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Coordination number studies of small molecules and amino acids

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COORDINATION NUMBER STUDIES

OF SMALL MOLECULES AND AMINO ACIDS

by

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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.

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Chapter I

General Introduction

Most biological processes occur in water. A water molecule evolves each time a peptide bond forms between amino acid residues in the creation of a polypeptide. And, the structure and conformational transitions of biologically relevant molecules depend on the presence of water.[1] Thus, molecular hydration is a cogent matter to theoretical and experimental chemists.

Coordination number represents an average probability of occupancy for the regions available to water molecules about an atom. As such, it is a measure of molecular hydration and a probe of the probable water structure at an atom site.

Coordination number determination is the subject of ardent pursuit by both experimental and theoretical scientists.[2-10] However, routine application of available methods is impractical. Rigorous statistical thermodynamic simulation based on Monte Carlo or molecular dynamics methods[2-9] are a source of coordination number data, however these processes demand enormous amounts of real and computer time. In addition, alternative methods for hydration analysis assume coordination number proportional to exposed molecular surface area or volume and typically neglect bulk solvent or temperature effects.[11-13]

A procedure has been developed that predicts molecular coordination in dilute aqueous solution. The model is parameterized against *ab initio* Monte Carlo simulations of dilute aqueous solutions and calculates molecular solvation shell volumes from which coordination number is obtained directly. The model

reproduces Monte Carlo simulation coordination numbers to within 5%.[14] The salient features of the model are its speed and simplicity.

Chapter II

General Method

The coordination number model consists of 3 elements: (i) a linear function parameter that relates atom volume and coordination number for an atom type in a specific environment; (ii) an inner shell cutoff that physically represents the most proximal solvent molecules in the atom's first solvation shell and (iii) an outer shell cutoff that delineates the furthest solvent molecules in the atom's first solvation shell.

The linear function parameters were derived from *ab initio* Monte Carlo simulations of dilute aqueous solutions of adenine, thymine, guanine, cytosine, uracil, ribose, deoxyribose, dimethyl phosphate (gg, gt, tt conformations) and the glycine zwitterion; the simulations were run at 25°C with water-water and solute water interactions represented by the MCY water-water potential and the Clementi et.al. solute-water potentials, respectively.[15,16] Recent studies show that all available potential functions produce comparable coordination numbers.[17,18] Thus, the choice of potential function is flexible.

The model consists of six classes, each with unique average inner and outer cutoffs: acidic hydrogen (OH, NH), covalent hydrogen (CH), covalent oxygen (C=O,-O-), ionic oxygen ($PO^{=}$,$CO^{=}$), carbon and nitrogen; mathematically, the inner and outer cutoffs represent the first increase and minimum in the radial distribution function respectively. The model uses the standard Monte Carlo method to calculate molecular solvation shell volume; it defines box size, generates random numbers and tabulates those inside and outside the

cutoffs. Simulations were run on an IBM PC at 4.77 MHz with an 8087 math coprocessor. Each simulation took approximately 40 minutes.

Chapter III

Coordination Number and Hydration Free Energy of Small Molecules

III.A. Introduction

Simple prototype molecules have functional groups that are present in the most complex biologically important molecules and drugs. And, a clear understanding of the trends implicit in the hydration of small, simple prototype molecules is vital to an informed, intelligent attack of more complex species. We therefore use the coordination number model to predict coordination numbers for seven classes of prototype molecules: alkanes, alcohols, amines, aromatics, esters, ethers and ketones and compare the results with experimental free energy of hydration data. Beyond this, we invoke simulation results to decompose Cabani and coworkers' experimental hydration free energy data[19] into CH_2, hydrocarbon and functional group contributions. This is, to our knowledge, the first systematic analysis of molecular hydration coordination founded on rigorous Monte Carlo simulations of aqueous solutions.

III.B. Method

The decomposition of experimental ΔG_{Hyd} data proceeds as follows: since simulation gives the coordination number at each atom, total molecular coordination is known, as are those for hydrocarbon and functional group. Differences between experimental ΔG_{Hyd} and coordination number for successive members of any straight chain series produce that quantity for a CH_2 unit. And, dividing the difference between ΔG_{Hyd} for two successive members of such a series by

the difference in their coordination numbers gives the CH_2 contribution to ΔG_{Hyd} per CH_2 water molecule. Moreover, the difference in experimental ΔG_{Hyd} between successive members of a non-alkane series divided by the difference in their hydrocarbon coordination numbers gives the CH_2 contribution to ΔG_{Hyd} per hydrocarbon water molecule, the series average of which, times the specific molecule's hydrocarbon coordination number, produces its hydrocarbon ΔG_{Hyd}. This quantity, subtracted from the experimental ΔG_{Hyd}, gives the ΔG_{Hyd} for the functional group which, when divided by the functional group coordination number, gives the functional group contribution to ΔG_{Hyd} per functional group water molecule. Finally, ΔG_{Hyd} for a CH_2 unit divided by CH_2 coordination number gives the CH_2 contribution to ΔG_{Hyd} per CH_2 water molecule. We distinguish between hydrocarbon as the entire molecule minus functional group and CH_2 as an interior methylene excluding the carbon bearing the functional group.

III.C. Results and Discussion

We use the coordination number, CN, model to examine molecular hydration in 100 molecules of seven general classes: alkanes, alcohols, amines, esters, ethers, ketones and aromatic hydrocarbons. Specifically:

1. Alkanes: Ethane through hexane straight chains as well as mono and di-methylated and cyclized forms (Table III.1).

2. Alcohols: Alkan-1-ols, methanol through hexanol as well as alkan-2 and 3-ols, methylated and cyclized forms (Table III.2).
3. Amines: Primary amines, methyl through hexyl as well as di-alkylated and aromatic species (Table III.3).
4. Esters: Methyl through butyl alkanacetates as well as methyl alkanoates, acetate through pentanoate (Tables III.4 and III.5).
5. Ethers: Symmetric ethers, methyl through butyl and substituted forms (Table III.6).
6. Ketones: Alkan-2-ones, acetone through heptanone as well as 3 and 4-ones and mono and di-methylated species (Table III.7).
7. Aromatics: Benzene, naphthalene, phenanthrene, pyrene as well as di- and tri-alkylated species (Table III.8).

We discuss the results of the CN simulation for the seven series and invoke them to analyze the experimental ΔG_{Hyd} data.

All lines are fit by standard least squares regression methods.

III.C.1. Coordination Numbers

Tables III.1-8 present CN data for the seven classes. Each table contains, by column, a numerical index which corresponds to a data point on that class graph, molecule name, experimental hydration free energy (kcal/mol), functional group and hydrocarbon contributions to total CN and total CN.

Collectively, the CN data for linear chains reveals several general trends: Each CH_2 addition to a straight chain series produces a constant average increase in total CN of 3.03±0.17 water molecules. This is consistent with the average increase in alkane coordination per CH_2 unit of 3.04±0.15 water molecules. Furthermore, in molecules of greater than two carbons, functional group coordination remains essentially constant with increased chain length. For example, average CN at the NH_2 of primary amines is 2.17±0.03 water molecules and 2.44±0.06 water molecules at the carbonyl of ketones. Finally, molecules of two carbon length show marked decreases in functional group coordination relative to their one carbon counterparts while alpha carbon hydrogens experience a large increment in coordination: OH group coordination decreases from 2.98 to 2.19 in going from methanol to ethanol while the CH_2 group has 5.97 water molecules, 2.92 more than the average alcohol CH_2 increment of 3.05±0.17 water molecules.

We present a decomposition of alkan-1-ol CN's in Table III.9 to illustrate CN fluctuations with chain length. Ethanol total CN is 3.74 water molecules greater than that for methanol; the increment is also larger than the 3.05±0.17 water molecule average alcohol increment per CH_2 unit and accounts for only 63% of the 5.97 water molecules at ethanol's CH_2 group; the remaining water molecules come from reorganization at neighboring OH and CH_3 -- 1.44 waters are lost by CH_3, 0.79 by OH. Propanol total CN is 3.07 water molecules greater

than ethanol; coordination at the new CH_2 group, beta carbon, is 5.53 waters, again larger than the average alcohol CH_2 CN increment and due to the reorganizational losses of waters from neighboring terminal CH_3 and alpha carbon: 1.3 waters from the terminal CH_3 and 1.2 from alpha carbon hydrogens, which, when added to the 3.05 average alcohol CH_2 water increment, account exactly for the total CN at the beta carbon. Increasing chain length from propanol through octanol reveals that CN at the terminal CH_3 equilibrates at an average 8.83 water molecules and, at each new CH_2 adjacent to terminal CH_3, at 4.21 waters. The remaining CH_2's of octanol (C_2-C_6) equilibrate at an average 3.2 water molecules, in good agreement with the average alcohol CH_2 CN increment of 3.05 ± 0.17 water molecules. Thus, reorganizational water acquisition is restricted to the newest CH_2 units. Marchese and Beveridge describe reorganization or redistribution of water molecules among groups within neighboring regions of space in the simulation analysis of formamide hydration where a water molecule participates in hydration of both carbonyl and methine groups.[20] Analogous reorganization occurs in other series.

Analysis of cyclic hydrocarbon hydration reveals that CN decreases monotonically as a single ring increases in size or as the number of rings increase in polycyclic species. For example, CN for the six carbon framework of benzene is 1.89. This is in good agreement with Monte Carlo simulations of benzene which show two water molecules: one above and below the molecular plane.[21] Coord-

ination number for the carbons of naphthalene is 3.58, 0.2 water molecules less than twice that for benzene carbons and 1.76 waters per ring; carbons of phenanthrene and pyrene have CN's of 4.87 and 5.73 respectively, 0.77 and 1.79 water molecules less than corresponding multiples of the benzene framework, and 1.63 and 1.43 waters per ring. A least squares plot of CN versus natural log of the number of aromatic rings graphically represents this trend by a straight line of slope 2.7749, intercept 1.8117, standard deviation 0.13 and correlation coefficient 1.00. A fit of CN versus natural log of carbon number in nonaromatic rings produces a straight line of slope 10.2271, intercept 10.2398, standard deviation 0.26 and correlation coefficient 1.00.

III.C.2. Free Energy

Plots of experimental free energy of hydration, ΔG_{Hyd}, versus total CN (Tables III.1-8, Figures III.1-7) and total CN as well as hydrocarbon and functional group CN versus ΔG_{Hyd} (Tables III.1-8, Figures III.8-15) were made to explore the relationship between CN and experimental hydration free energy. Tables III.10 and III.12 list the slope (m), intercept (b), standard deviation (s) and correlation coefficient (r) least squares regression parameters for each series of plots. Internal methylene, hydrocarbon and functional group average contributions to ΔG_{Hyd} per water molecule appear in Table III.11; all averages were calculated subject to the statistical Q test.

ΔG_{Hyd} versus total CN plots for alkanes, alcohols, amines, esters, ethers and ketones produce straight lines of positive slope with high correlation coefficient ($\geq$ 0.98). Thus, there is strong linear correlation between ΔG_{Hyd} and total CN. Moreover, the positive slope is a manifestation of the progressive destabilizing trend in ΔG_{Hyd} for each homologous series due to the increasing number of CH_2 groups and their associated waters.

The destabilization phenomenon appears clearly in CN versus ΔG_{Hyd} plots where we decompose total CN into hydrocarbon and functional group contributions. For the ethane through hexane series, total CN increases while the change in CH_2 CN is constant with an average CN per CH_2 unit of 3.04$\pm$0.15 water molecules (Table III.1, Figure III.8). Coordination number decomposition plots for the remaining series appear in Figures III.9-15, Table III.12. In all series, slopes of the hydrocarbon and total CN lines are essentially equal, whereas those for functional group are virtually zero and indicative of little or no change in CN. Thus, the principal contribution to hydration destabilization lays in the changes in hydrocarbon coordination with the addition of methylene groups.

The average methylene coordination increment over the seven series is constant at 3.03$\pm$0.17 water molecules, and alkane CH_2 contribution to ΔG_{Hyd} per CH_2 water molecule is a positive quantity and constant at an average 0.04$\pm$0.00 kcal/mol, whereas there is widespread fluctuation in CH_2 free energy

per water molecule for nonalkanes (Table III.11). The slopes of the hydrocarbon CN versus ΔG_{Hyd} plots reflect this fluctuation in their range from a low of 13.61 in the alkanacetates to 27.66 in alkyl amines (Table III.12). Decomposition of ΔG_{Hyd} into ΔG_{Hyd} per water molecule for methylene group, hydrocarbon and functional group over all series, shows the free energy destabilization per water molecule ranges from 0.02 to 0.09 kcal/mol for CH_2 and 0.03 to 0.08 kcal/mol for hydrocarbon, while functional group free energy stabilization per water molecule ranges from -0.09 to -8.21 kcal/mol (Table III.11).

Alkane, alcohol, amine, ether and ketone ΔG_{Hyd} versus CN plots show deviations from the regression lines. Generally, branched species produce positive deviations whereas those due to cyclization are negative. Structural isomer pairs of straight and branched species place the branched member at more positive ΔG_{Hyd} and lower CN values relative to its straight chain analog on the regression line. Examples include: isopentane - pentane, neopantane - pentane, isohexane -hexane (Table III.1, Figure III.1, points 7-4,10-4,8-5); 2-methyl-1-propanol -butanol (Table III.2, Figure III.2, points 11-4); 3-methyl-2-butanone - 2-pentanone (Table III.7, Figure III.6, points 8-3); see Figures III.2 and III.6 for additional examples. Cyclization reduces molecular size and CN relative to straight chain analogues; and, ΔG_{Hyd} experiences a decrease with cyclization in all series: cycloalkanes, tetrahydrofurans, cycloalcohols and pyridines.

Functional group placement changes from terminal to internal carbons have a mixed effect on CN and tend to increase ΔG_{Hyd}. For example: 1, 2- and 3-pentanol have virtually identical CN's whereas 2 and 3-pentanol have slightly higher ΔG_{Hyd} (Table III.2, Figure III.2, points 5-8-9); on the other hand, 3-hexanol has both higher CN and ΔG_{Hyd} than 1-hexanol (Table III.2, Figure III.2, points 10-6); and 2-butanol has a slightly lower CN and higher ΔG_{Hyd} than 1-butanol (Table III.2, Figure III.2, points 7-4).

Finally, Table III.8, Figure III.7 present the effects of methylation on aromatic ring CN and ΔG_{Hyd}. Three bands appear on the ΔG_{Hyd} versus total CN plot: substituted benzenes (top), substituted naphthalenes (middle) and phenanthrene and pyrene. Methyl substitution increases CN significantly and has a nominal effect on ΔG_{Hyd}: of the substituted benzenes, propyl and butyl benzene show substantive energetic destabilization (Table III.8, Figure III.7, points 3-4) relative to benzene (Table III.8, Figure III.7, point 9) and disubstituted naphthalenes are slightly more stable (Table III.8, Figure III.7, points 12-15) than the unsubstituted or mono substituted naphthalenes (Table III.8, Figure III.7, points 10-11); however, no trend is apparent at this point.

III.D. Conclusions

The seven classes of prototype molecules simulated elucidate several trends: there is a strong linear correlation between ΔG_{Hyd} and total CN; the

average correlation coefficient over all series is 0.99. Beyond this, total ΔG_{Hyd} and hydrocarbon ΔG_{Hyd} are proportional to their CN counterparts in the straight chains. Moreover, functional group CN remains constant within each series.

Each CH_2 addition to a linear chain produces a constant average increase in total CN of 3.03 ± 0.17 water molecules over all series. However, overall CH_2 ΔG_{Hyd} per CH_2 water molecule is unstable at an average 0.05 ± 0.02 kcal/mol. On the other hand, functional group, hydrocarbon and CH_2 ΔG_{Hyd} per water molecule remain constant within each series.

Clearly, CN simulation is a quick, valuable tool for delineating a measurable quantity, ΔG_{Hyd}, with unprecedented speed and accuracy and thoroughness heretofore unknown without a formidable time investment.

Table III.1

Alkane Hydration Coordination Numbers

No.	Molecule	ΔG_{Hyd}[a]	Coordination Number (CH_3)[b]	(HC)[c]	(Total)
1	Ethane	1.83			20.13
2	Propane	1.96			23.21
3	Butane	2.08			26.15
4	Pentane	2.33			29.06
5	Hexane	2.49			32.30
6	Isobutane	2.32	7.85	17.45	25.30
7	Isopentane	2.38	7.02	19.98	26.99
8	Isohexane	2.52	6.96	22.90	29.85
9	3-Methylpentane	2.51	7.06	22.73	29.79
10	Neopentane	2.50	13.67	13.86	27.53
11	2,2-Dimethylbutane	2.59	12.03	17.46	29.49
12	Cyclopropane	0.75			21.59
13	Cyclopentane	1.20			26.39
14	Cyclohexane	1.23			28.61
15	Cycloheptane	0.80			30.29

a. Experimental free energy of hydration in Kcal/mole (Reference 19).
b. Coordination number for branching methyl group(s).
c. HC = Hydrocarbon.

Table III.2

Alcohol Hydration Coordination Numbers

No.	Molecule	ΔG_{Hyd}[a]	Coordination Number (OH)	(HC)[b]	(Total)
1	Methanol	-5.12	2.98	11.48	14.46
2	Ethanol	-5.02	2.19	16.01	18.20
3	1-Propanol	-4.83	2.33	18.94	21.27
4	1-Butanol	-4.72	2.42	22.05	24.47
5	1-Pentanol	-4.48	2.27	24.98	27.25
6	1-Hexanol	-4.37	2.42	28.02	30.44
7	2-Butanol	-4.58	1.98	22.40	24.38
8	2-Pentanol	-4.39	1.93	25.28	27.21
9	3-Pentanol	-4.36	1.65	25.63	27.28
10	3-Hexanol	-4.08	1.56	29.38	30.94
11	2-Methyl-1-Propanol	-4.53	1.85	21.22	23.07
12	3-Methyl-1-Butanol	-4.42	2.35	23.34	25.69
13	2-Methyl-2-Butanol	-4.43	1.72	24.73	26.45
14	2-Methyl-2-Pentanol	-3.93	1.78	27.02	28.80
15	4-Methyl-2-Pentanol	-3.74	1.98	26.20	28.17
16	2-Methyl-3-Pentanol	-3.89	1.93	25.55	27.47
17	2,3-Dimethyl-2-Butanol	-3.92	1.47	26.23	27.71
18	Cyclopentanol	-5.50	2.67	22.60	25.28
19	Cyclohexanol	-5.48	2.32	24.87	27.18

a. Experimental free energy of hydration in Kcal/mole (Reference 19).
b. HC = Hydrocarbon.

Table III.3

Amine Hydration Coordination Numbers

No.	Molecule	ΔG_{Hyd}[a]	Coordination Number (NH_n)[b]	(HC)[c]	(Total)
1	Methylamine	-4.56	2.42	10.93	13.35
2	Ethylamine	-4.50	2.16	15.08	17.24
3	Propylamine	-4.39	2.19	18.05	20.25
4	Butylamine	-4.30	2.22	21.20	23.42
5	Pentylamine	-4.10	2.16	23.97	26.13
6	Hexylamine	-4.03	2.14	27.50	29.64
7	Dimethylamine	-4.29	1.30	18.84	20.14
8	Diethylamine	-4.07	0.57	27.19	27.76
9	Dipropylamine	-3.66	0.71	33.53	34.24
10	Dibutylamine	-3.33	0.62	39.32	39.94
11	Pyridine	-4.70	2.37	18.50	20.88
12	2-Methylpyridine	-4.63	1.52	23.92	25.44
13	3-Methylpyridine	-4.77	2.40	23.01	25.41
14	2-Ethylpyridine	-4.33	1.32	26.21	27.93
15	3-Ethylpyridine	-4.60	2.37	25.98	28.35
16	2,3-Dimethylpyridine	-4.83	1.54	26.94	28.49
17	3,5-Dimethylpyridine	-4.84	2.39	27.03	29.42
18	2,4-Dimethylpyridine	-4.87	1.35	28.34	29.69

a. Experimental free energy of hydration in Kcal/mole (Reference 19).
b. NH_n represents the functional group.
c. HC = Hydrocarbon.

Table III.4

Alkanacetate Hydration Coordination Numbers

No.	Molecule	ΔG_{Hyd}[a]	Coordination Number (CH_3COO)	(R)[b]	(Total)
1	Methylacetate	-3.32	13.88	10.51	24.39
2	Ethylacetate	-3.10	13.11	14.67	27.78
3	Propylacetate	-2.86	13.33	17.63	30.96
4	Butylacetate	-2.55	13.08	20.71	33.80

a. Experimental free energy of hydration in Kcal/mole (Reference 19).
b. R = Alkyl group.

