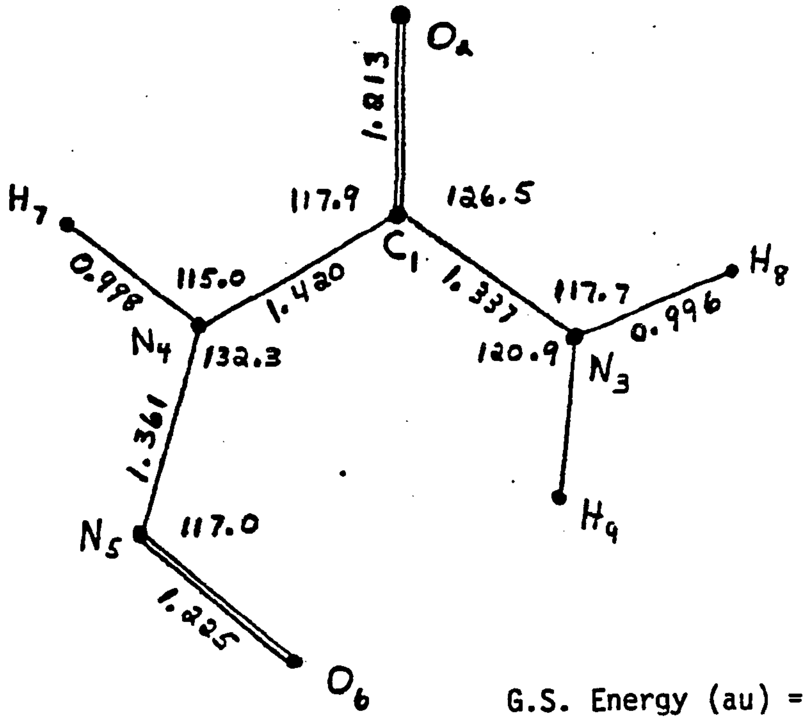
Structural Configuration and Optimized Geometric Parameters for 1,2,3-Oxadiazoline Intermediate Obtained by SCF 3-21G Calculations



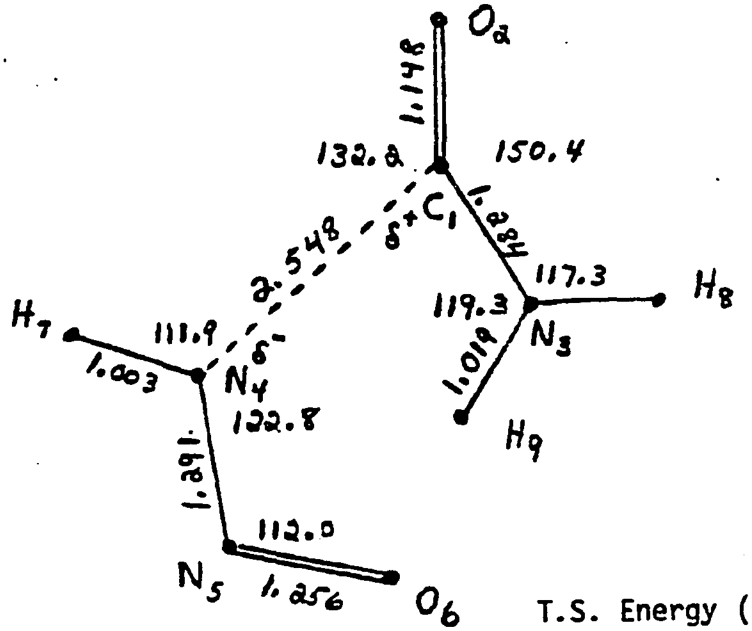
Energy (au) = -260.2469

FIGURE 8-A

Ground State and Transition State Structures of syn N-Nitrosourea Obtained by SCF 3-21G Calculations