Table III.5

Alkanoate Hydration Coordination Numbers

No.	Molecule	ΔG_{Hyd}[a]	Coordination Number (COOR)[b]	(HC)[c]	(Total)
1	Methylacetate	-3.32	13.77	10.62	24.39
5	Methylpropanoate	-2.93	12.86	15.11	27.97
6	Methylbutanoate	-2.83	13.06	17.83	30.89
7	Methylpentanoate	-2.57	12.82	20.93	33.75
8	Ethylpropanoate	-2.80	16.65	14.42	31.07
9	Propylpropanoate	-2.46	20.00	14.43	34.43
10	Pentylpropanoate	-1.99	25.53	14.78	40.31
11	Ethylbutanoate	-2.50	16.65	17.57	34.23
12	Propylbutanoate	-2.28	19.94	17.84	37.79

a. Experimental free energy of hydration in Kcal/mole (Reference 19).
b. R = Alkyl group.
c. HC = Hydrocarbon.

Table III.6

Ether Hydration Coordination Numbers

No.	Molecule	ΔG_{Hyd}[a]	Coordination Number (-O-)	(HC)[b]	(Total)
1	Methylether	-1.90	1.39	19.50	20.89
2	Ethylether	-1.64	0.27	28.13	28.39
3	Propylether	-1.15	0.30	34.35	34.64
4	Butylether	-0.83	0.34	40.69	41.02
5	Methylpropylether	-1.66	0.84	26.67	27.51
6	Tetrahydrfuran	-3.47	1.23	23.49	24.72
7	2-Methyltetrahydrofuran	-3.30	0.92	26.44	27.45
8	2,5-Dimethyltetrahydrofuran	-2.92	0.80	29.19	29.98

a. Experimental free energy of hydration in Kcal/mole (Reference 19).
b. HC = Hydrocarbon.

Table III.7

Ketone Hydration Coordination Numbers

No.	Molecule	ΔG_{Hyd}[a]	Coordination Number (C=O)	(HC)[b]	(Total)
1	Acetone	-3.85	3.34	18.93	22.27
2	2-Butanone	-3.64	2.42	23.17	25.59
3	2-Pentanone	-3.53	2.41	26.17	28.58
4	2-Hexanone	-3.29	2.53	29.17	31.69
5	2-Heptanone	-3.04	2.40	32.40	34.80
6	3-Pentanone	-3.41	1.54	27.81	29.35
7	4-Heptanone	-2.93	1.70	33.37	35.07
8	3-Methyl-2-butanone	-3.24	2.33	24.80	27.13
9	4-Methyl-2-pentanone	-3.06	1.72	28.50	30.22
10	2,4-Dimethyl-3-pentanone	-2.74	1.41	31.10	32.51

a. Experimental free energy of hydration in Kcal/mole (Reference 19).
b. HC = Hydrocarbon.

Table III.8

Aromatic Hydration Coordination Numbers

No.	Molecule	ΔG_{Hyd}[a]	Coordination Number (R)[b]	(HC)[c]	(Total)
1	Toluene	-0.89	16.14	9.31	25.45
2	Ethylbenzene	-0.80	14.77	13.54	27.31
3	Propylbenzene	-0.53	14.90	16.65	31.56
4	Butylbenzene	-0.40	14.89	19.46	34.35
5	o-Xylene	-0.90	12.72	15.73	28.45
6	m-Xylene	-0.84	11.20	18.46	29.67
7	p-Xylene	-0.81	11.20	18.37	29.58
8	1,2,4-Trimethylbenzene	-0.86	7.79	25.06	32.85
9	Benzene	-0.87	20.90	0.0	20.90
10	Naphthalene	-2.39	26.74	0.0	26.74
11	1-Methylnaphthalene	-2.37	22.41	8.06	30.47
12	1,3-Dimethylnaphthalene	-2.47	17.22	17.39	34.61
13	1,4-Dimethylnaphthalene	-2.82	17.32	16.41	33.72
14	2,3-Dimethylnaphthalene	-2.78	18.28	15.68	33.96
15	2,6-Dimethylnaphthalene	-2.63	17.36	17.32	34.68
16	Phenanthrene	-3.95	31.41	0.0	31.41
17	Pyrene	-4.47	32.64	0.0	32.64

a. Experimental free energy of hydration in Kcal/mole (Reference 19).
b. R = Aryl group.
c. HC = Hydrocarbon.

Table III.9

Alcohol Coordination Number Decomposition

		CH_2								
Molecule	**OH**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**CH_3**	**Total**
Methanol	2.98								11.48	14.46
Ethanol	2.19	5.97							10.04	18.20
Propanol	2.33	4.77	5.53						8.74	21.27
Butanol	2.42	4.76	4.10	4.32					8.86	24.47
Pentanol	2.27	4.78	4.16	3.02	4.14				8.89	27.25
Hexanol	2.42	4.86	4.03	3.21	3.06	4.17			8.75	30.44
Octanol	2.39	4.67	3.98	3.06	3.00	2.94	3.02	4.22	8.92	36.33

Table III.10

Regression Parameters For ΔG_{Hyd} vs Total Coordination Number

Series	m[a] (Kcal/mol-H_2O)	b[b] (Kcal/mol)	s[c]	r[d]
Ethane - Hexane	0.05592	0.6744	0.04195	0.9909
Methanol - Hexanol	0.04991	-5.8836	0.04802	0.9895
Methyl - Hexylamine	0.03508	-5.0736	0.04814	0.9794
Methyl - Butylacetate	0.08088	-5.3216	0.04836	0.9928
Methyl - Butylether	0.05521	-3.1045	0.08686	0.9891
Acetone - 2-Heptanone	0.06323	-5.2777	0.04451	0.9924

a. Slope.
b. Intercept.
c. Standard deviation.
d. Correlation coefficient.

Table III.11

Average Functional Group Contributions to ΔG_{Hyd}

Series	Group	CH_2/H_2O^a	HC/H_2O^b	$Group/H_2O^c$
			(Kcal/mol)	
Alkane		0.04±0.00		
Alcohol	OH	0.03±0.02	0.06±0.00	-2.38±0.25
Amine	NH_2	0.02±0.01	0.03±0.00	-2.25±0.11
Ester	CH_3COO	0.06±0.02	0.08±0.00	-3.15±0.01
	$COOCH_3$	0.07±0.00	0.07±0.00	-0.31±0.01
Ether	-O-	0.09±0.03	0.05±0.00	-8.21±1.42
Ketone	C=O	0.05±0.02	0.06±0.00	-1.96±0.26
Aromatic	C_6H_5	0.04±0.03	0.05±0.00	-0.09±0.01
Average		**0.05±0.02**		

a. Hydration free energy per water molecule associated with a methylene group.

b. Hydration free energy per water molecule associated with the hydrocarbon chain.

c. Hydration free energy per water molecule associated with the functional group.

Table III.12

Regression Parameters For Coordination Number versus ΔG_{Hyd}

Series	m[a] (H_2O/Kcal/mol)	b[b] (H_2O)	s[c]	r[d]
Ethane - Hexane				
(Total)	17.56	-11.37	0.7432	0.9909
(CH_2)	-0.62	4.50	0.3531	0.4767
Methanol - Hexanol				
(Total)	19.07	116.89	0.9424	0.9897
(Hydrocarbon)	20.22	116.42	1.1288	0.9849
(OH)	-0.41	-0.48	0.2841	0.4313
Methyl - Hexylamine				
(Total)	27.34	139.61	1.3439	0.9794
(Hydrocarbon)	27.66	138.78	1.4020	0.9782
(NH_2)	-0.32	0.83	0.0888	0.6529
Methyl - Butylacetate				
(Total)	12.19	65.28	0.5937	0.9928
(Hydrocarbon)	13.61	54.36	0.8016	0.9886
(CH_3COO)	-0.82	10.91	0.3079	0.7347
Methylacetate - Methylpentanoate				
(Total)	12.66	66.12	0.8933	0.9833
(Hydrocarbon)	13.92	56.68	0.6844	0.9918
($COOCH_3$)	-1.27	9.44	0.2417	0.8941
Acetone - 2-Heptanone				
(Total)	15.58	82.64	0.6986	0.9924
(Hydrocarbon)	16.43	82.99	0.9139	0.9884
(C=O)	-0.86	-0.36	0.3497	0.6642
Toluene - Butylbenzene				
(Total)	17.61	41.20	0.3007	0.9981
(Hydrocarbon)	18.44	26.82	1.3280	0.9685
(C_6H_5)	-1.76	14.02	0.4856	0.6229

a. Slope.
b. Intercept.
c. Standard deviation.
d. Correlation coefficient.

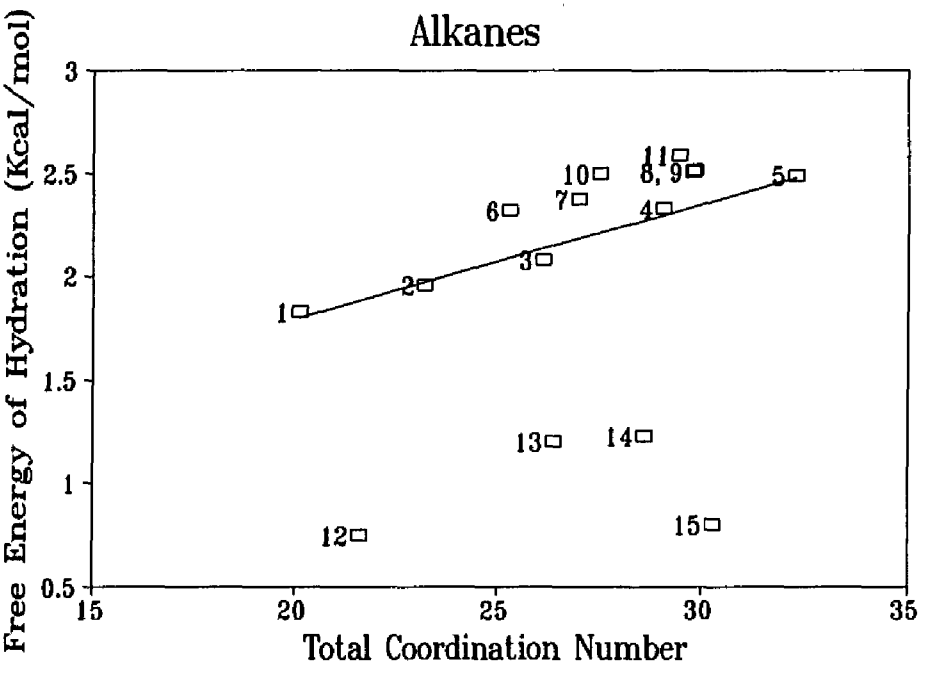

Figure III.1 Alkanes. Solid line represents least squares fit of total free energy of hydration and total coordination number for straight chain alkanes. Refer to Table III.1 for molecule identification and associated data.

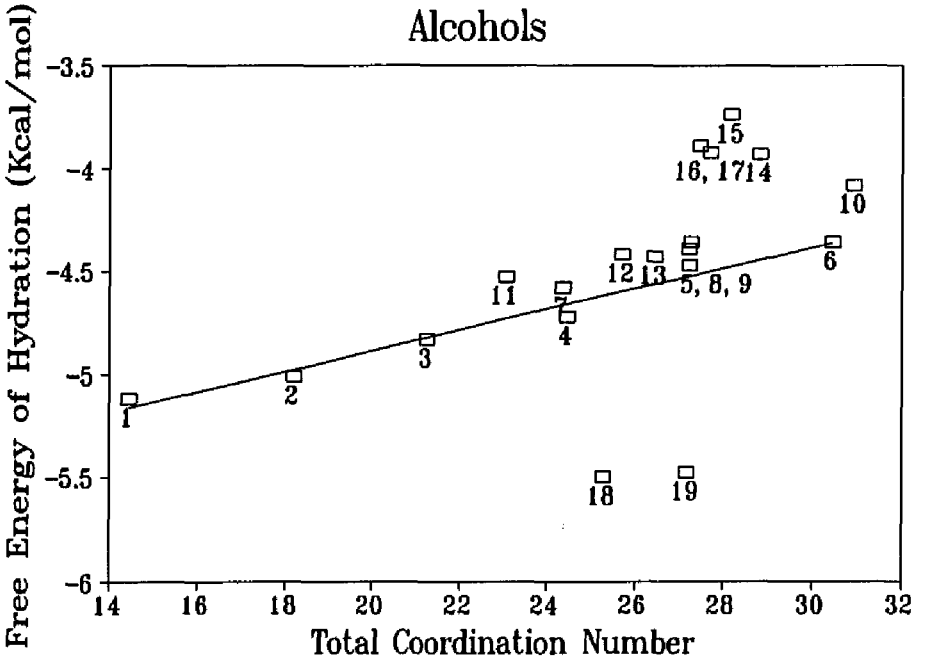

Figure III.2 Alcohols. Solid line represents least squares fit of total free energy of hydration and total coordination number for alkan-1-ols. Refer to Table III.2 for molecule identification and associated data.

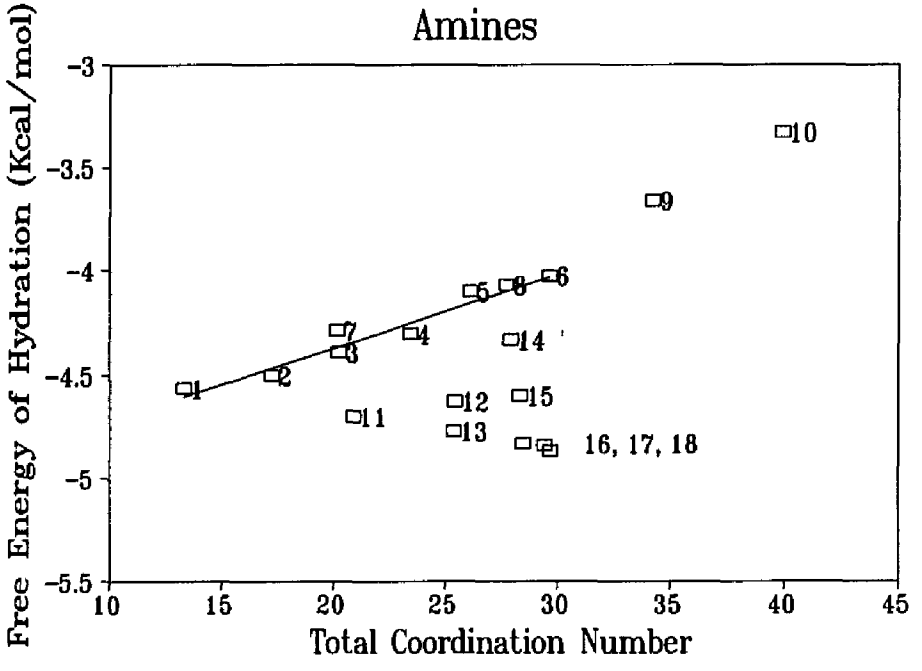

Figure III.3 Amines. Solid line represents least squares fit of total free energy of hydration and total coordination number for primary amines. Refer to Table III.3 for molecule identification and associated data.

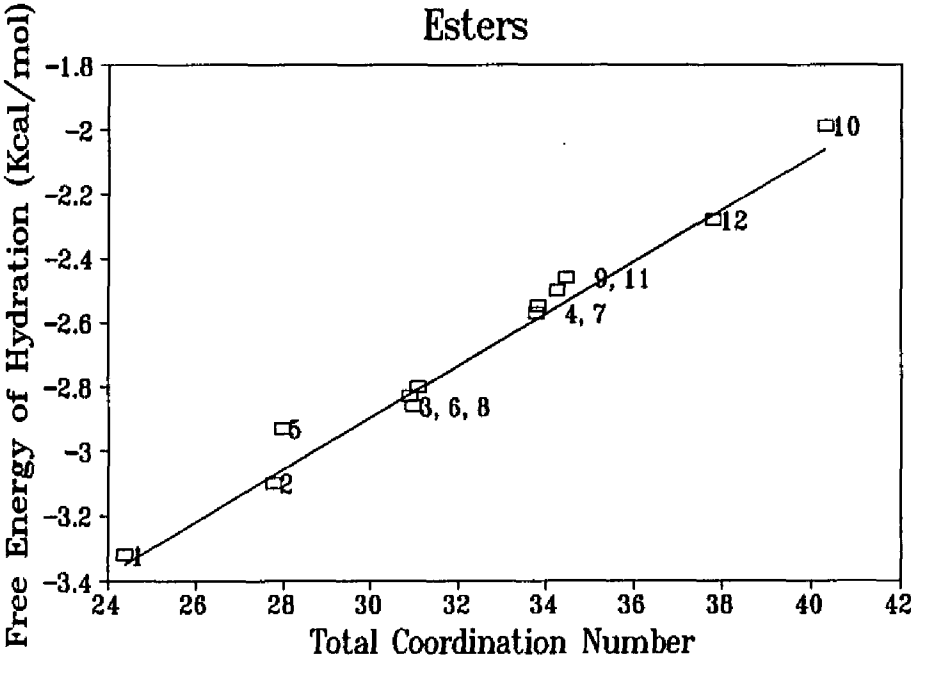

Figure III.4 Esters. Solid line represents least squares fit of total free energy of hydration and total coordination number for alkanacetates. Refer to Tables III.4 and III.5 for molecule identification and associated data.

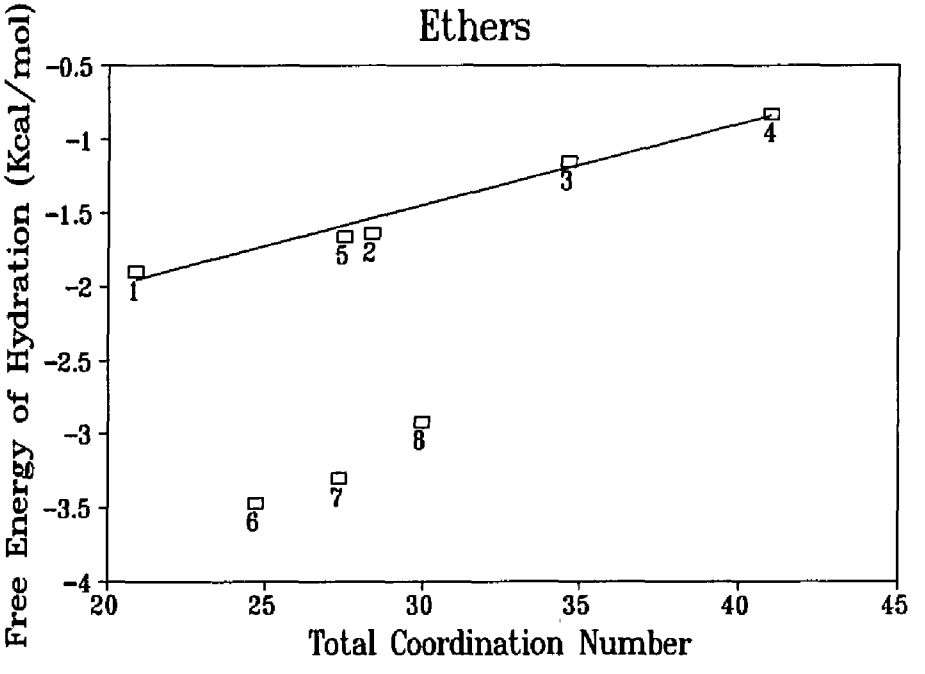

Figure III.5 Ethers. Solid line represents least squares fit of total free energy of hydration and total coordination number for symmetric ethers. Refer to Table III.6 for molecule identification and associated data.

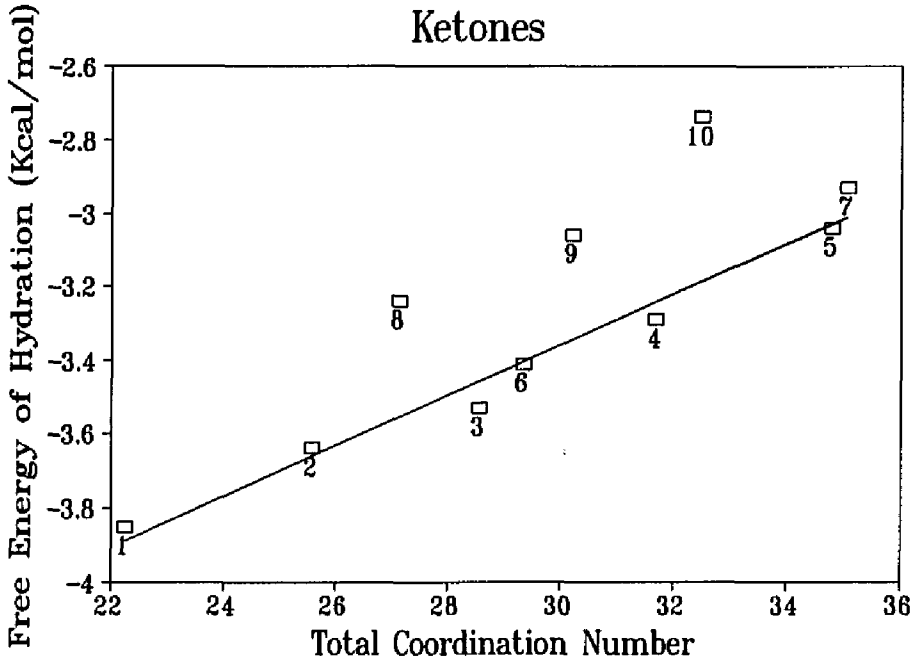

Figure III.6 Ketones. Solid line represents least squares fit of total free energy of hydration and total coordination number for alkan-2-ones. Refer to Table III.7 for molecule identification and associated data.