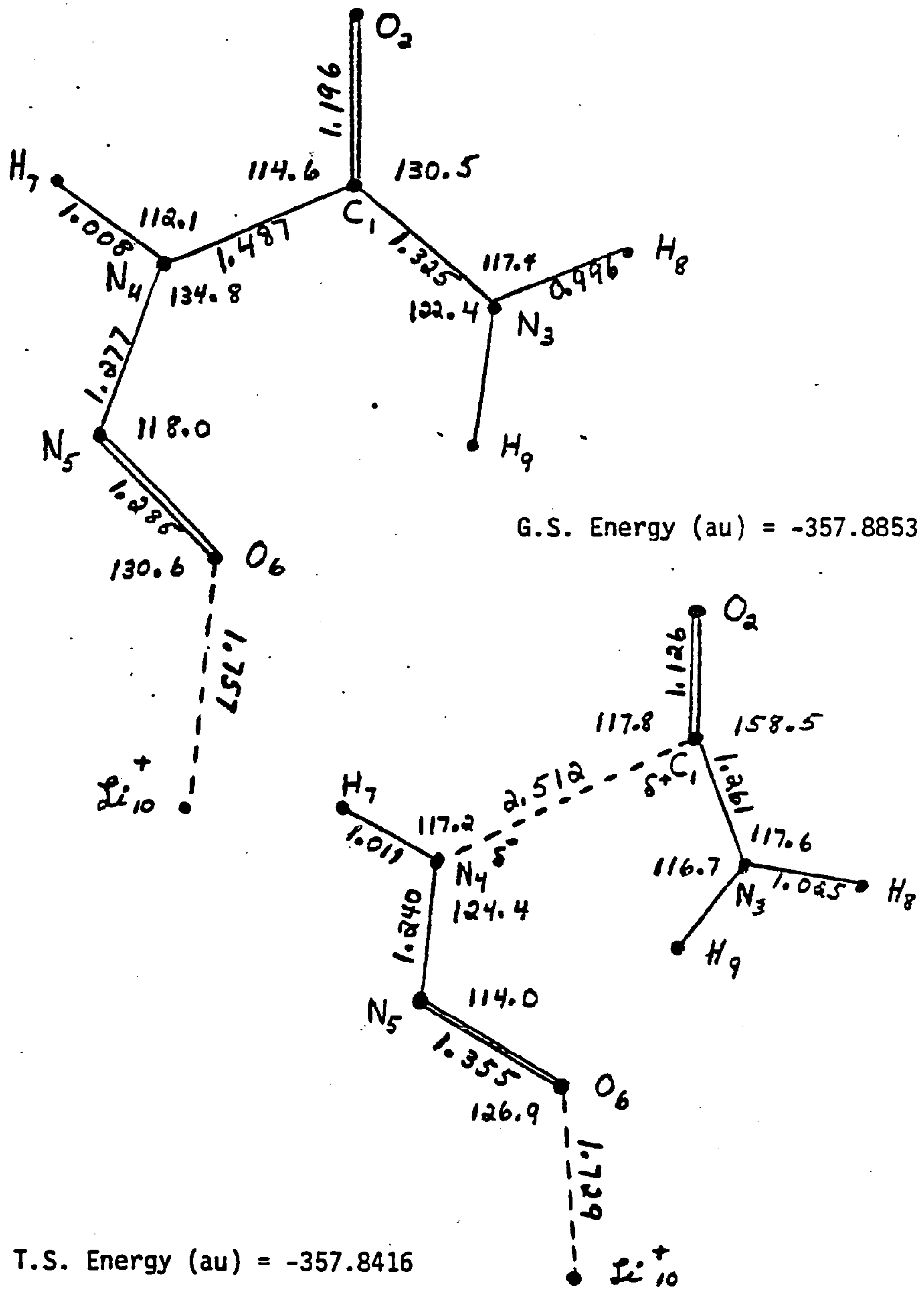
G.S. Energy (au) = -350.6240



T.S. Energy (au) = -350.4932

FIGURE 9-A

Ground State and Transition State Structures of Lithiated N-Nitrosourea Obtained by SCF 3-21G Calculations

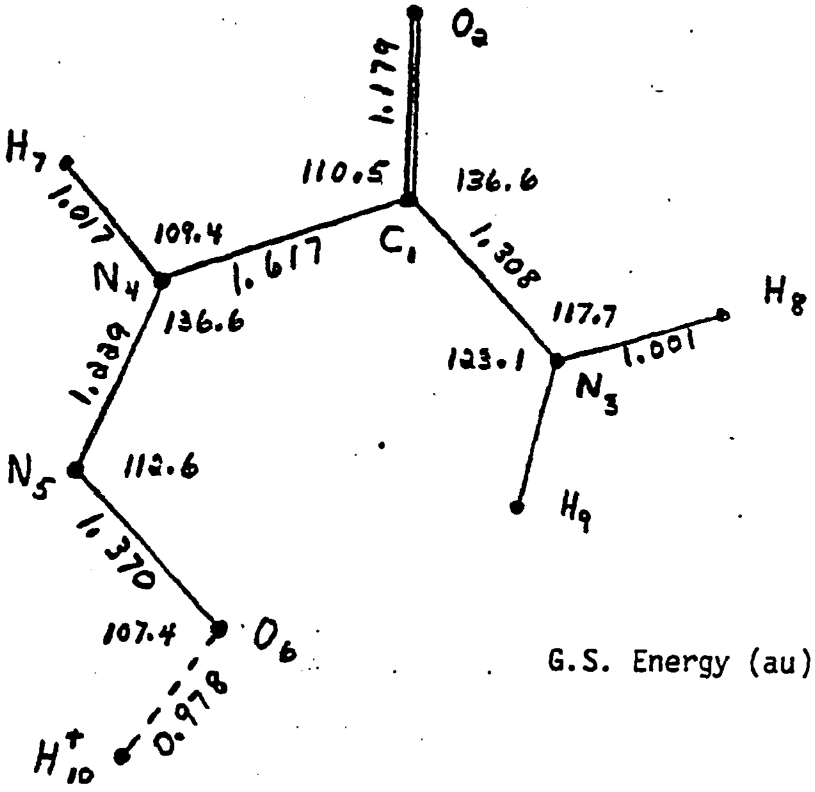


G.S. Energy (au) = -357.8853

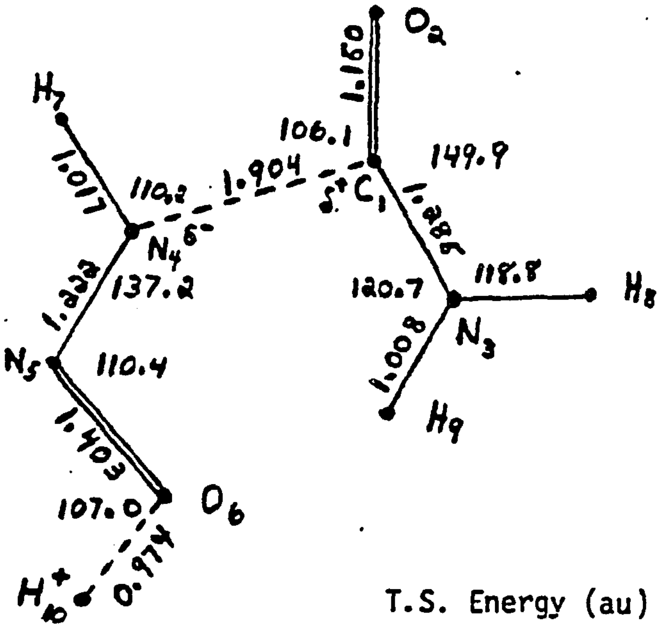
T.S. Energy (au) = -357.8416

FIGURE 10-A

Ground State and Transition State Structures of Protonated N-Nitrosourea Obtained by SCF 3-21G Calculations