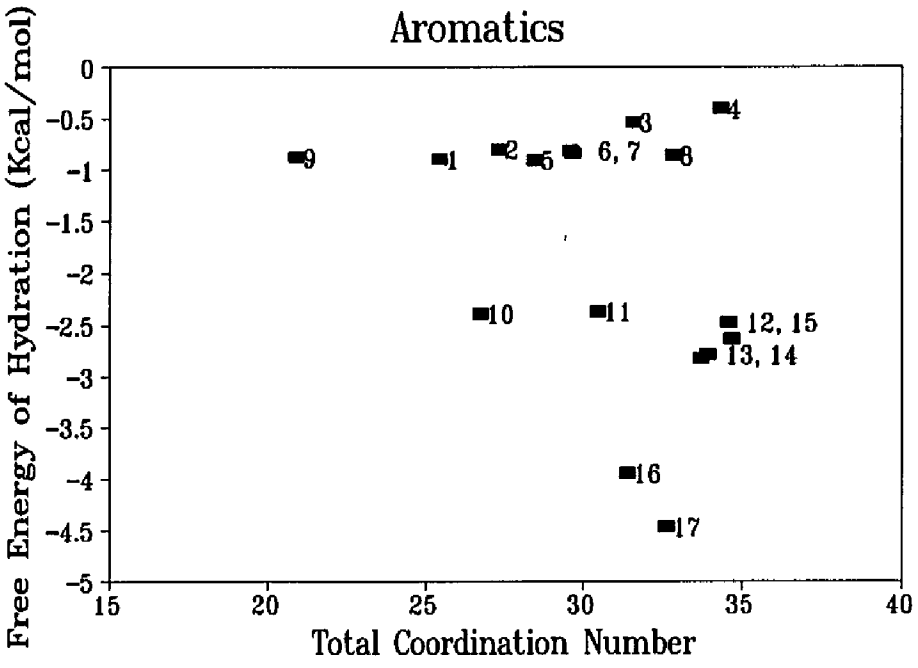

Figure III.7 Aromatics. Refer to Table III.8 for molecule identification and associated data.

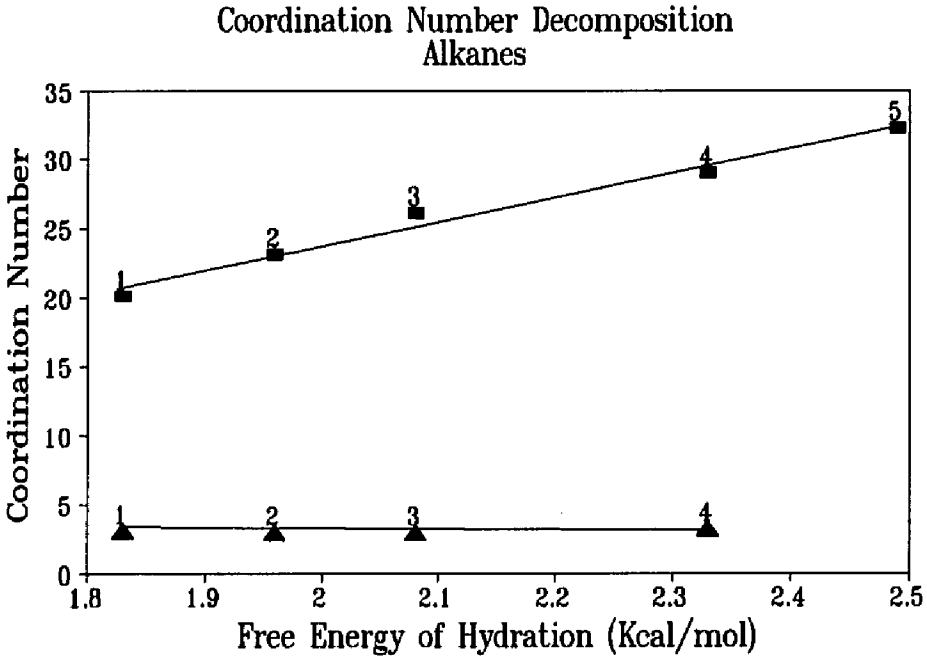

Figure III.8 Alkane Coordination Number Decomposition. Total coordination number (square), methylene increment (triangle) and fitted equations (solid lines) for straight chain alkanes. Data is from Table III.1.

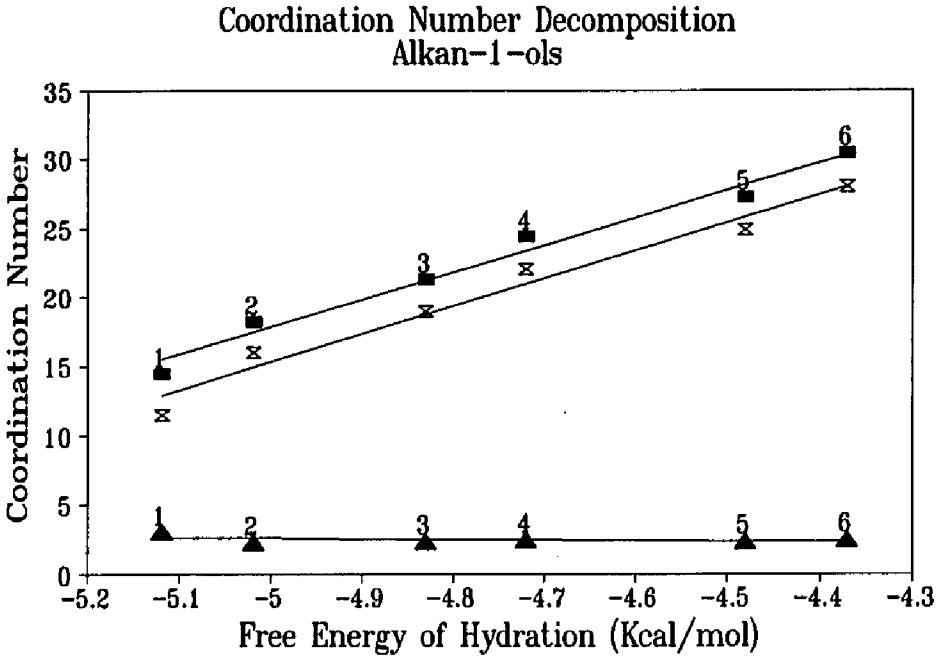

Figure III.9 Alkan-1-ol Coordination Number Decomposition. Total (square), hydrocarbon (hourglass), functional group (triangle) data and fitted equations (line) for straight chain alcohols. Data is from Table III.2.

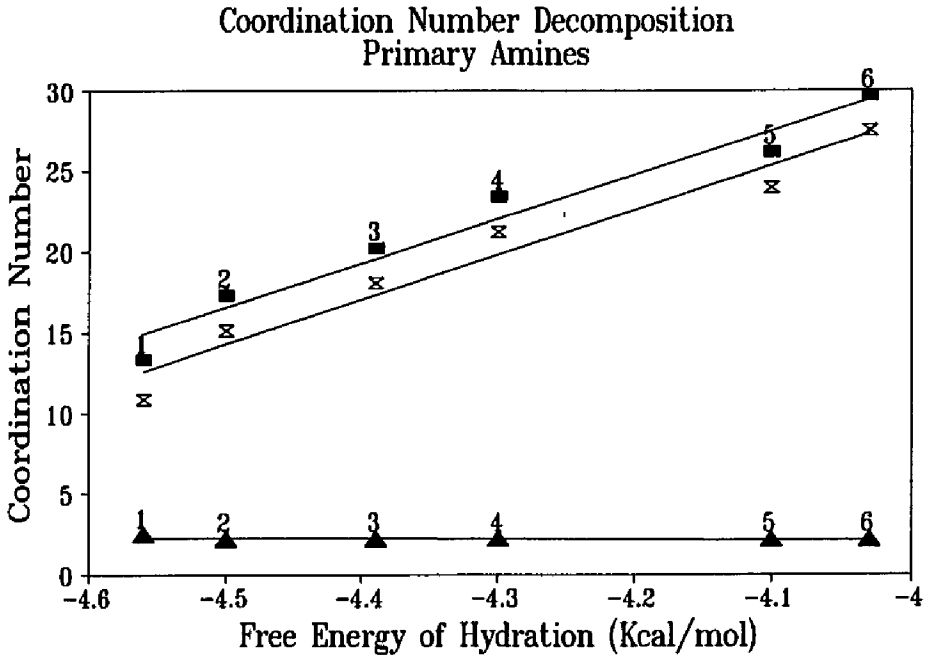

Figure III.10 Primary Amine Coordination Number Decomposition. Refer to Figure III.9 caption for details. Data is from Table III.3.

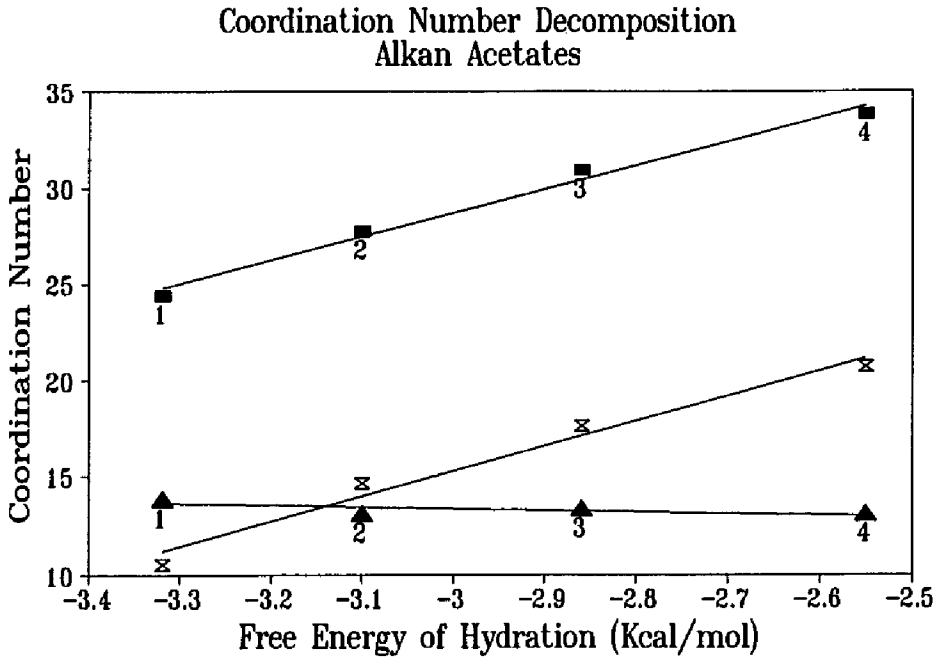

Figure III.11 Alkanacetate Coordination Number Decomposition. Refer to Figure III.9 caption for details. Data is from Table III.4.

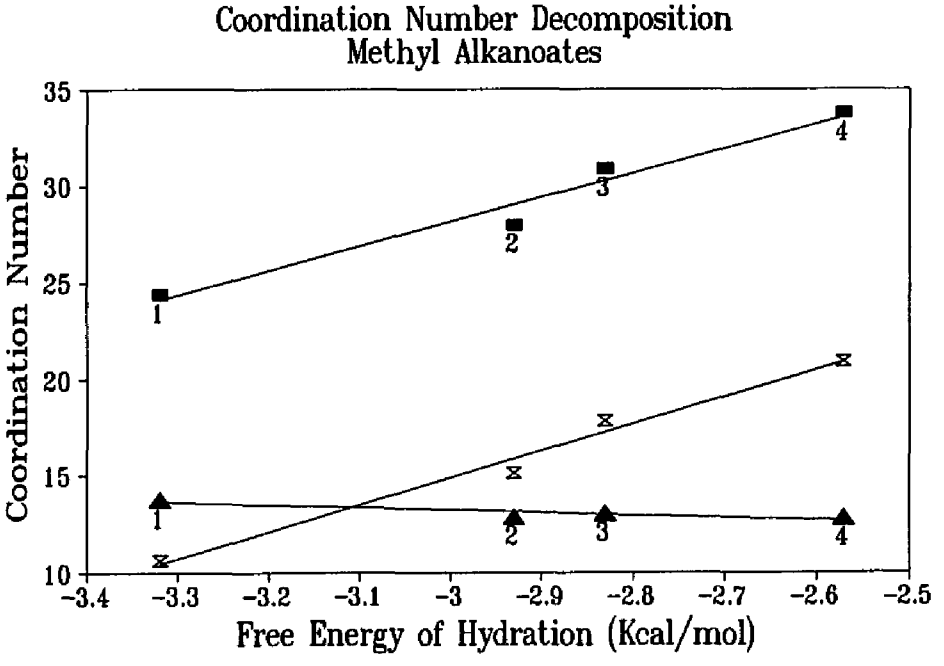

Figure III.12 Methyl Alkanoate Coordination Number Decomposition. Refer to Figure III.9 caption for details. Data is from Table III.5.

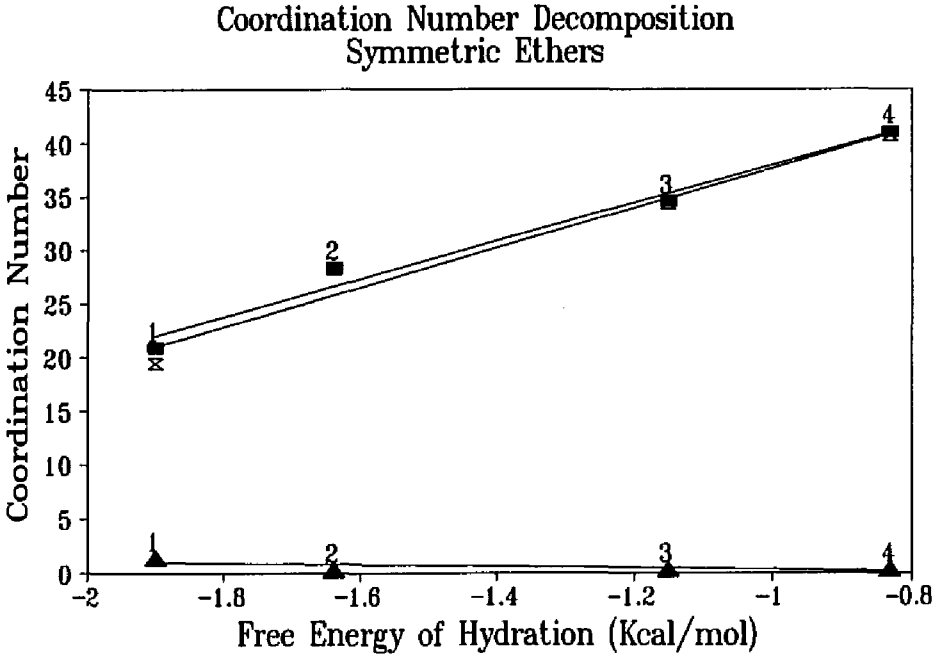

Figure III.13 Symmetric Ether Coordination Number Decomposition. Refer to Figure III.9 caption for details. Data is from Table III.6.

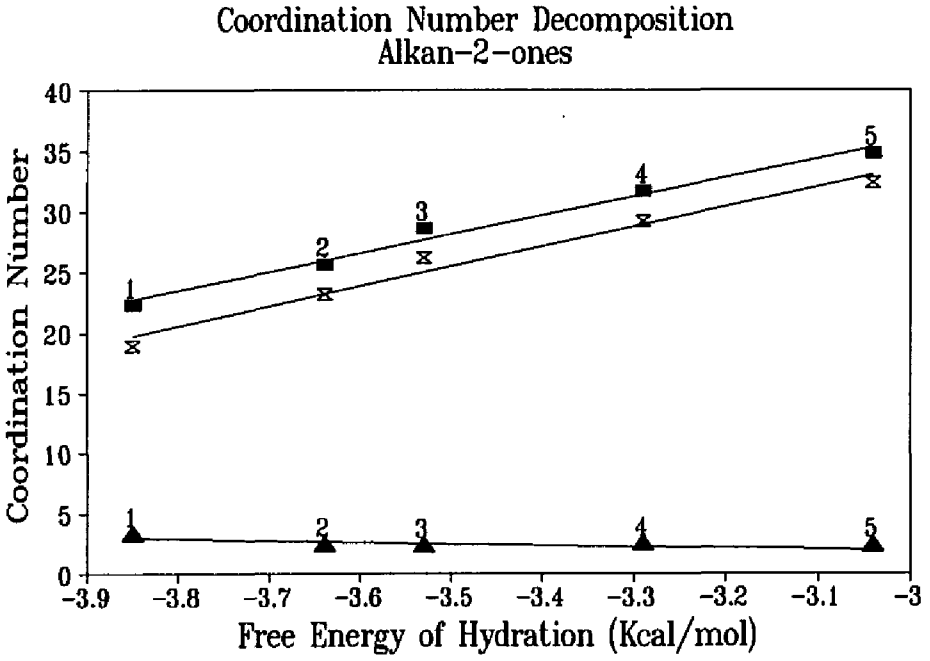

Figure III.14 Alkan-2-one Coordination Number Decomposition. Refer to Figure III.9 caption for details. Data is from Table III.7.

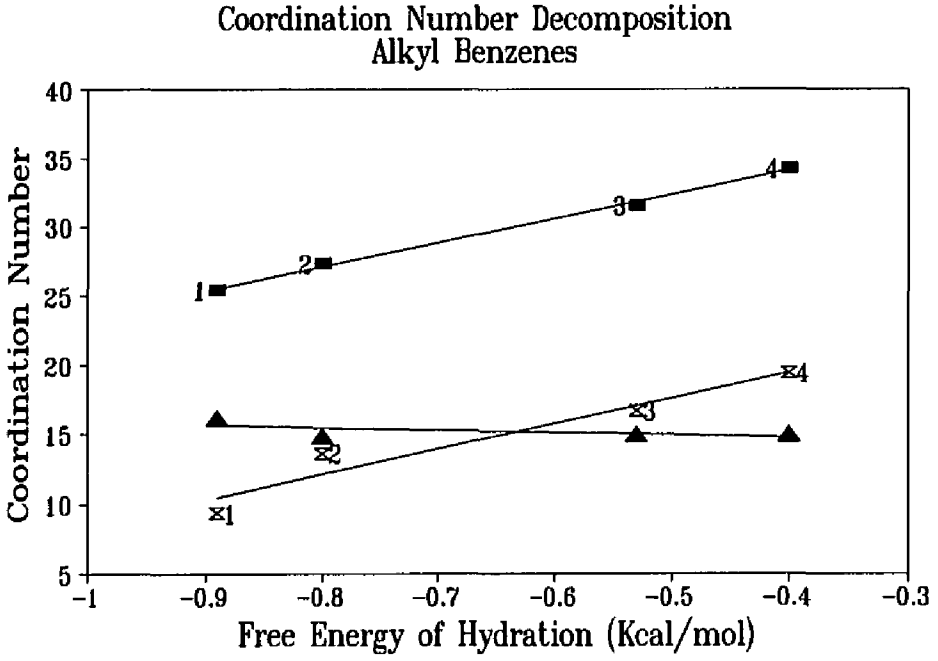

Figure III.15 Alkyl Benzene Coordination Number Decomposition. Refer to Figure III.9 caption for details. Data is from Table III.8.

Chapter IV

Amino Acid Coordination In Dilute Aqueous Solution

IV.A. Introduction

Proteins play a vital role in essentially all biological processes: enzymatic catalysis, oxygen transport, muscle contraction, immunity, nerve impulse generation and transmission and cell growth and differentiation control.[22] Proteins consist of at least one polypeptide chain; amino acids are the basic structural unit of polypeptides. A water molecule evolves each time a peptide bond forms between amino acid residues in the creation of a polypeptide. Moreover, most biological processes occur in water. Thus, the relationship between amino acids and water is of general interest.