G.S. Energy (au) = -350.9329



T.S. Energy (au) = -350.9311

FIGURE 11-A

ENERGY ASSOCIATED WITH C_1-N_4 BOND BREAKING

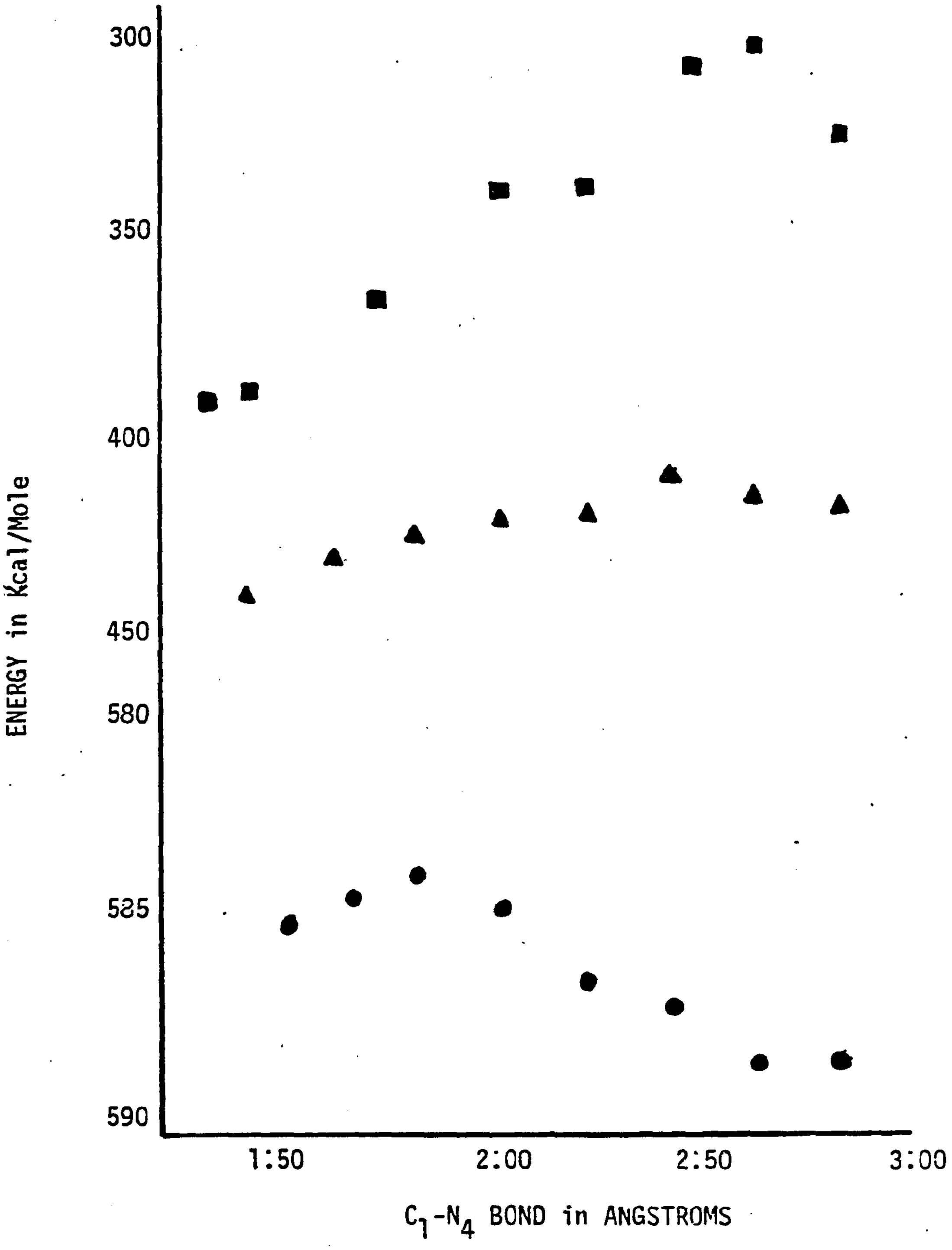
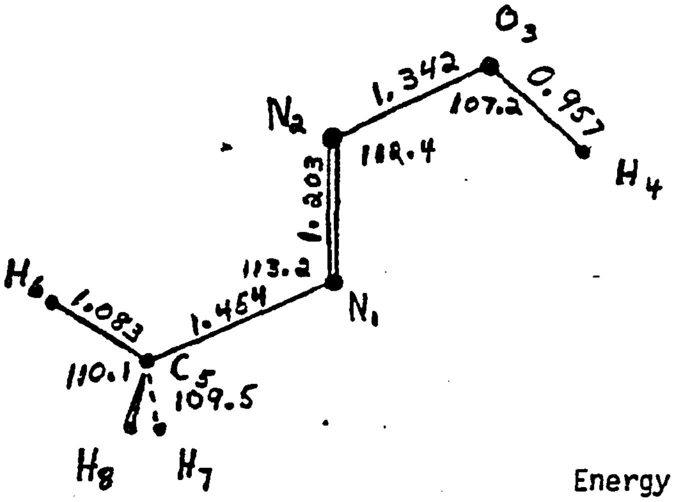
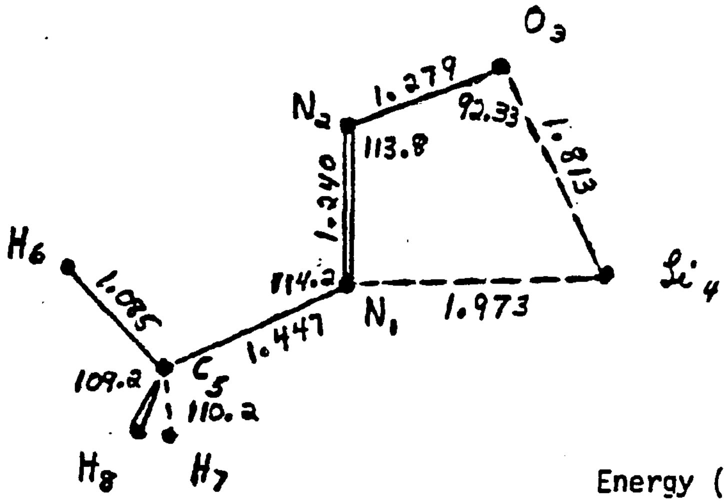


FIGURE 12-A

Structural Configurations of E-Methyldiazohydroxide and Its Lithium Diazotate Obtained by SCF 6-31G* Calculations



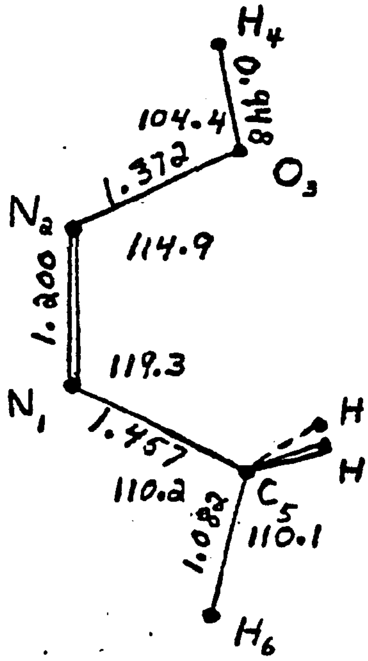
Energy (au) = -223.8596



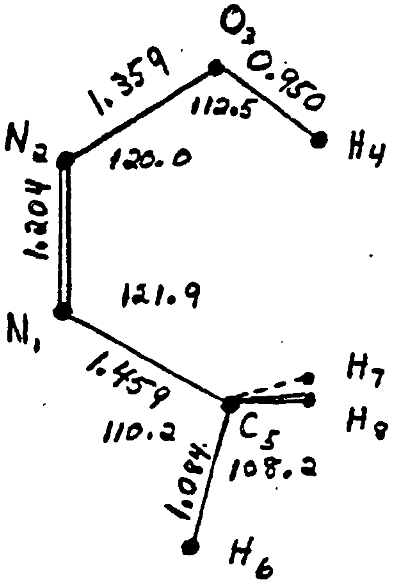
Energy (au) = -230.7873

FIGURE 13-A

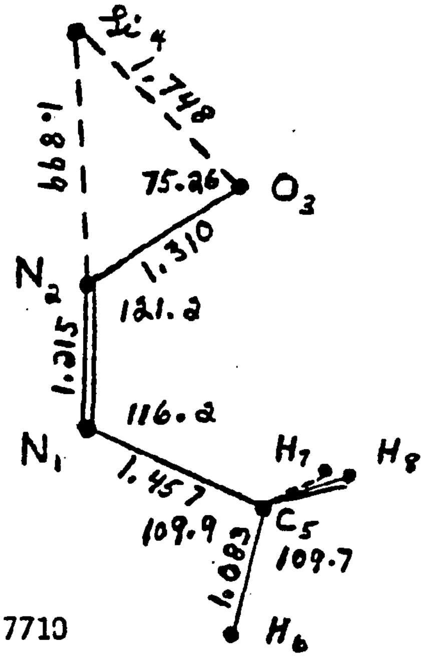
Structural Configurations of Z-Methyldiazohydroxide and Its Lithium Diazotate Obtained by SCF 6-31G* Calculations



Energy (au) = -223.8535



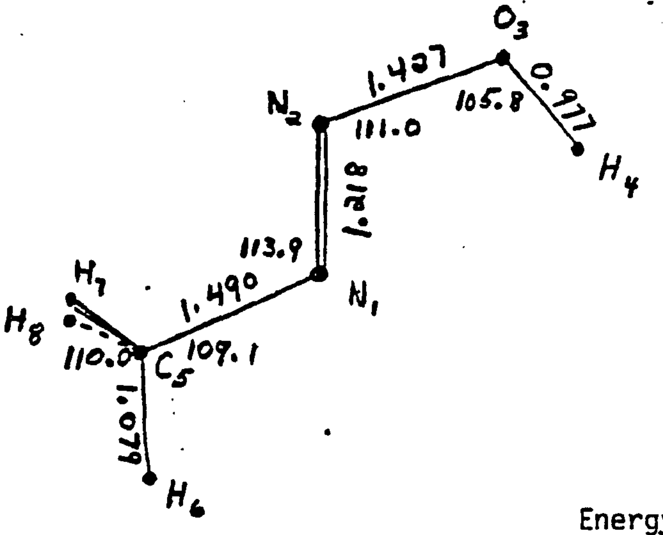
Energy (au) = -223.8392



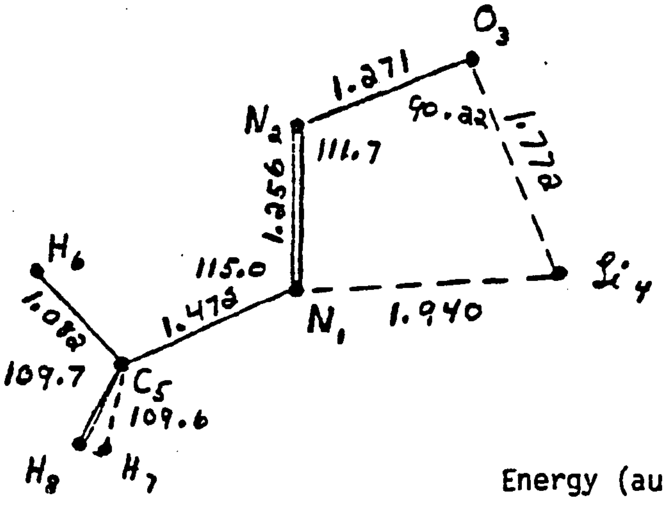
Energy (au) = -230.7710

FIGURE 14-A

Structural Configurations of E-Methyldiazohydroxide and Its Lithium Diazotate Obtained by SCF 3-21G Calculations