The purpose of this chapter is to present the coordination number results of neutral amino acid simulations and relate them to the x-ray diffraction elucidated hydration patterns of amino acid residues in proteins by Thanki, *et al.*[23] Other experimental studies using alternative methods such as infrared spectrophotometry[24] and ultrasound[25] to examine amino acid hydration numbers exist; however, the amino acids are in zwitterionic form.

IV.B. Results and Discussion

Amino acid coordinates were extracted from those collected by Clementi, *et al.*[26] Analysis proceeds as follows: simulation gives coordination number at each atom; thus, group and total coordination number is a simple sum over atoms.

We use the CN model to delineate amino acid hydration and present overviews of simulation CN's followed by side chain, backbone, functional group and atom analysis.

The 20 neutral amino acid simulations show an overall average total CN of 21.25 $\pm$ 4.24 water molecules, average side chain CN of 13.25 $\pm$ 4.71 waters and average backbone CN of 8.00 $\pm$ 0.84 waters (Figures IV.1-20, Table IV.1). These are notably small fluctuations in total CN for molecules with vastly different side chains consisting of aliphatic, hydroxyl, aromatic, basic, acidic, secondary amino, amide and sulfur containing moieties.

Overall side chain methylene CN is 3.66 $\pm$ 0.96 water molecules. This is a remarkably small error bar for CH_2 environments encompassing the complete set of side chains and comparable to the average CH_2 CN of 3.03 $\pm$ 0.17 water molecules previously reported for a linear chain.[27] On the other hand, average side chain methyl CN in Ala, Val, Leu, Ile, Thr and Met is 7.37 $\pm$ 1.11 water molecules (Figures IV.2-5, IV.7, IV.20). Hydroxyl side chain CN at the OH of Ser, Thr and Tyr is 2.22 $\pm$ 0.51 water molecules (Figures IV.6, IV.7, IV.9) whereas acidic side chain CN at the COOH of Asp and Glu is 4.59 waters (Figures IV.14, IV.15), amide side chain CN at the $CONH_2$ of Asn and Gln is 4.32 waters (Figures IV.17, IV.18) and basic side chain CN at the NH_2 of Lys and Arg is 2.07 waters (Figures IV.11, IV.12).

Backbone CN decomposition by group reveals an average NH_2 CN of 1.93 $\pm$ 0.23 water molecules over the 20 amino acids. The average CN at the N of NH_2 is 0.30 $\pm$ 0.15 water molecules whereas average CN at each of the hydrogens of NH_2 is 0.80 $\pm$ 0.10 waters and 0.87 $\pm$ 0.40 waters respectively. Alpha carbon hydrogen average CN is 1.61 $\pm$ 0.42 water molecules and average CN for backbone COOH is 4.46 $\pm$ 0.49 waters. Average CN at the carbonyl carbon of COOH is 0.04 $\pm$ 0.03 water molecules, 2.51 $\pm$ 0.34 waters are at the carbonyl oxygen of COOH, 0.95 $\pm$ 0.32 waters at the carboxyl oxygen and 0.96 $\pm$ 0.10 waters at the carboxyl hydrogen.

Analysis of experimental x-ray diffraction hydration patterns[23] focuses on 16 best resolved protein structures. Generally, nitrogen, carbonyl, hydroxyl and carboxyl oxygen are common coordination sites in both x-ray diffraction and CN model results. The numbers of water molecules at each site however show no strict agreement. Moreover, the x-ray results evince no clear patterns for apolar side chains, whereas CN model produces an average CH_2 CN of 3.66 $\pm$ 0.96 waters for the entire amino acid series.

Janin,[28] Wolfendon, *et al.*,[29] Ghose and Crippen,[30] and Chothia[31] proposed hydrophobicity scales. Plots of amino acid total coordination number versus each scale reveal no obvious correlations.

IV.C. Conclusions

Fluctuations in the CN's over the 20 neutral amino acids are small relative to the differences in side chain composition: total CN deviates from the average by 20 percent whereas side chain CN deviates 36 percent and backbone 11 percent. Beyond this, side chain methylene CN deviates by 26 percent and is comparable to the CN for methylene in a linear chain; while side chain methyl CN fluctuates by 15 percent. Similarly, backbone group average CN shows little change over the 20 amino acids: average backbone NH_2 CN deviates 12 percent, alpha carbon hydrogen average CN 26 percent and average carboxylic acid functionality 11 percent.

Table IV.1

Coordination Number Decomposition[a]

Amino Acid	Backbone	NH_2	COOH	H	R[b]	Total
Gly	10.76	2.34	5.47	2.94	2.99	13.75
Ala	8.32	2.09	4.44	1.79	8.51	16.82
Val	6.80	1.92	3.70	1.18	14.94	21.73
Leu	7.04	1.92	4.30	0.82	16.95	24.00
Ile	7.14	1.82	4.21	1.11	17.28	24.42
Ser	8.06	1.86	4.39	1.81	7.39	15.45
Thr	8.59	2.04	5.29	1.25	9.85	18.44
Phe	7.39	1.74	3.93	1.71	18.14	25.53
Tyr	7.42	1.75	3.83	1.83	17.21	24.62
Trp	7.62	1.60	4.40	1.62	21.73	29.35
Lys	8.47	1.72	5.44	1.31	15.38	23.85
Arg	7.51	1.80	4.00	1.71	14.71	22.22
His	8.34	1.89	4.73	1.72	15.47	23.80
Asp	8.12	1.77	4.68	1.67	8.30	16.42
Glu	7.88	2.01	4.56	1.32	12.03	19.91
Pro	9.03	2.69	4.79	1.55	15.47	24.50
Asn	8.00	1.81	4.42	1.77	7.55	15.56
Gln	8.07	1.92	4.20	1.95	10.35	18.42
Cys	7.81	1.99	4.10	1.72	11.30	19.11
Met	7.57	1.86	4.31	1.40	19.48	27.05
Average	8.00	1.93	4.46	1.61	13.25	21.25
Standard Dev.	0.84	0.23	0.49	0.42	4.71	4.24

a. Coordination numbers represent average hydration.
b. Side chain.

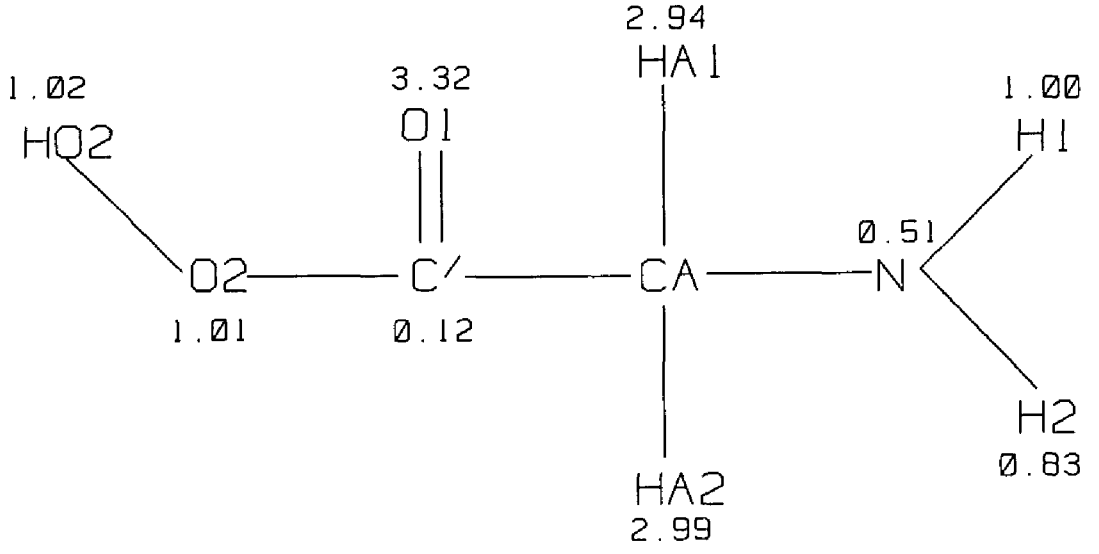

Figure IV.1 Coordination numbers per atom for glycine.

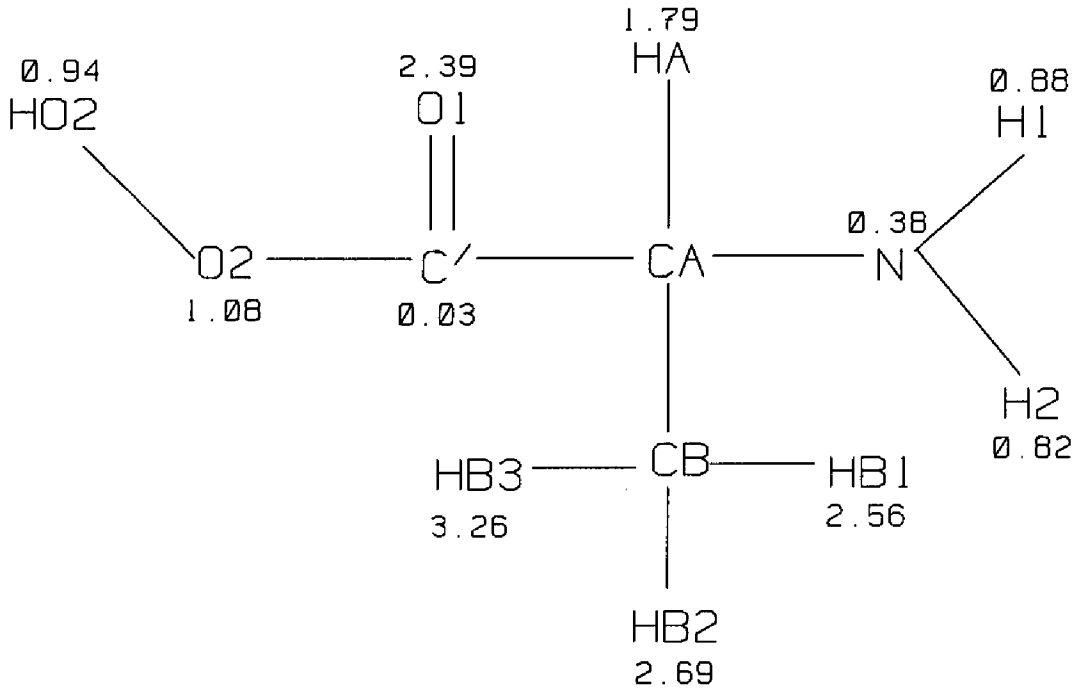

Figure IV.2. Coordination numbers per atom for alanine.

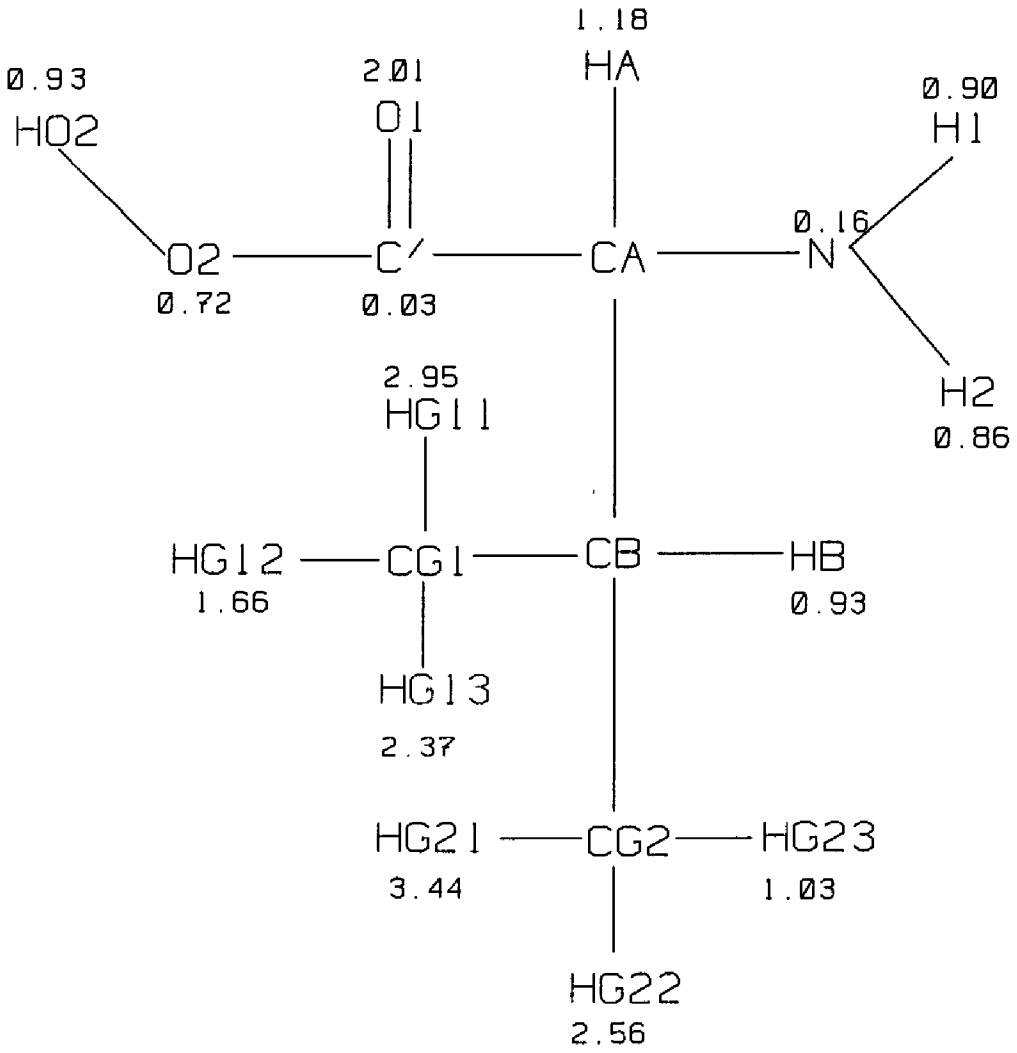

Figure IV.3. Coordination numbers per atom for valine.

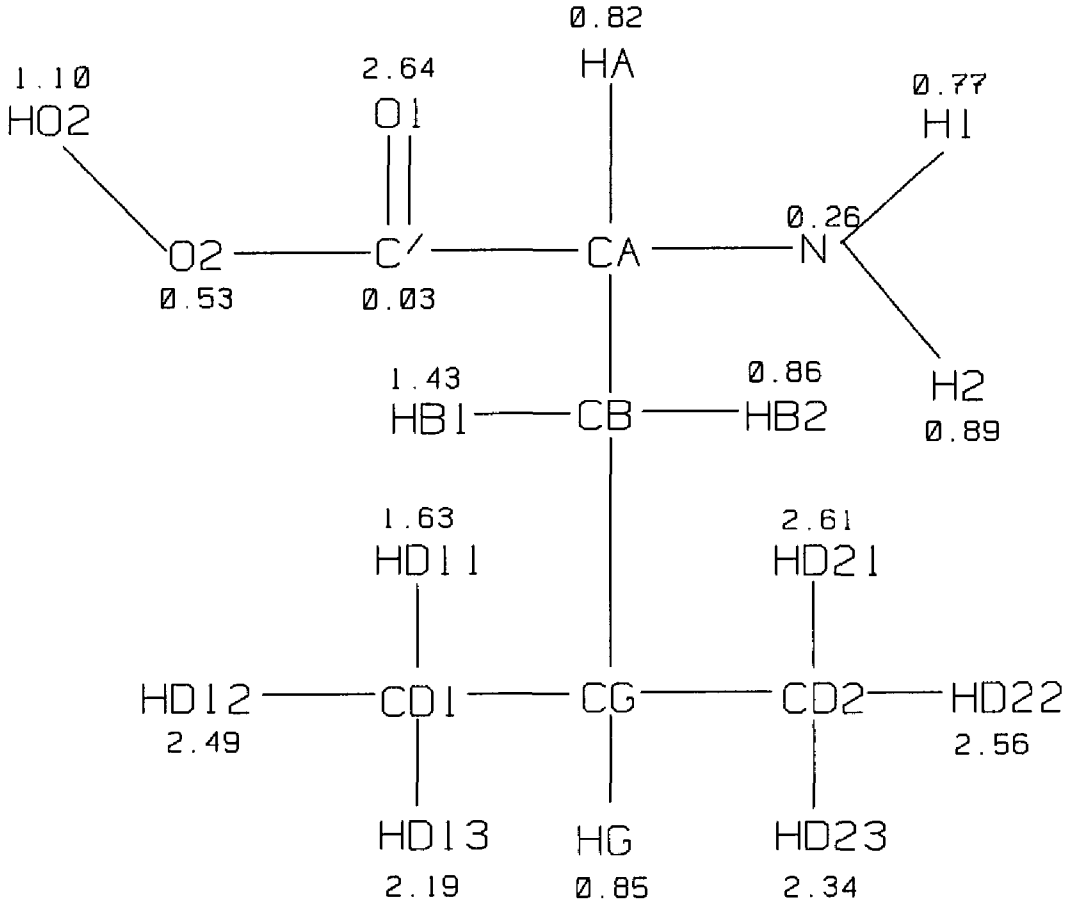

Figure IV.4. Coordination numbers per atom for leucine.

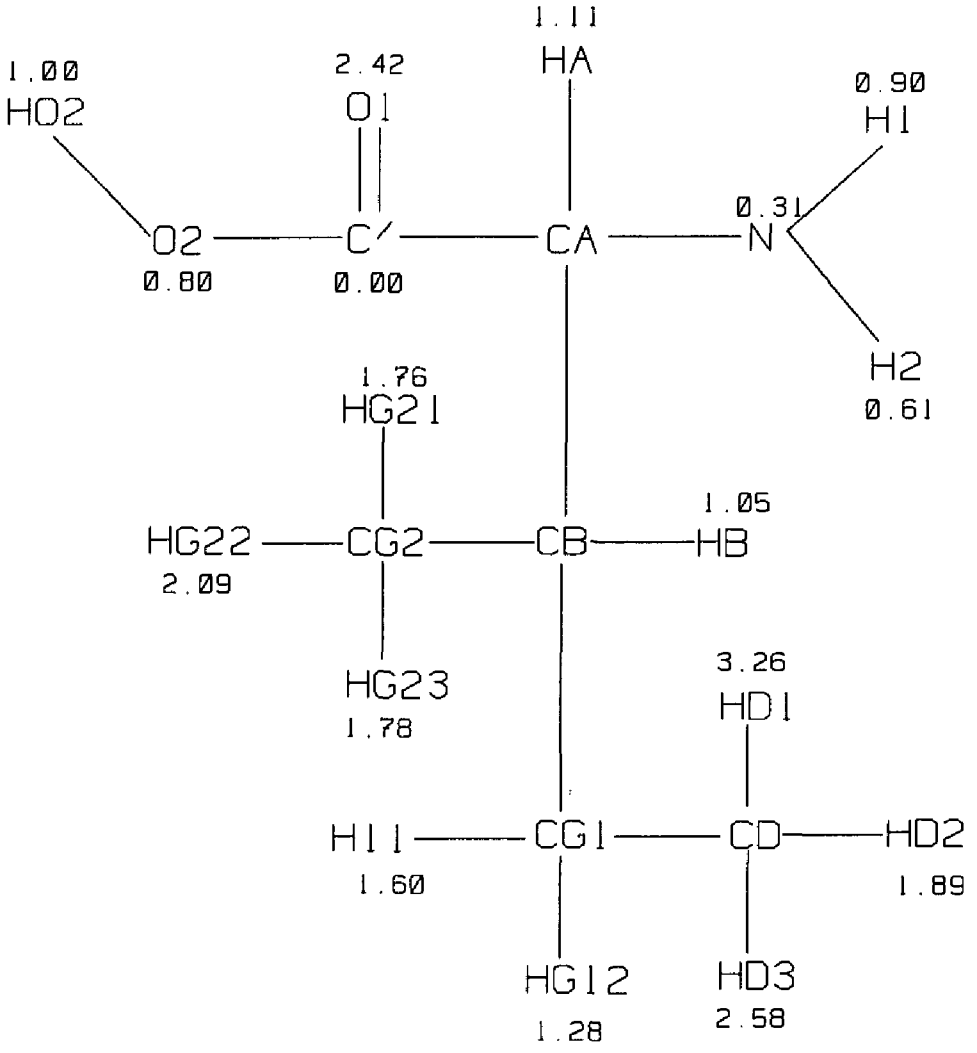

Figure IV.5. Coordination numbers per atom for isoleucine.