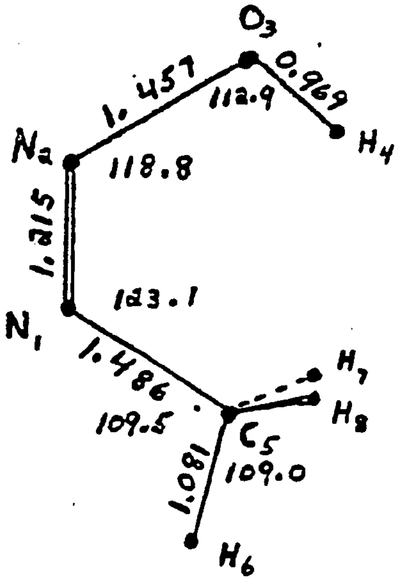
Energy (au) = -222.5843



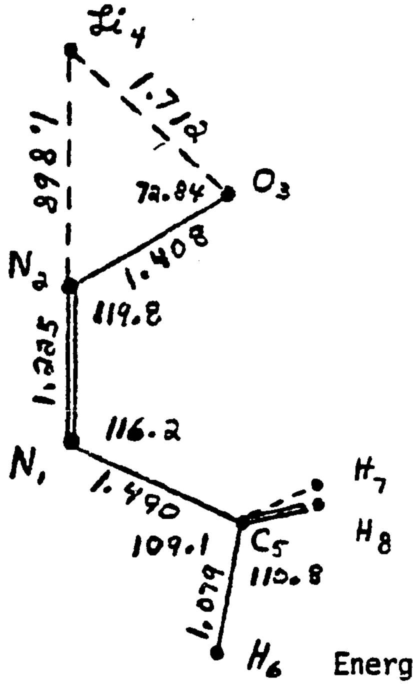
Energy (au) = -229.4864

FIGURE 15-A

Structural Configurations of Z-Methyldiazohydroxide and Its Lithium Diazotate Obtained by SCF 3-21G Calculations



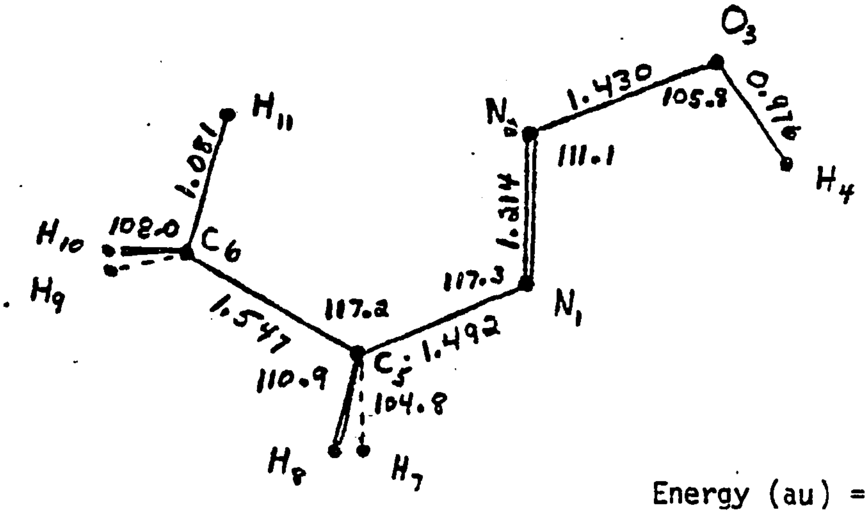
Energy (au) = -222.5685



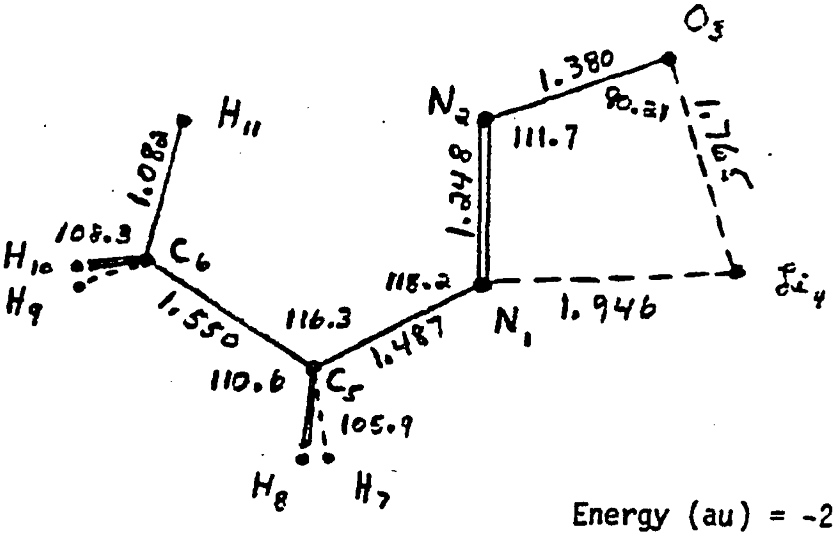
Energy (au) = -229.4732

FIGURE 16-A

Structural Configurations of E-Ethyldiazohydroxide and Its Lithium Diazotate Obtained by SCF 3-21G Calculations



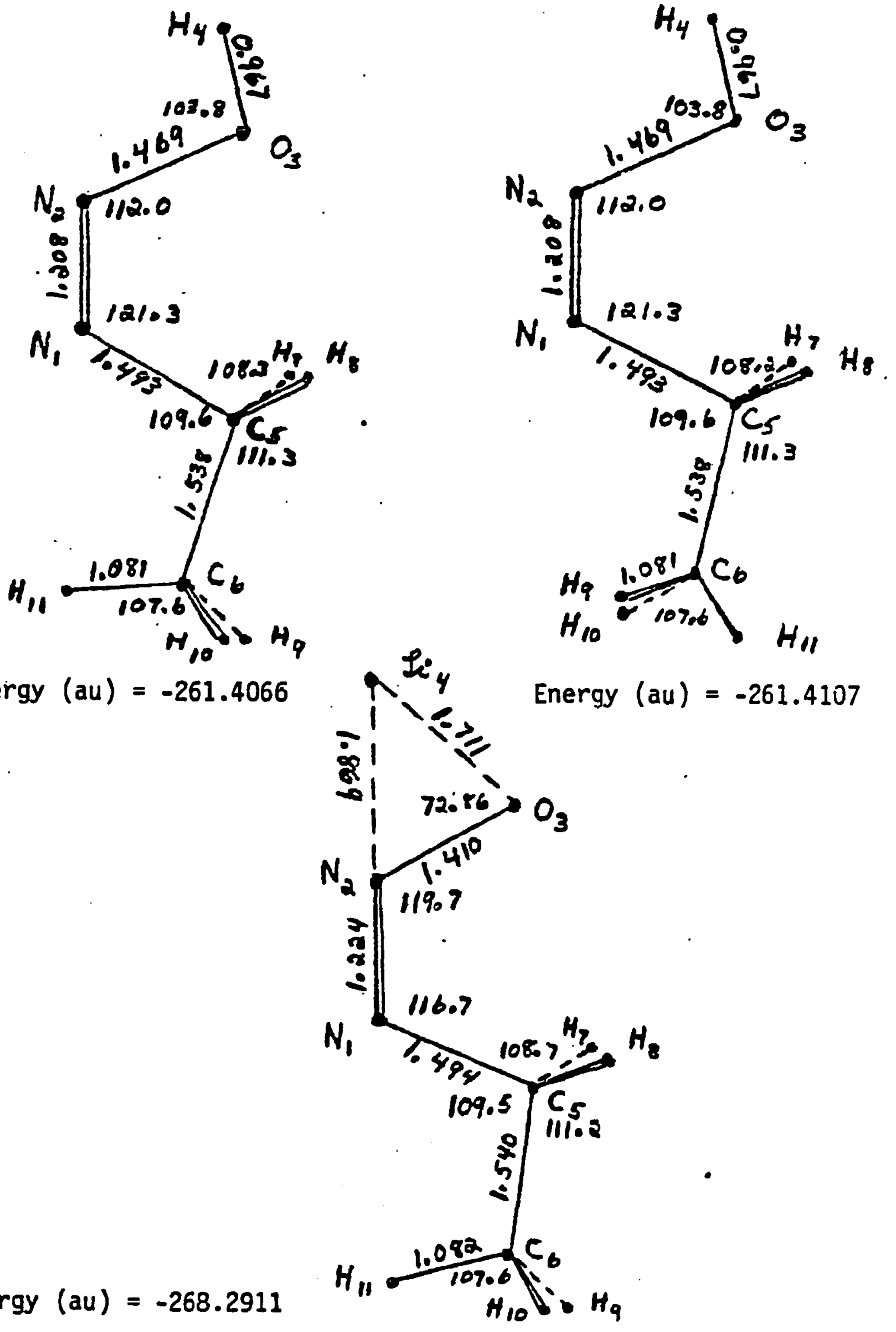
Energy (au) = -261.4030



Energy (au) = -268.3009

FIGURE 17-A

Structural Configurations of Z-Ethyldiazohydroxide and Its Lithium Diazotate Obtained by SCF 3-21G Calculations