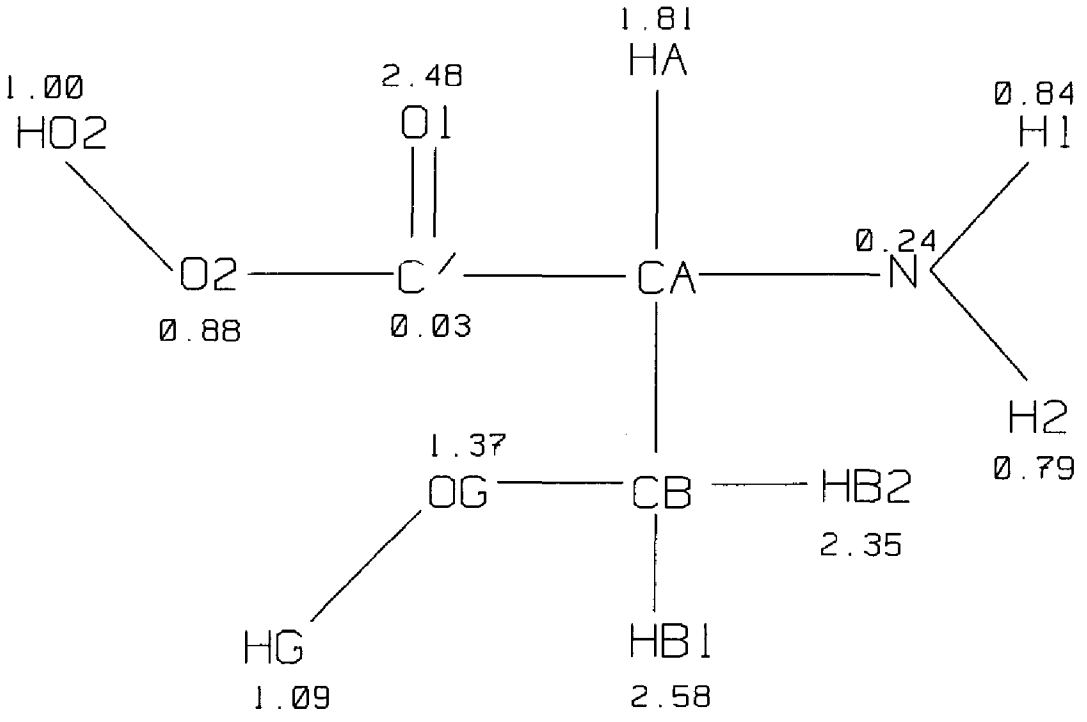

Figure IV.6. Coordination numbers per atom for serine.

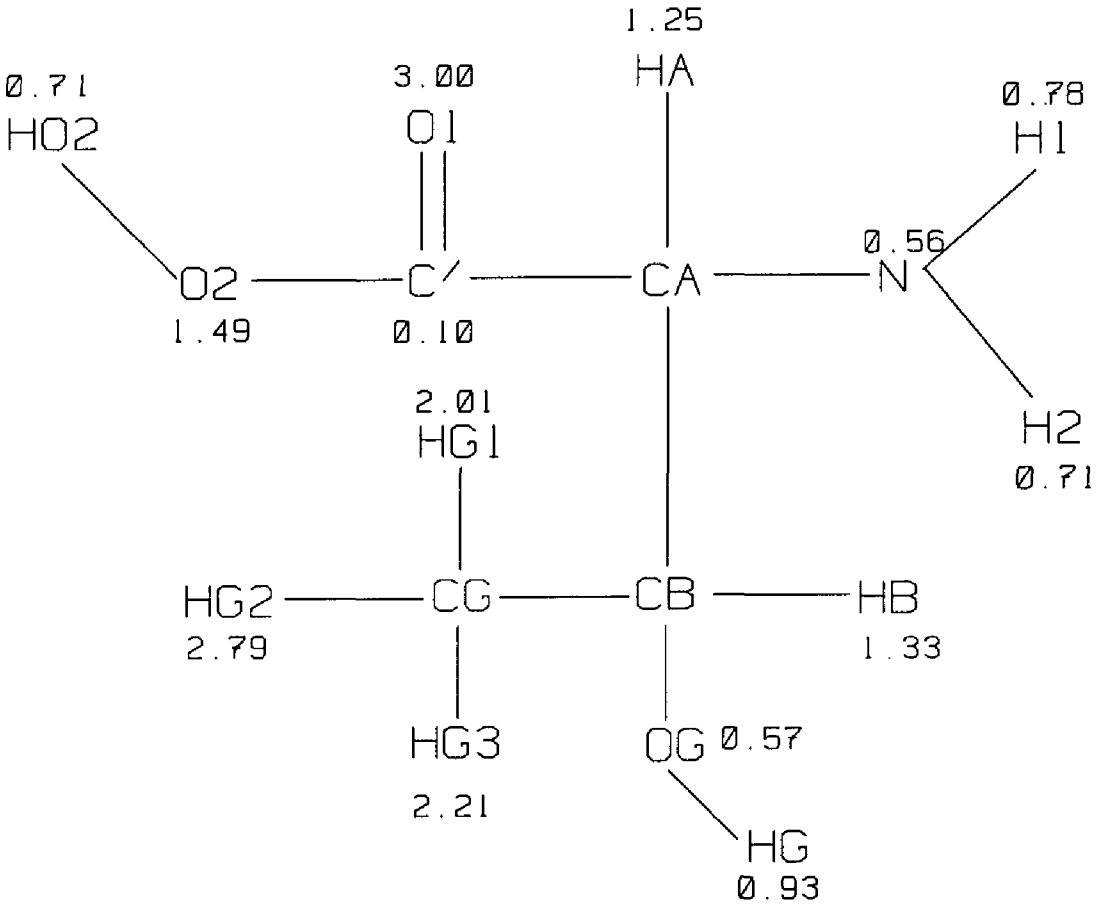

Figure IV.7. Coordination numbers per atom for threonine.

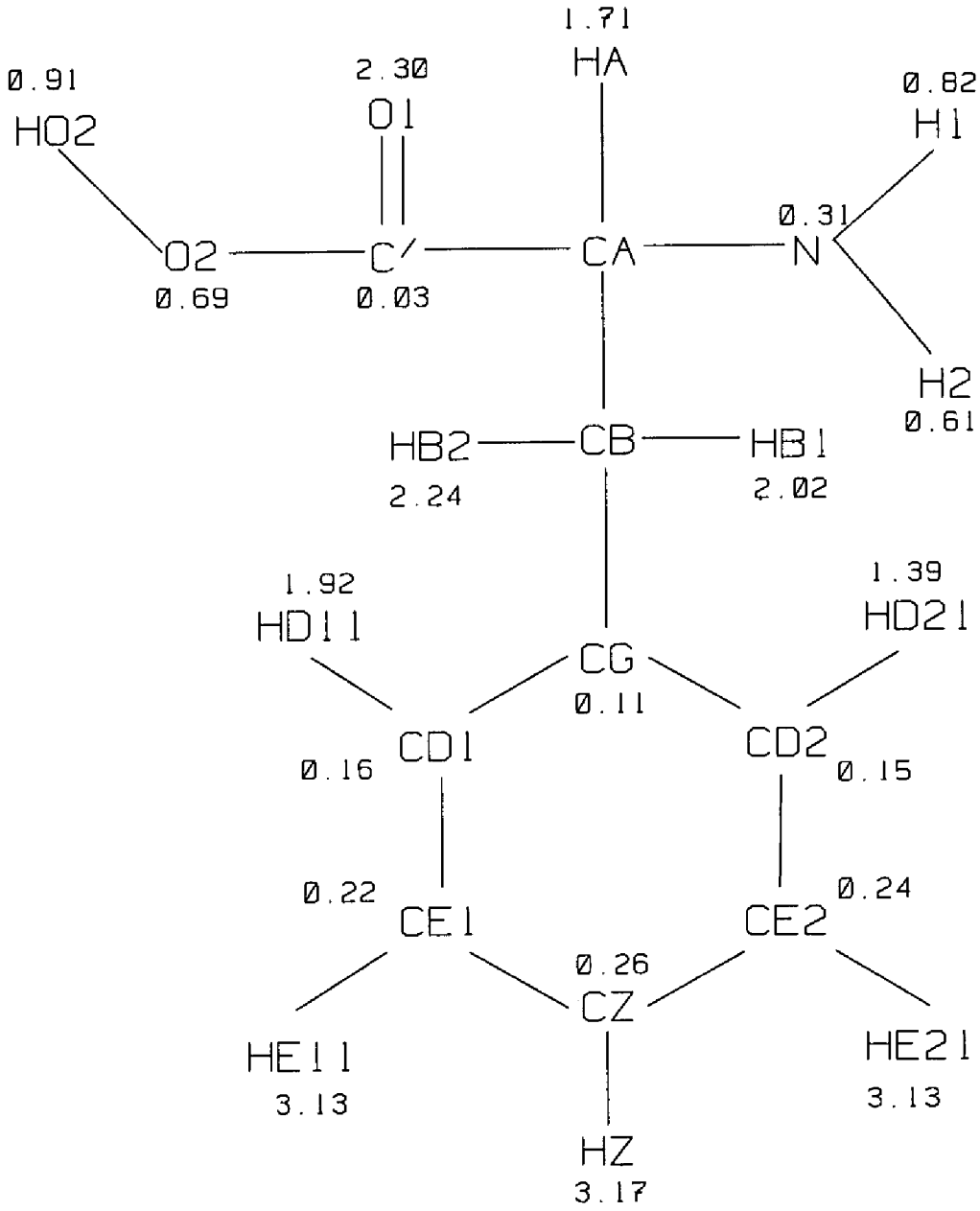

Figure IV.8. Coordination numbers per atom for phenylalanine.

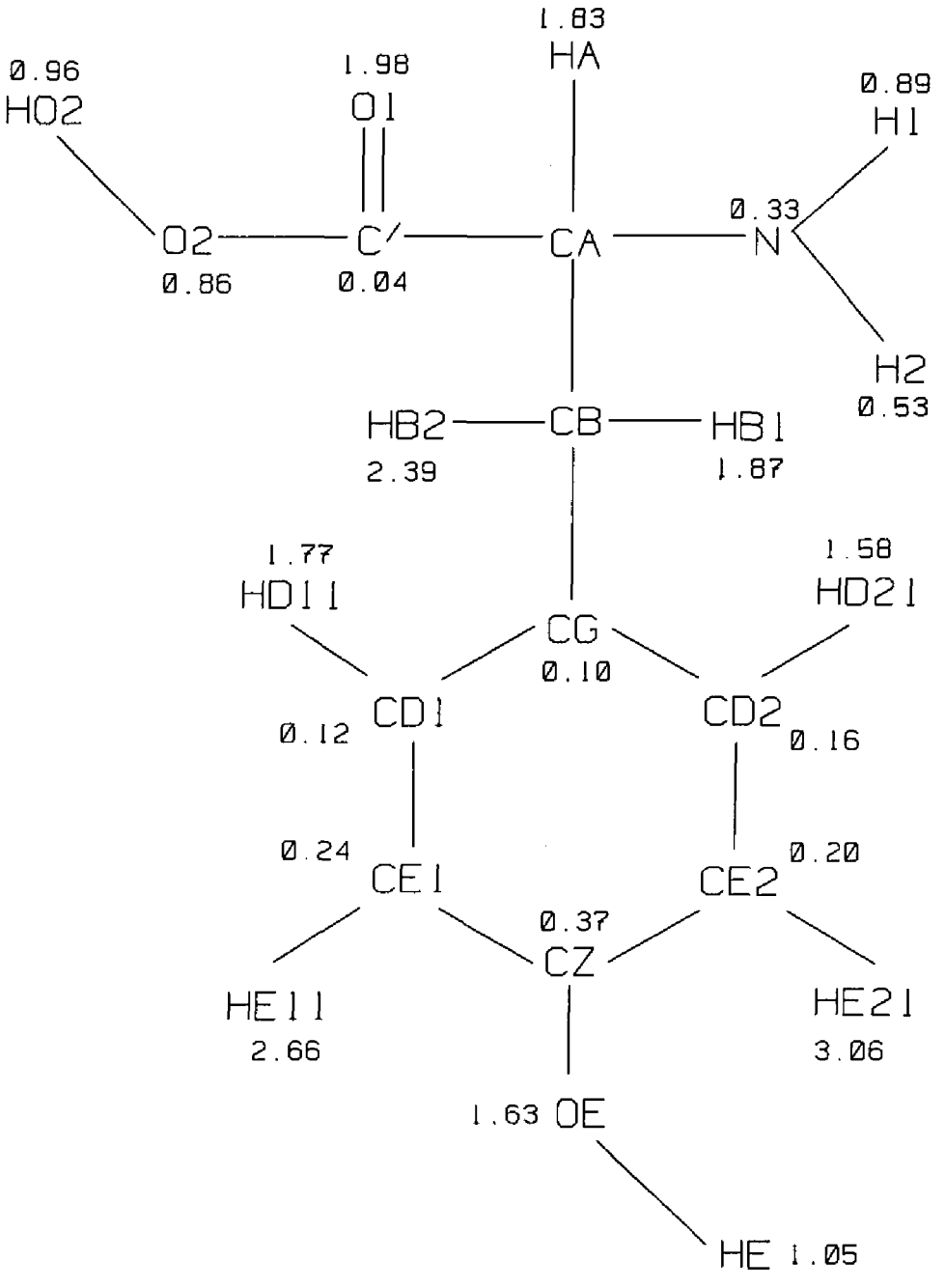

Figure IV.9. Coordination numbers per atom for tyrosine.

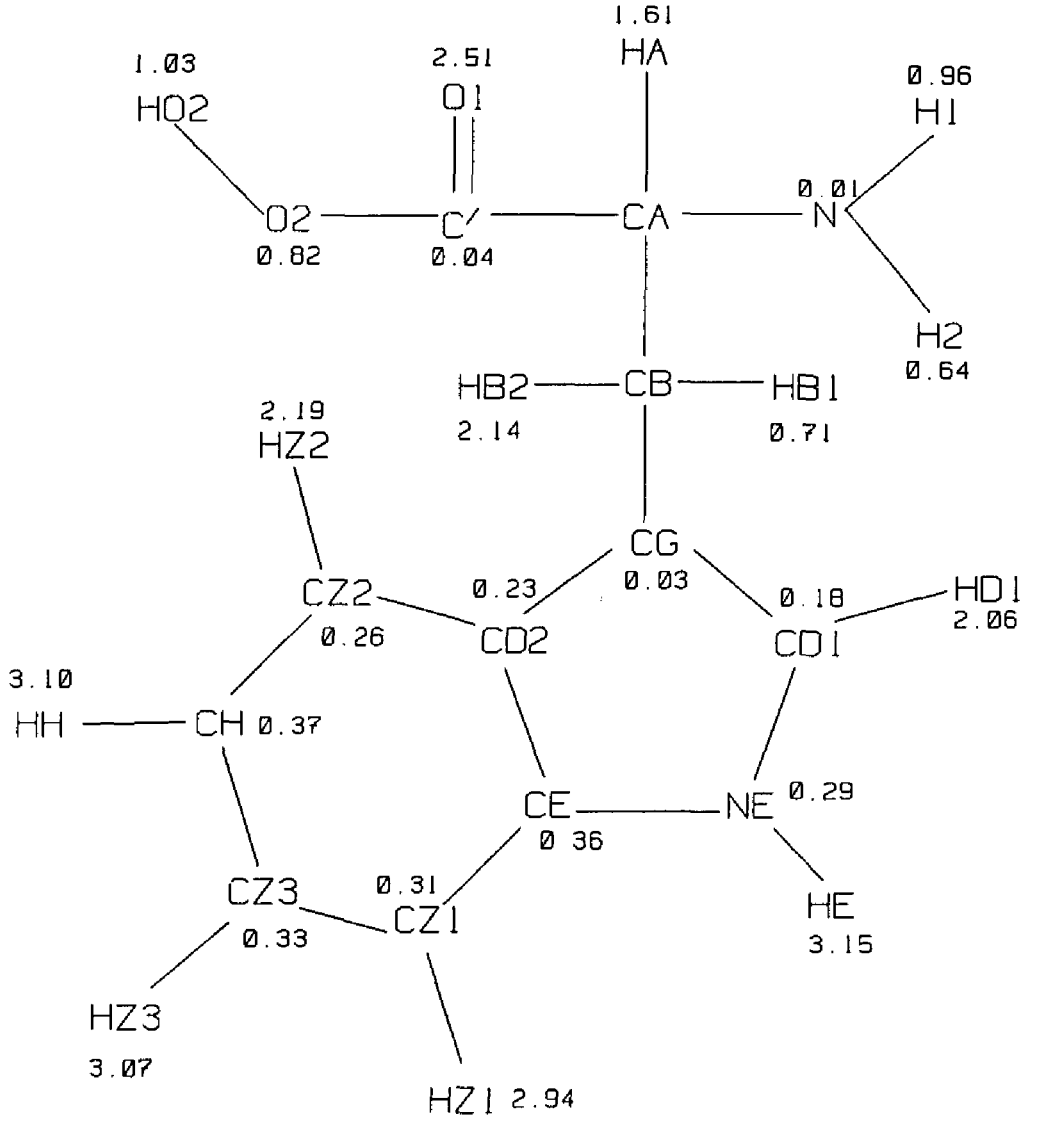

Figure IV.10. Coordination numbers per atom for tryptophan.

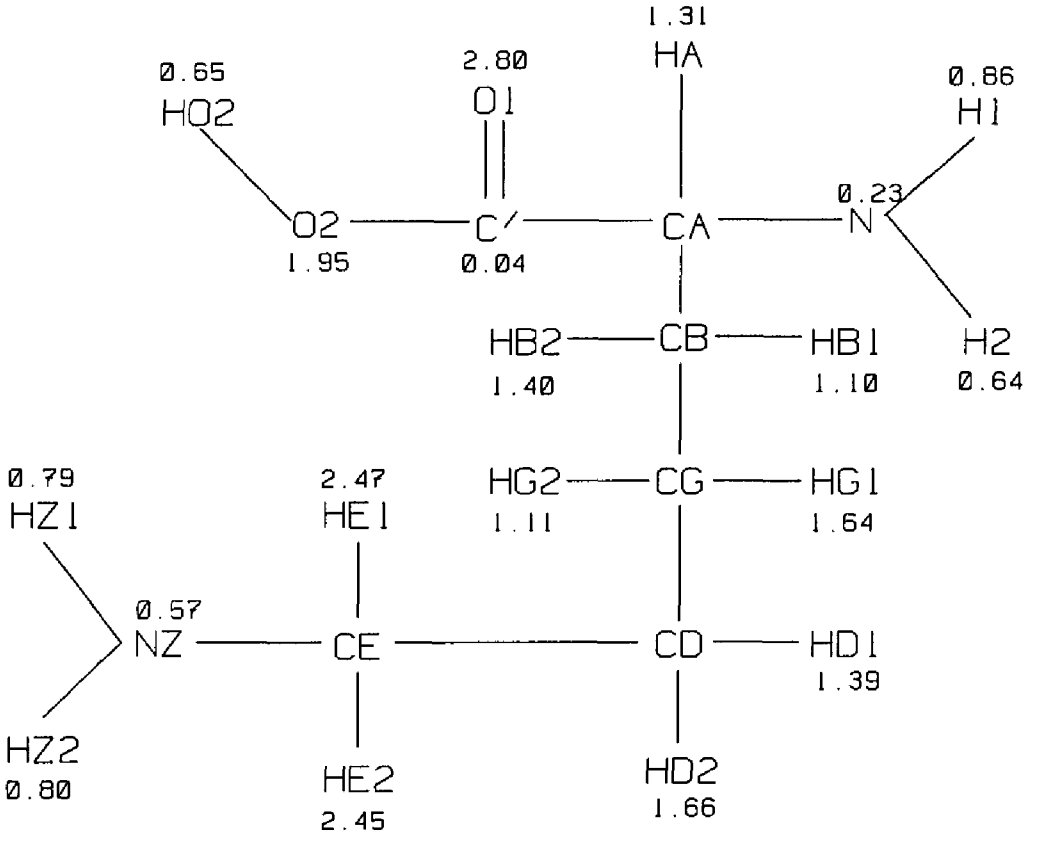

Figure IV.11. Coordination numbers per atom for lysine.

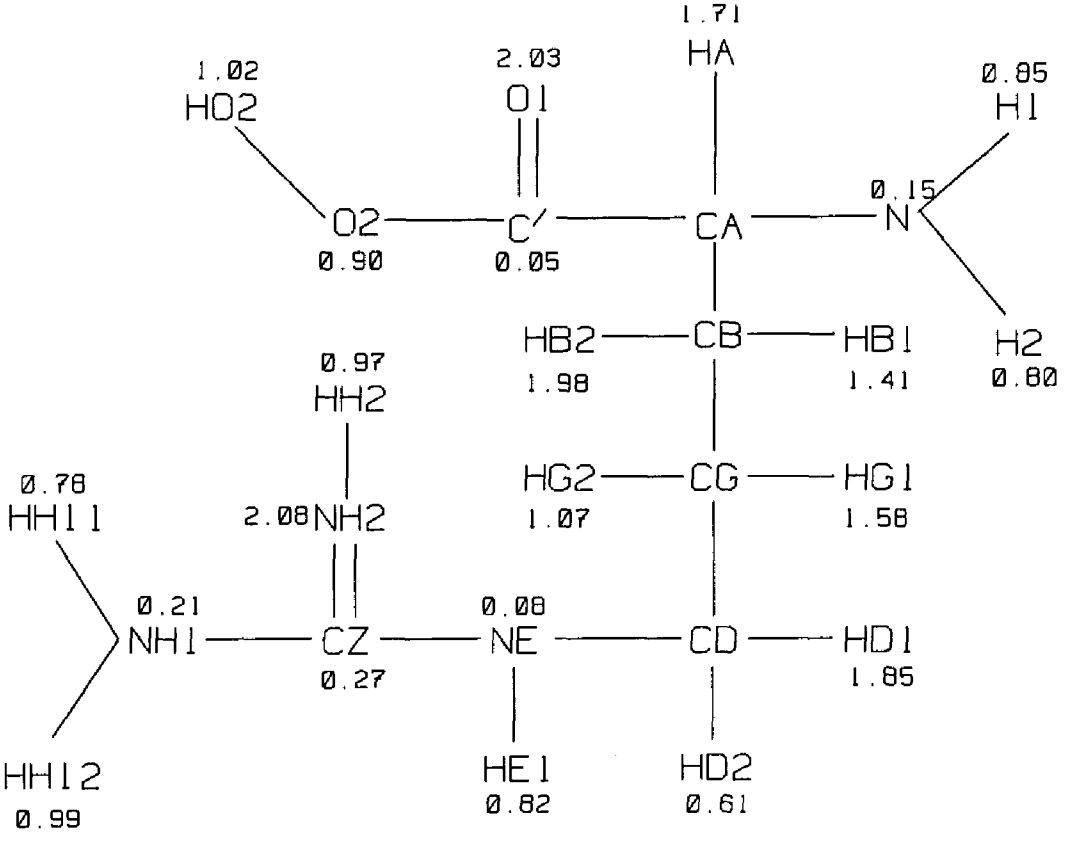

Figure IV.12. Coordination number per atom for arginine.

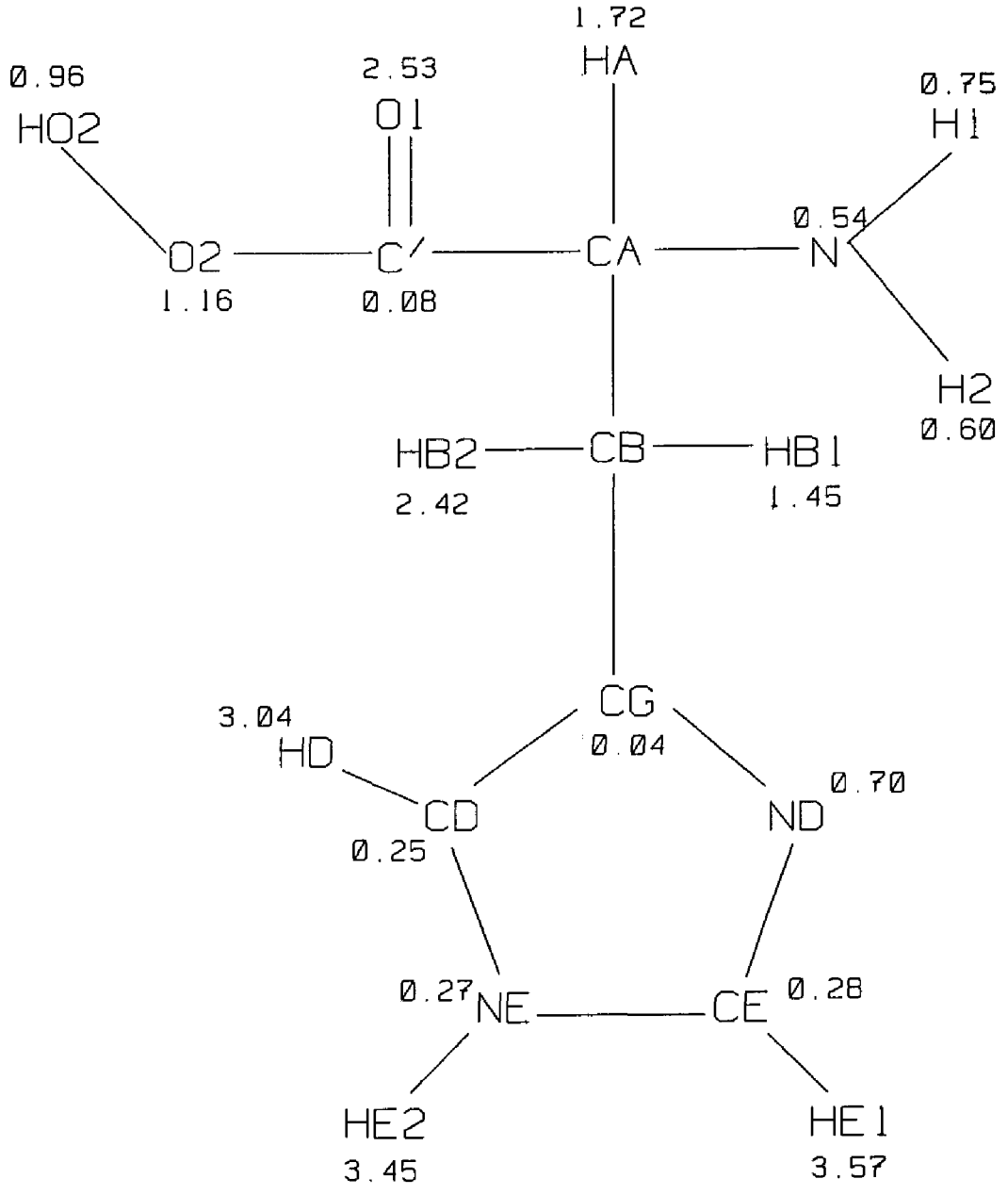

Figure IV.13. Coordination numbers per atom for histidine.

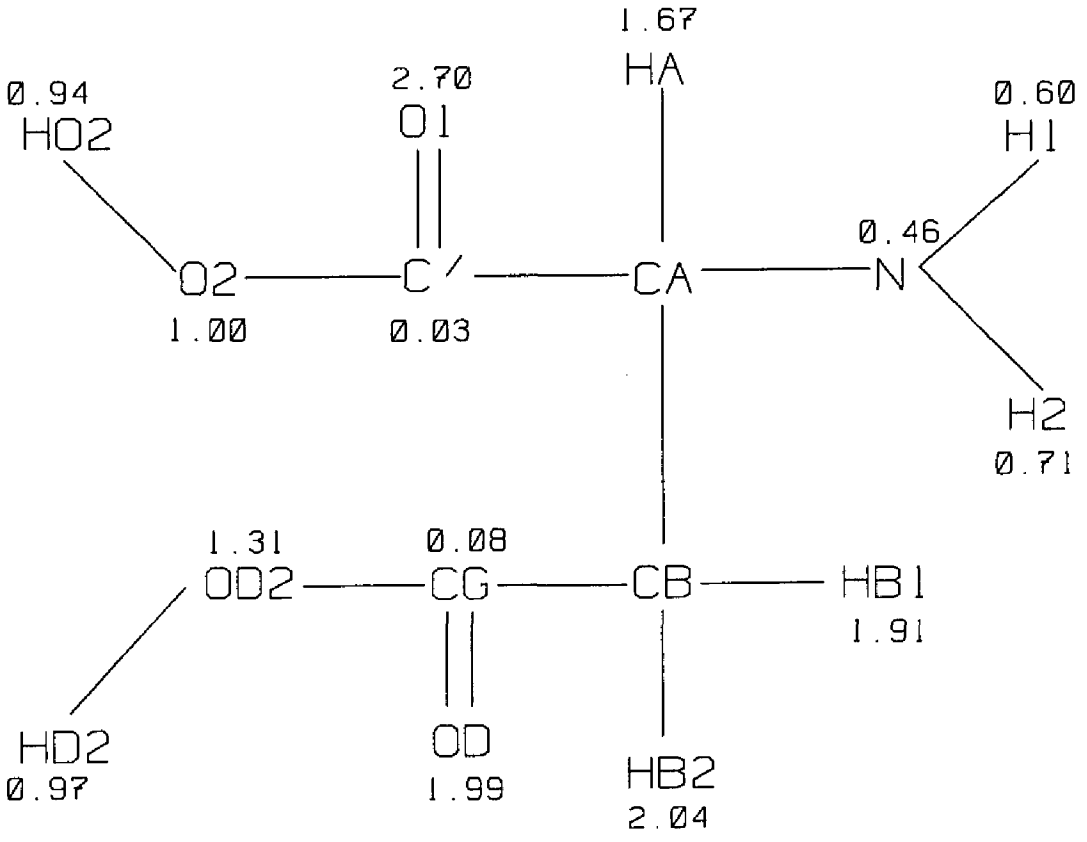

Figure IV.14. Coordination numbers per atom for aspartic acid.

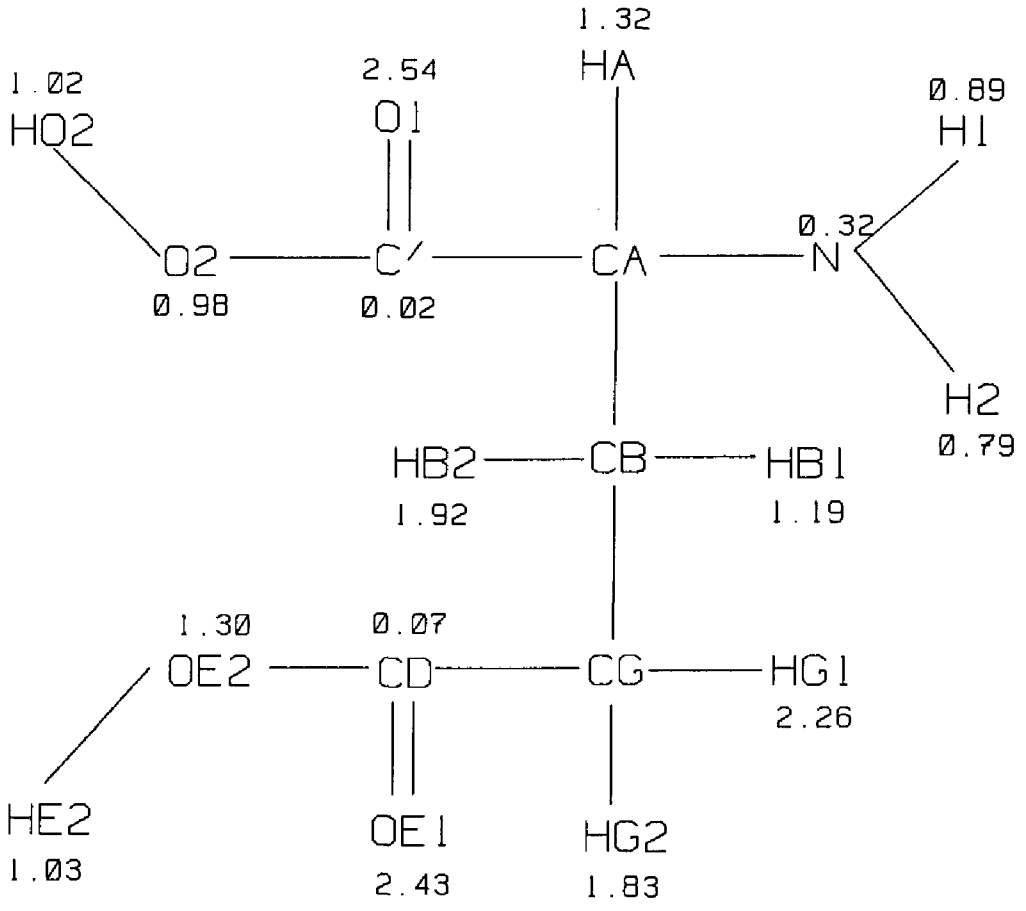

Figure IV.15. Coordination numbers per atom for glutamic acid.

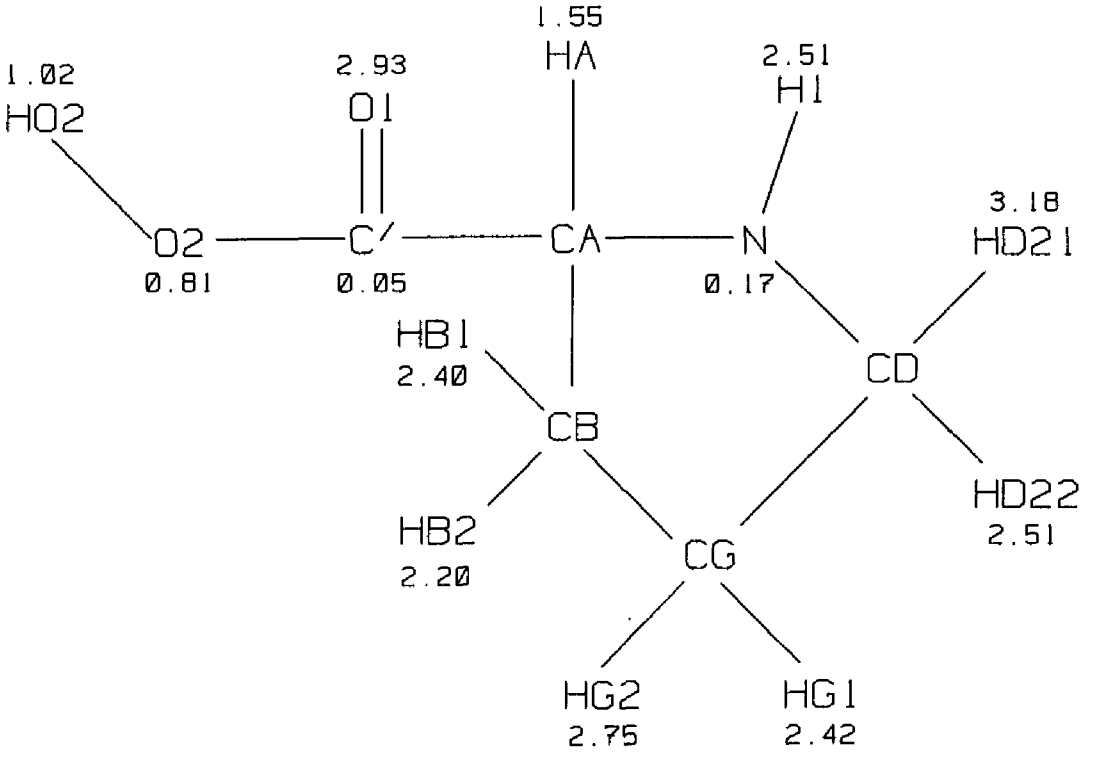

Figure IV.16. Coordination numbers per atom for proline.

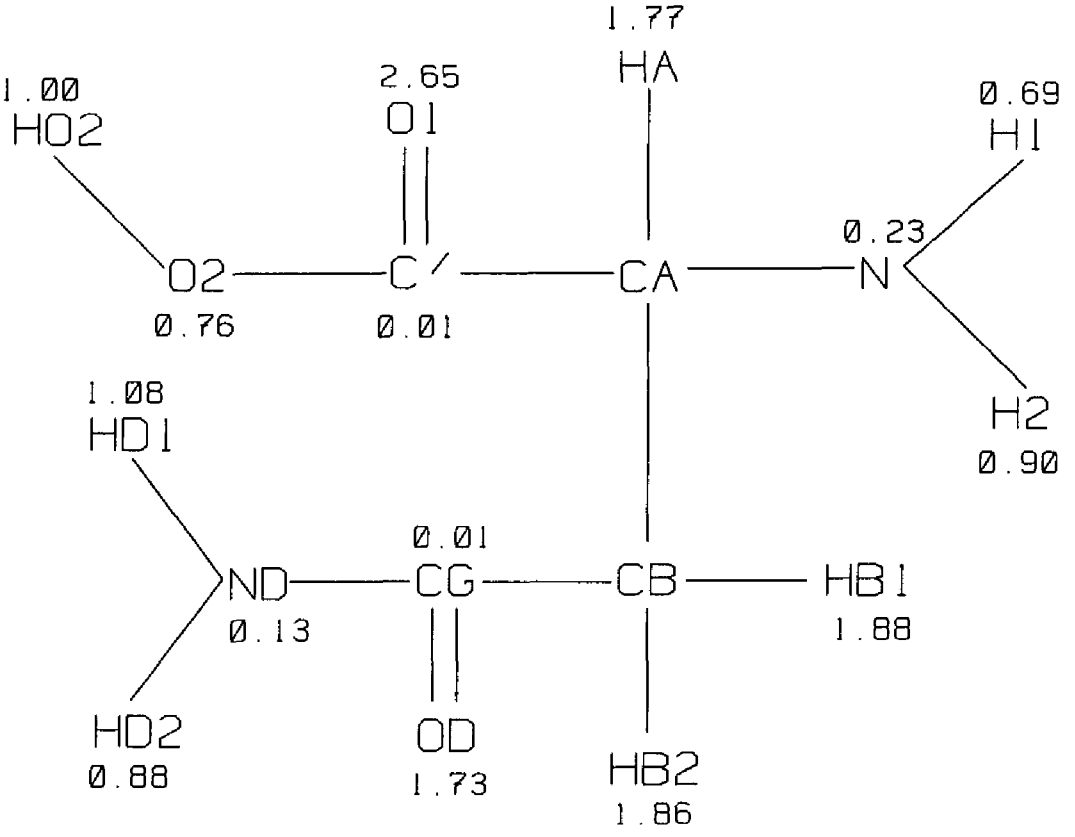

Figure IV.17. Coordination numbers per atom for asparagine.

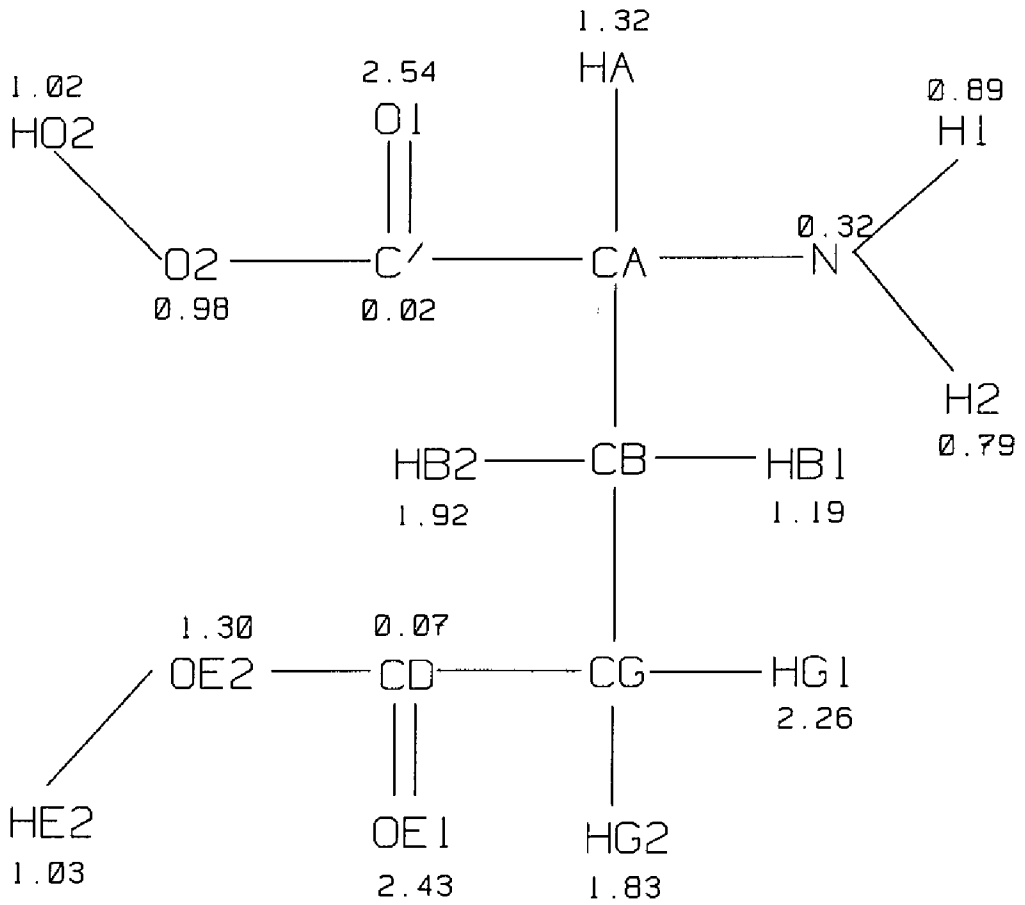

Figure IV.18. Coordination numbers per atom for glutamine.