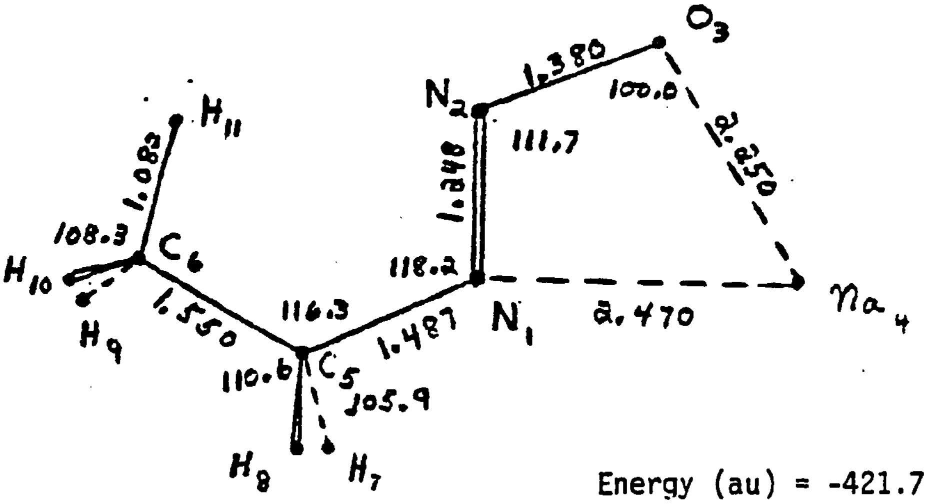
Energy (au) = -261.4066

Energy (au) = -261.4107

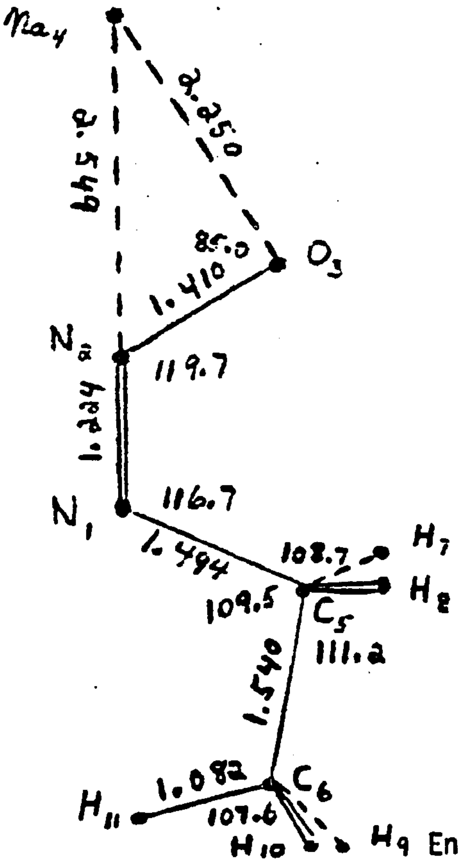
Energy (au) = -268.2911

FIGURE 18-A

Structural Configurations of the Sodium Diazotates of E and Z-Ethyldiazohydroxide Obtained by SCF 3-21G Calculations



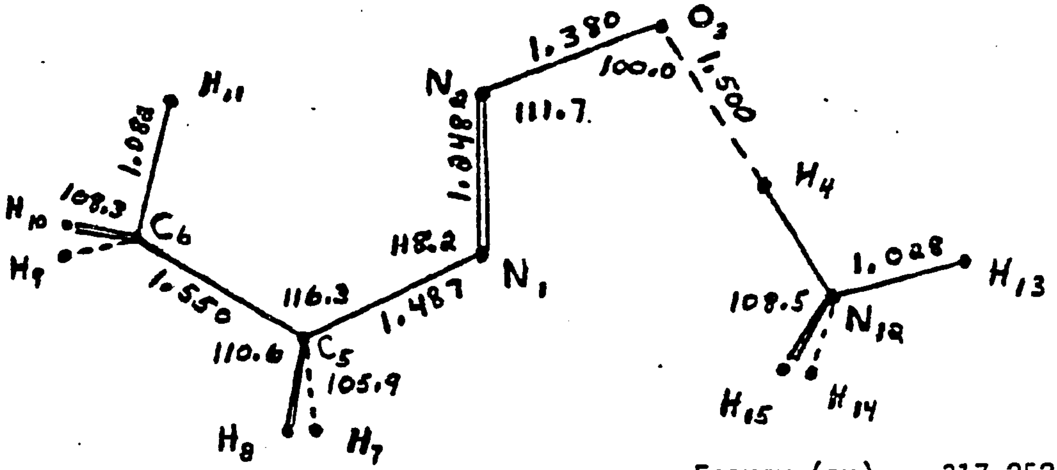
Energy (au) = -421.7291



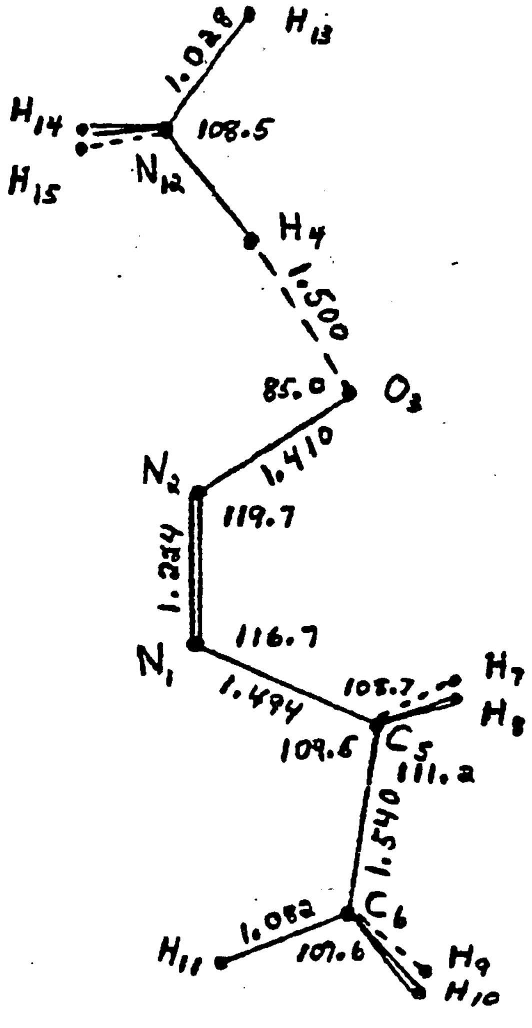
Energy (au) = -421.7153

FIGURE 19-A

Structural Configurations of the Ammonium Diazotates of E and Z-Ethyldiazohydroxide Obtained by SCF 3-21G Calculations



Energy (au) = -317.2523



Energy (au) = -317.2514