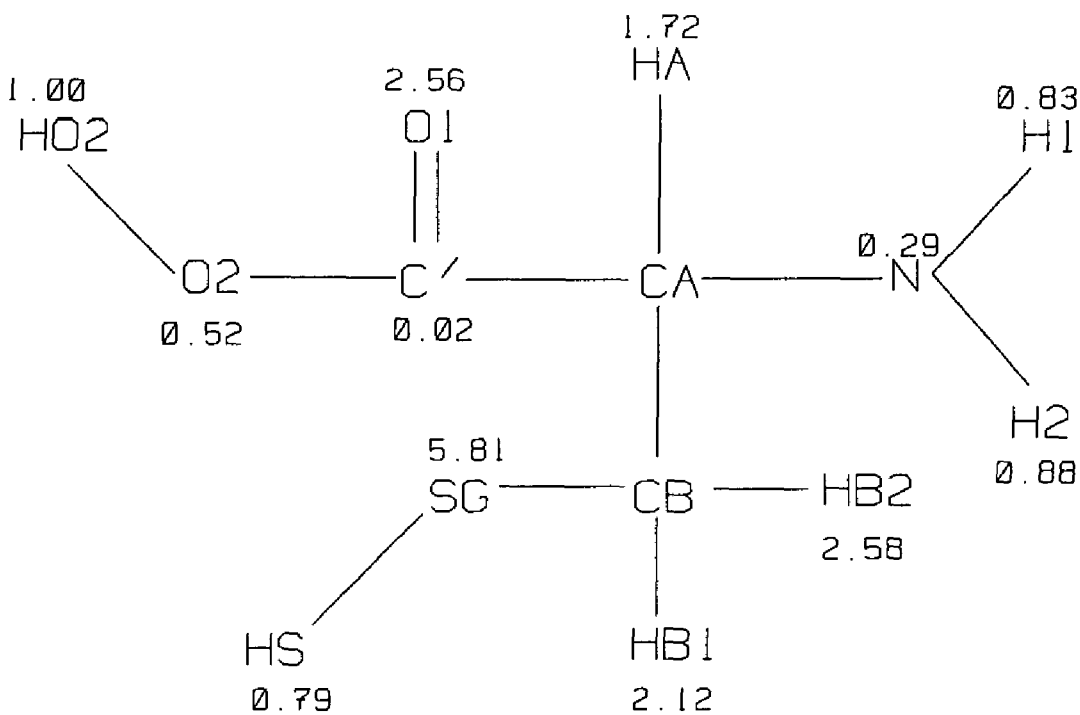

Figure IV.19. Coordination numbers per atom for cystine.

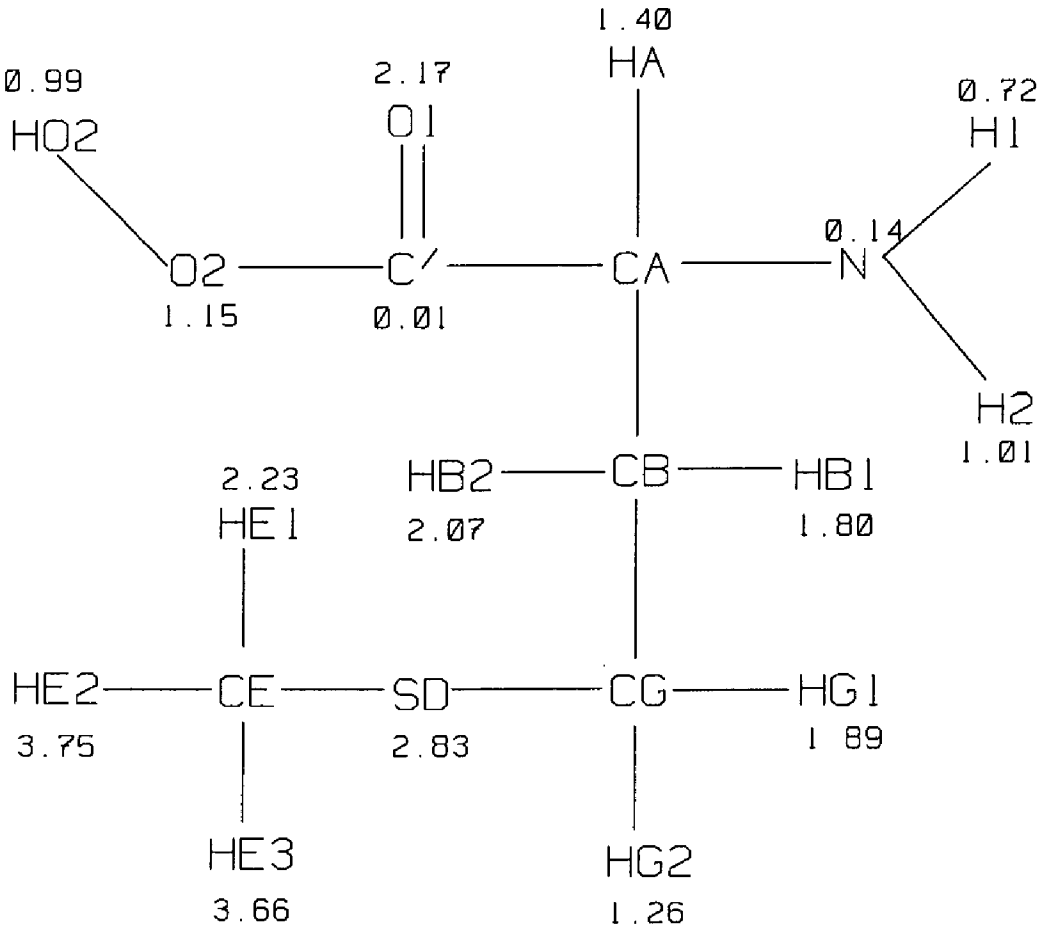

Figure IV.20. Coordination numbers per atom for methionine.

Chapter V

Coordination Number and Its Relation to Characteristic Volume, ED_{50}, Octanol/Water Partition Coefficients, Anesthetic Potency and Cutoff

V.A. Introduction

Most biological processes occur in water; our bodies are 75% water; the brain, 85% water; the structure and conformational transitions of biologically relevant molecules depend on the presence of water[1] and kinetic mechanisms and thermodynamic properties rely on water.

The purpose of this chapter is to relate calculated coordination numbers to experimentally determined quantities. Specifically, characteristic volume is the actual volume occupied by a mole of compound when the molecules are at rest;[32] it is directly proportional to the parachor, the molecular volume at temperatures where the surface tension is unity;[32,33] it relates the liquid state observable quantities: isothermal compressibility, surface tension, density and molecular weight;[32] and correlates with toxic doses necessary to achieve or inhibit a specific biological effect.[34-36]

We use the coordination number model to predict the coordination number for seven classes of prototype molecules: alkanes, alcohols, amines, aromatics, esters, ethers and ketones and compare the results with McGowan's characteristic volumes.[37] Moreover, we relate coordination number and toxic anesthetic doses of alcohols, octanol/water partition coefficients and membrane - buffer coefficients.

V.B. Results and Discussion

Analysis proceeds as follows: simulation gives the coordination number, CN, at each atom, thus total coordination number is the simple sum over all atoms. Similarly, McGowan's characteristic volume, V_x is the simple sum over all atomic V_x's.[37]

Several authors have proposed sets of atomic parachors or V_x's,[38-41] however we choose to show correlation with those of McGowan since they are derived from liquid state measurements and account for electronic structure and atom size.[42]

All lines are fit by standard least squares regression methods.

V.B.1 Characteristic Volume

The collective plot of McGowan's characteristic volumes versus coordination number for all members of the seven classes shows generalized linearity, correlation coefficient (r) = 0.90, standard deviation (s) = 1.1×10^{-5} (Tables V.1-2, Figure V.1). However, specific trends are clearly delineated when we decompose it into plots that depict each molecular class as a separate entity.

All class plots reveal a strict linear relationship between V_x and CN with average r = 1.00, average s = 0.20×10^{-5} (Figures V.2-11). Beyond this, within each class, there is specific linearity between molecules with similar substitution. This trend is observed in the straight chain and cyclic alkanes, each has r = 1.00,

s = 0.05 x 10^{-5}, 0.16 x 10^{-5} and slope (m) = 0.47 x 10^{-5}, 0.72 x 10^{-5} respectively (Tables V.1-2, Figures V.2-3) as well as the primary and secondary amines, each with r = 1.00, s = 0.13 x 10^{-5}, 0.29 x 10^{-5} and m = 0.42 x 10^{-5}, 0.43 x 10^{-5} respectively (Tables V.1-2, Figures V.5-6) and alkylated benzenes and aromatics with r = 0.99, 1.00, s = 0.31 x 10^{-5}, 0.33 x 10^{-5} and m = 0.45 x 10^{-5}, 0.70 x 10^{-5} respectively (Tables V.1-2, Figures V.10-11) as well as other series (Tables V.1-2).

The error between calculated and least squares predicted V_x ranges from a low of 0.4% for alkanes to an high of 3.2% for alcohols; the average error over all separate series is 2.1% whereas that for the generalized prototype plot is 10.6% Thus, agreement in the class plots represents a vast improvement over that for the collective classes.

There is a linear relation between V_x and CN (Figures V.2-11). V_x however, does not account for decreased volume with branching whereas the CN model reflects diminished solute volume in branched species relative to its straight chain counterpart. This phenomenon manifests itself in positive deviations from the V_x versus total CN line in the isomeric alkane pairs: isopentane - pentane, isohexane - hexane, 2,2-dimethylbutane - hexane (Table V.1, Figure V.2, points 6-4, 7-5, 9-5) and alcohol isomer pairs: 2-methyl-1-propanol - butanol, 3-methyl-1-butanol - pentanol (Table V.1, Figure V.4, points 25-16, 26-17).

Clearly, there is a linear relationship between CN and V_r. Thus, a correlation also exists between CN, isothermal compressibility, surface tension, density, molecular weight and doses needed to induce toxic effects.

V.B.2 Anesthetic Activity

Pringle, Brown and Miller[43] and Meyer and Hemmi[44] have studied the potency and anesthetic activity of homologous series of aliphatic alcohols as general anesthetics by measuring ED_{50} values, the dose sufficient to effect narcosis in 50% of the specimen population.[43] Our plot of alcohol ED_{50} values versus total CN indicates a linear relationship; specifically, ED_{50} values are inversely proportional to CN with r = 0.99, s= 0.21×10^{-5} and slope = -0.17×10^{-5} (Table V.1, Figure V.12). This relationship suggests that the number of water molecules surrounding the alcohols may participate in the anesthetic process.

The octanol/water partition coefficient is an established model of a compound's affinity for the lipid phase in biological systems.[45] As such, it should be a probe of the hydration - dehydration process. Octanol/water partition coefficients have been associated with narcotic potency since Meyer and Overton observed in 1901 that the narcotic potency of organic compounds such as alcohols, ketones and esters reflect their octanol/water partition coefficients.[46] The log(octanol/water partition coefficient)[47,48] versus total CN plot for alcohols shows a striking linear correlation, r = 1.00, s = 0.02×10^{-5} , m = 0.20×10^{-5}

(Table V.1, Figure V.13). These data suggest that coordination correlates with narcotic potency.

Pringle, Brown and Miller studied the potency and general anesthetic cutoff, anesthetic inactivity, of several members of an homologous series of aliphatic alcohols by measuring the membrane - aqueous buffer partition coefficient in red blood cells and intestinal brush border membranes.[43] The log of the *in vitro* membrane - buffer partition coefficient versus alcohol total CN plot confirms the compelling linear correlation observed in the octanol/water partition coefficient vs total CN plot with r = 1.00, s = 0.03×10^{-5}, m = 0.20×10^{-5} (Table V.1, Figure V.14). Moreover, the *in vitro* study indicates anesthetic cutoff occurs at tetradecanol and the CN model places tetradecanol as a deviation from the least squares line. This correlation supports the suggestion that CN characterizes the hydration - dehydration process and drug potency.

V.C. Conclusions

There is a strict linear relationship between characteristic volume and coordination number in the seven classes of prototype molecules (average r = 1.00, average s = 0.20×10^{-5}). Hence, a direct correlation exists between coordination number and the experimentally measurable quantities: isothermal compressibility, surface tension, density and molecular weight.

Beyond this, there is a strong linear correspondence between coordination number and toxic anesthetic ED_{50} values of alcohols, octanol/water partition coefficients and *in vitro* membrane - buffer alcohol partition coefficients as well as general anesthetic cutoff. Thus, coordination number can be a valuable tool in the analysis of biochemical activity.

Table V.1

Coordination Numbers, Characteristic Volumes, Partition Coefficients and ED_{50}'s

No.	Molecule	V_x[a] $(m^3\ mol^{-1})x10^5$	CN[b]	ED_{50}[c] $Mx10^5$	LogP[d]	LogP[e]
1	Ethane	3.90	20.13			
2	Propane	5.31	23.21			
3	Butane	6.72	26.15			
4	Pentane	8.13	29.06			
5	Hexane	9.54	32.30			
6	Isopentane	8.13	26.99			
7	Isohexane	9.54	29.85			
8	3-Methylpentane	9.54	29.79			
9	2,2-Dimethylbutane	9.54	29.49			
10	Cyclopentane	7.05	26.39			
11	Cyclohexane	8.45	28.61			
12	Cycloheptane	9.86	30.29			
13	Methanol	3.08	14.46			
14	Ethanol	4.49	18.20	12	-0.37	-0.8539[f]
15	1-Propanol	5.90	21.27	5.4	0.25	
16	1-Butanol	7.31	24.47	1.2	0.88	0.1761[f]
17	1-Pentanol	8.72	27.25			
18	1-Hexanol	10.13	30.44	0.07	2.03	1.1139[f]
19	1-Octanol		36.34	0.006		2.1818[f]
20	1-Decanol		42.07	0.0013		3.0871[f]
21	1-Dodecanol		45.90	0.00054	5.12	3.7296[g]
22	1-Tetradecanol		48.27			3.2956[g]
23	2-Butanol	7.31	24.38			
24	3-Hexanol	10.13	30.94			
25	2-Methyl-1-propanol	7.31	23.07			
26	3-Methyl-1-butanol	8.72	25.69			
27	Cyclopentanol	7.63	25.28			
28	Cyclohexanol	9.04	27.18			
29	Methylamine	3.49	13.35			
30	Ethylamine	4.90	17.24			
31	Propylamine	6.31	20.25			
32	Butylamine	7.72	23.42			
33	Dimethylamine	4.90	20.14			
34	Diethylamine	7.72	27.76			
35	Dipropylamine	10.54	34.24			
36	Dibutylamine	13.36	39.94			

Table V.1 (Cont.)

No.	Molecule	V_X[a] $(m^3\ mol^{-1})x10^5$	CN[b]	ED_{50}[c] $Mx10^5$	LogP[d]	LogP[e]
37	Methylacetate	6.06	24.39			
38	Ethylacetate	7.47	27.78			
39	Propylacetate	8.88	30.96			
40	Butylacetate	10.28	33.80			
41	Methylpropanoate	7.47	27.97			
42	Methylbutanoate	8.88	30.89			
43	Methylpentanoate	10.28	33.75			
44	Methylether	4.49	20.89			
45	Ethylether	7.31	28.39			
46	Propylether	10.13	34.64			
47	Butylether	12.95	41.02			
48	Acetone	5.47	22.27			
49	2-Butanone	6.88	25.59			
50	2-Pentanone	8.29	28.58			
51	2-Hexanone	9.70	31.69			
52	2-Heptanone	11.11	34.80			
53	3-Pentanone	8.29	29.35			
54	4-Heptanone	11.11	35.07			
55	Toluene	8.57	25.45			
56	Ethylbenzene	9.98	27.31			
57	Propylbenzene	11.39	31.56			
58	Butylbenzene	12.80	34.35			
59	o-Xylene	9.98	28.45			
60	m-Xylene	9.98	29.67			
61	p-Xylene	9.98	29.58			
62	1,2,4-Trimethylbenzene	11.39	32.85			
63	Benzene	7.16	20.90			
64	Naphthalene	10.85	26.74			
65	Phenanthrene	14.54	31.41			

a. Characteristic Volume calculated according to reference 37.
b. Coordination Number calculated according to reference 14.
c. ED_{50} values for tadpole narcosis from reference 43.
d. Log(Octanol/water partition coefficients) from reference 47.
e. Log(Membrane-Buffer partition coefficient) from reference 43.
f. Red blood cells from reference 49.
g. Intestional brush border membranes from reference 50.

Table V.2

Parameters for Linear Fits of Data

Class	Data Points[a]	m[b] ($x10^5$)	b[c] ($x10^5$)	r[d]	s[e] ($x10^5$)	Error[f] (%)
Alkane	1-5	0.4664	-5.4826	1.00	0.05	0.4
Cycloalkane	10-12	0.7152	-11.8777	1.00	0.16	1.0
Alcohol	13-18,23-28	0.4479	-3.4404	0.99	0.32	3.2
1° Amine	29-32	0.4231	-2.2476	1.00	0.13	1.6
2° Amine	33-36	0.4259	-3.8691	1.00	0.29	2.6
Ester	37-43	0.4564	-5.1881	1.00	0.87	0.8
Ether	44-47	0.4220	-4.4639	1.00	0.19	1.8
Ketone	48-54	0.4482	-4.5858	1.00	0.14	1.1
Alkylated Benzenes	55-58	0.4465	-2.5594	0.99	0.31	1.9
Aromatics	63-65	0.6992	-7.5684	1.00	0.33	0.6
Collective Prototype	1-18,23-65	0.3964	-2.4667	0.90	1.09	10.6

a. Numbers refer to molecules in Table V.1.
b. m = slope.
c. b = y-intercept
d. r = correlation coefficient.
e. s = standard deviation.
f. Average error between calculated and fitted characteristic volumes.

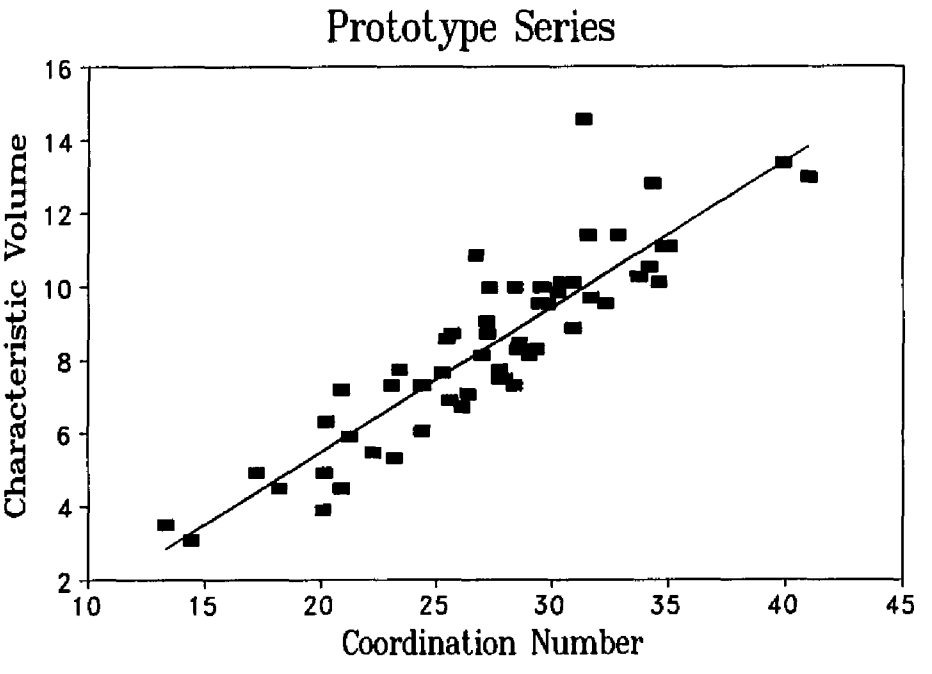

Figure V.1 Prototype Series. Characteristic volume (m^3 mol^{-1} x 10^5) and total coordination number for the sixty five molecules found in Table V.1. Solid line repesents least squares fit.

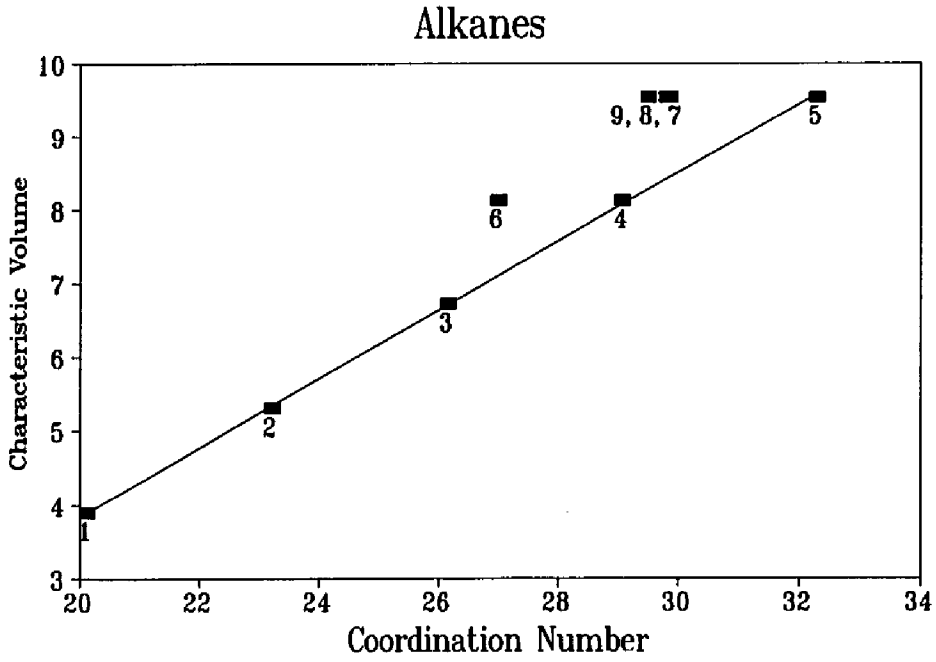

Figure V.2 Alkanes. Solid line represents least squares fit of characteristic volume ($m^3mol^{-1}x10^5$) and total coordination number for straight chain alkanes. Table V.1 contains molecule identification and Table V.2 regression parameters.

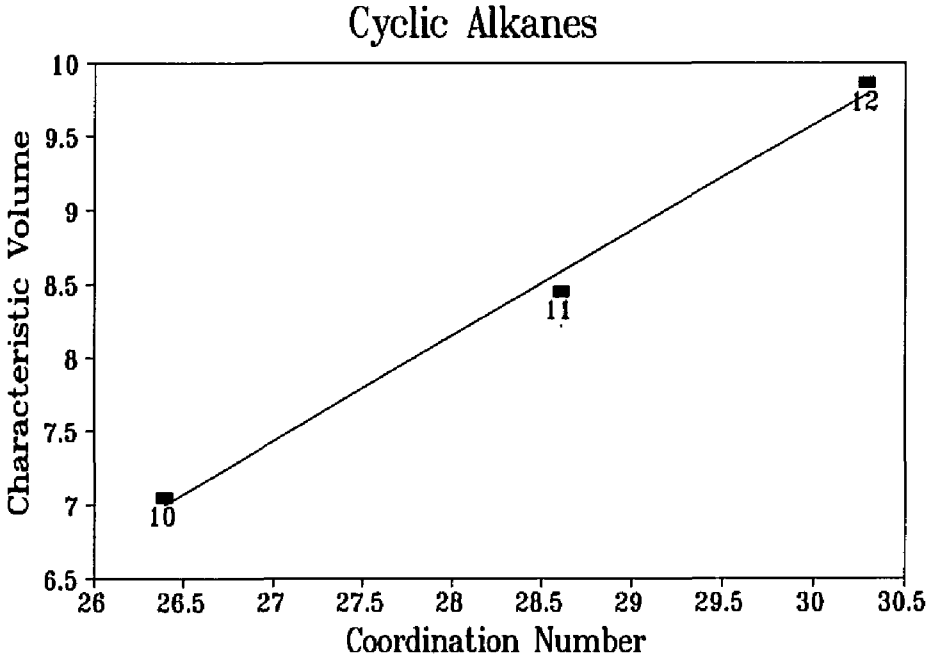

Figure V.3 Cyclic Alkanes. Refer to Figure V.2 caption for complete information.

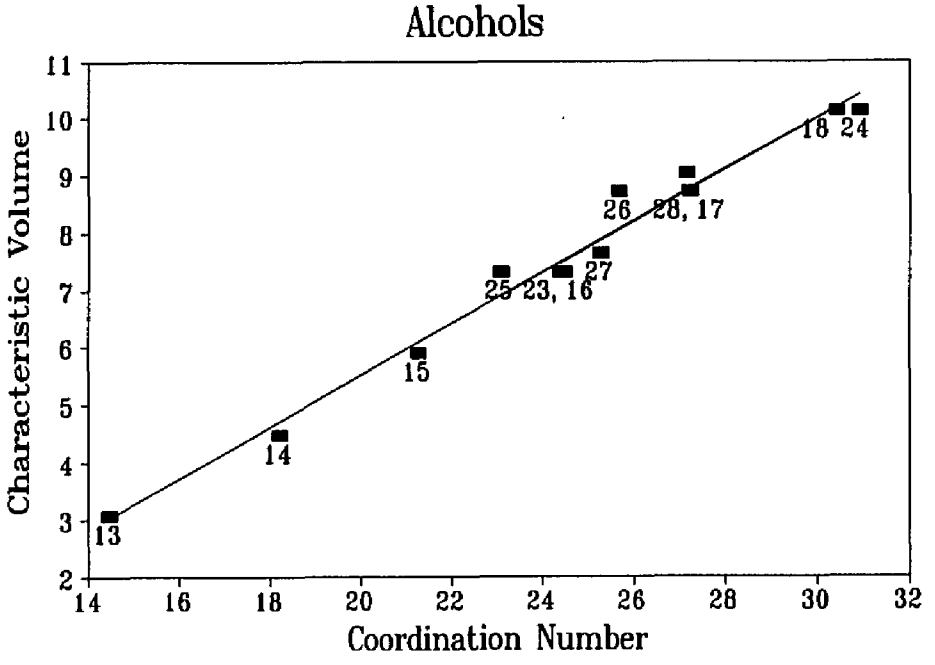

Figure V.4 Alcohols. Refer to Figure V.2 caption for complete information.

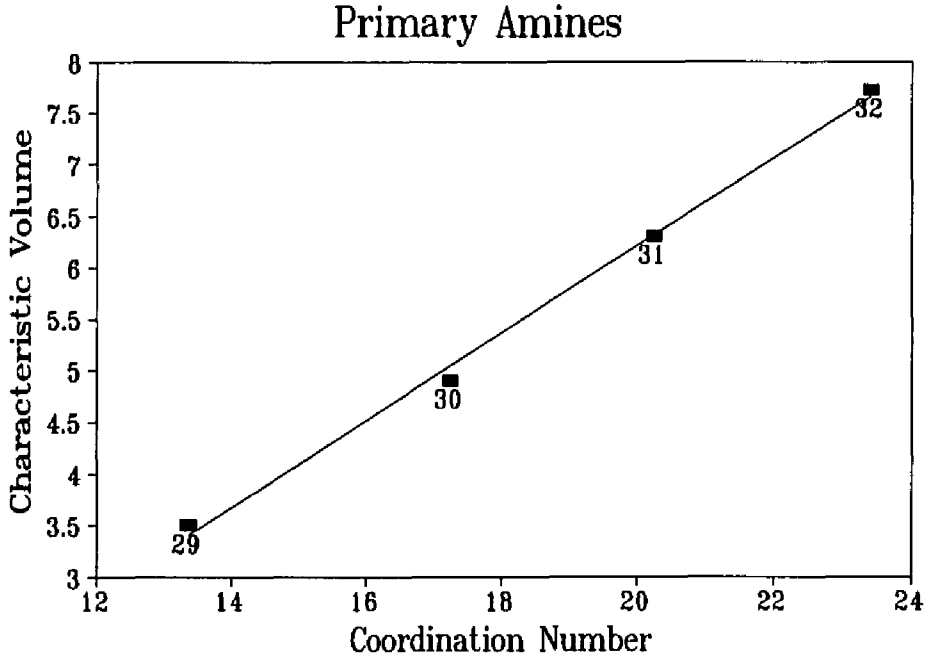

Figure V.5 Primary Amines. Refer to Figure V.2 caption for complete information.

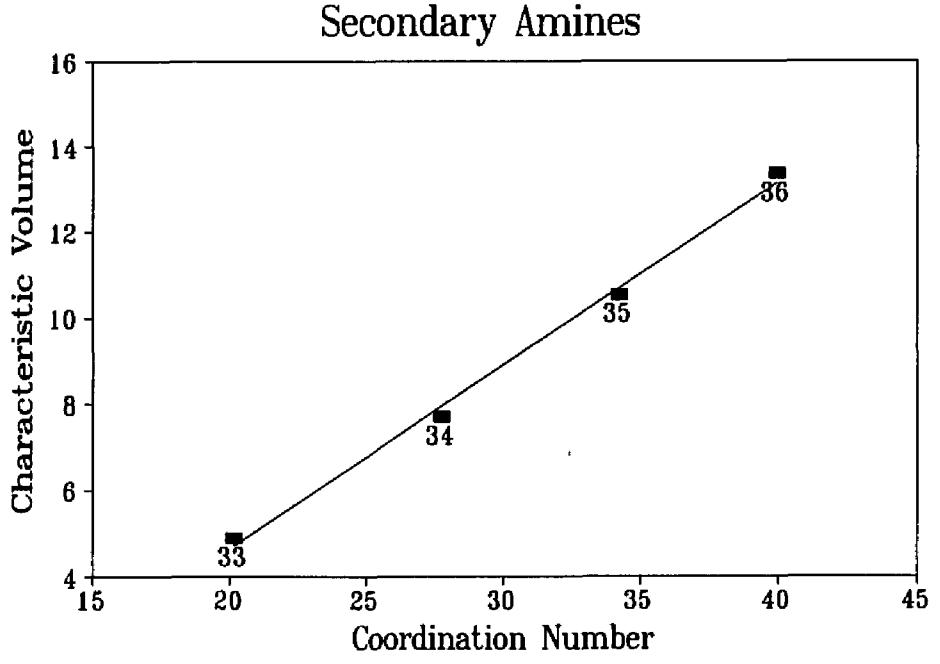

Figure V.6 Secondary Amines. Refer to Figure V.2 for complete information.

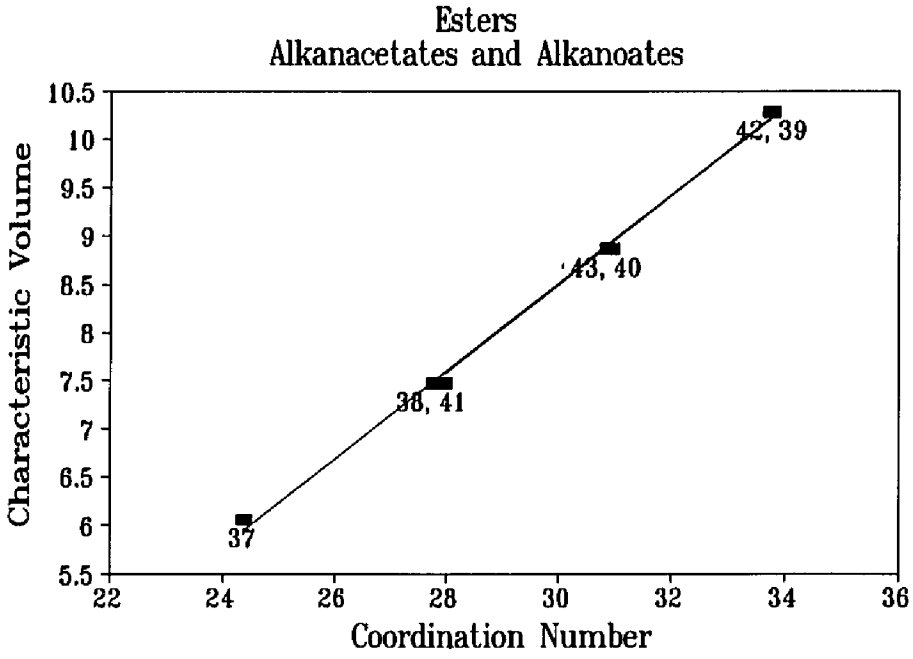

Figure V.7 Esters (alkanacetates and alkanoates). Refer to Figure V.2 for complete information.

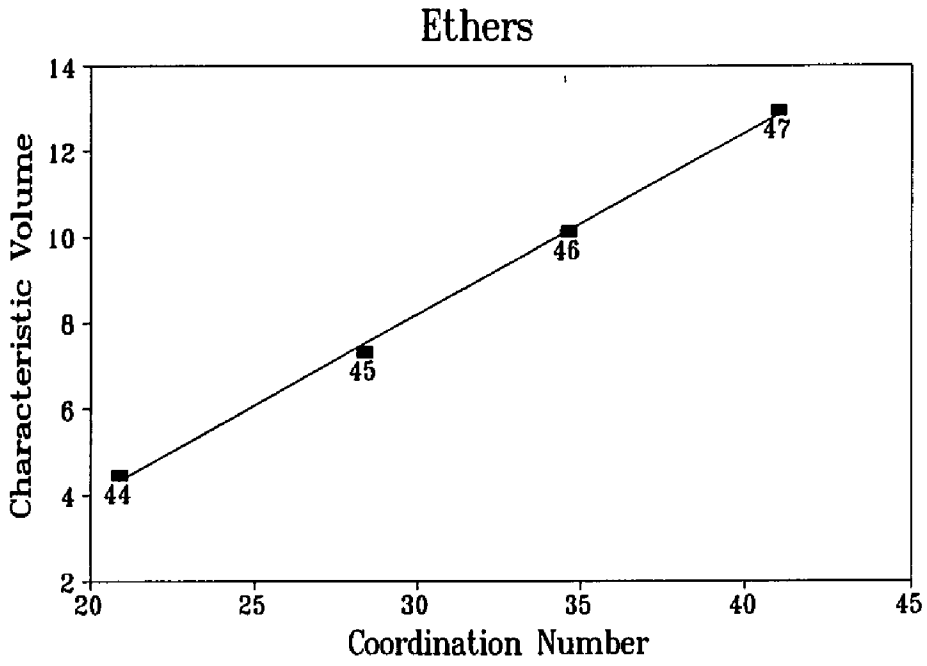

Figure V.8 Ethers. Refer to Figure V.2 for complete information.

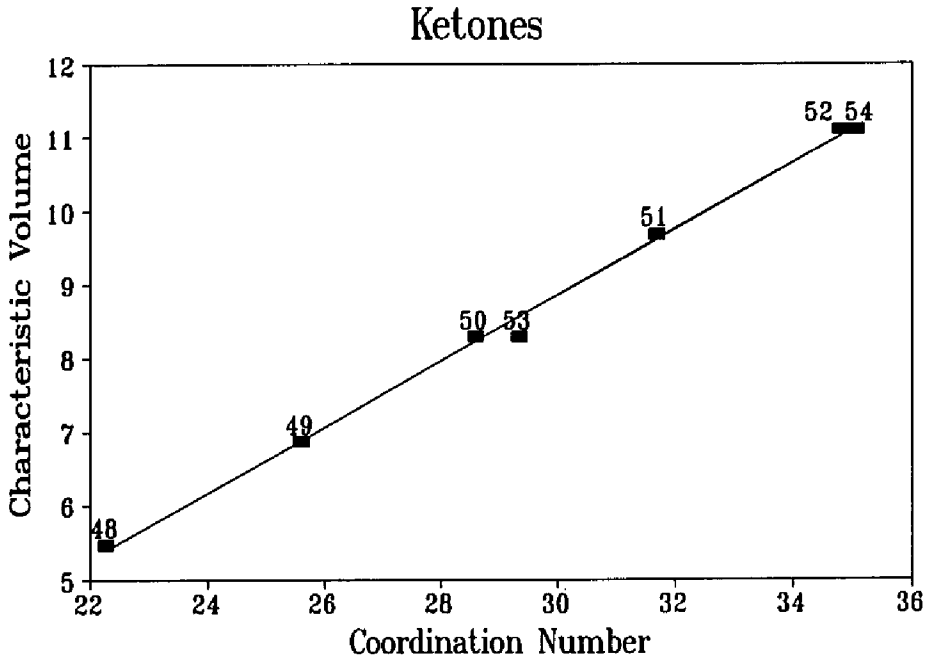

Figure V.9 Ketones. Refer to Figure V.2 for complete information.

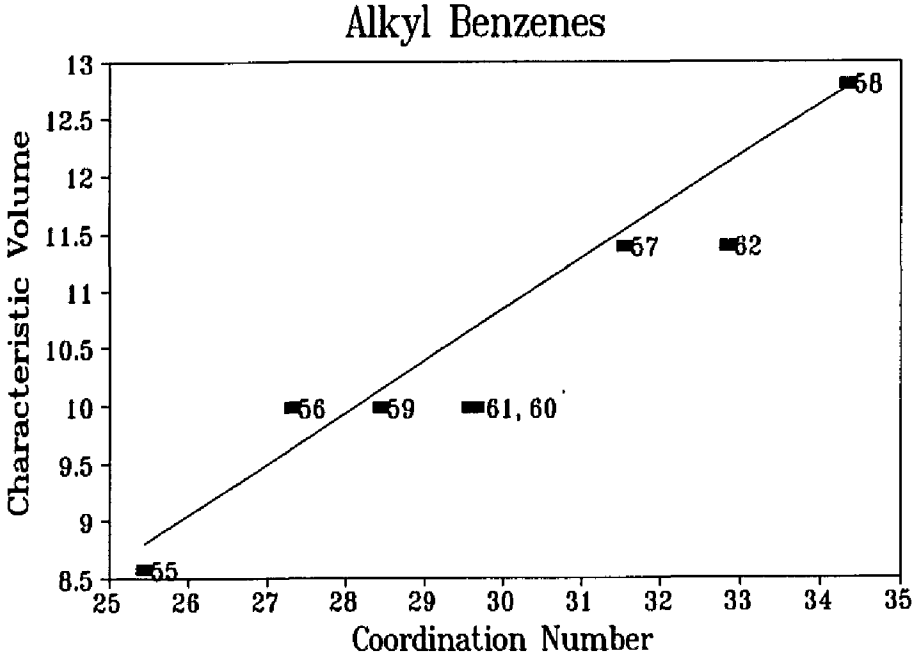

Figure V.10 Alkyl Benzenes. Refer to Figure V.2 caption for complete information.

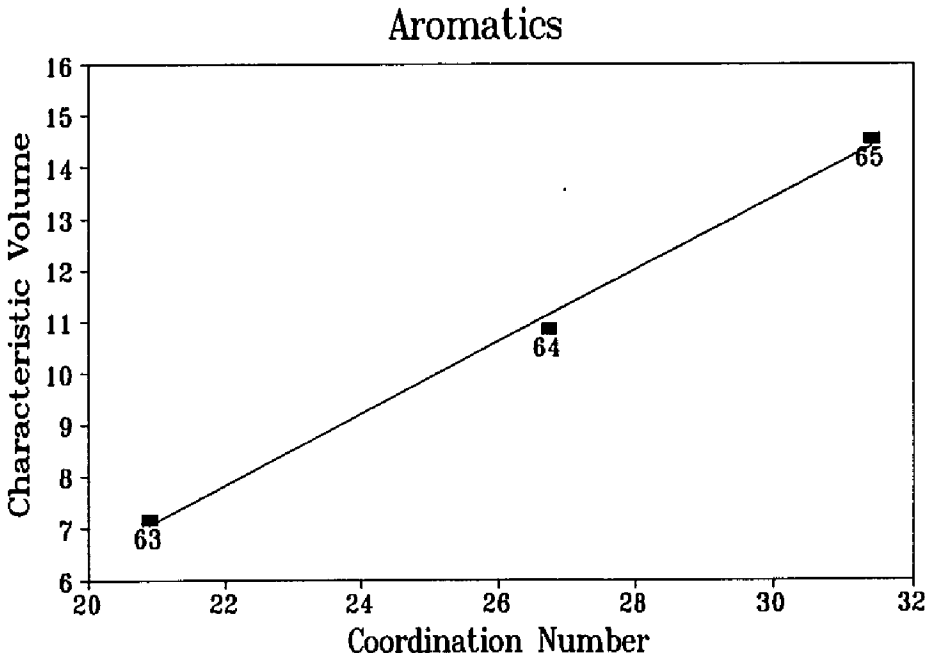

Figure V.11 Aromatics. Refer to Figure V.2 for complete information.

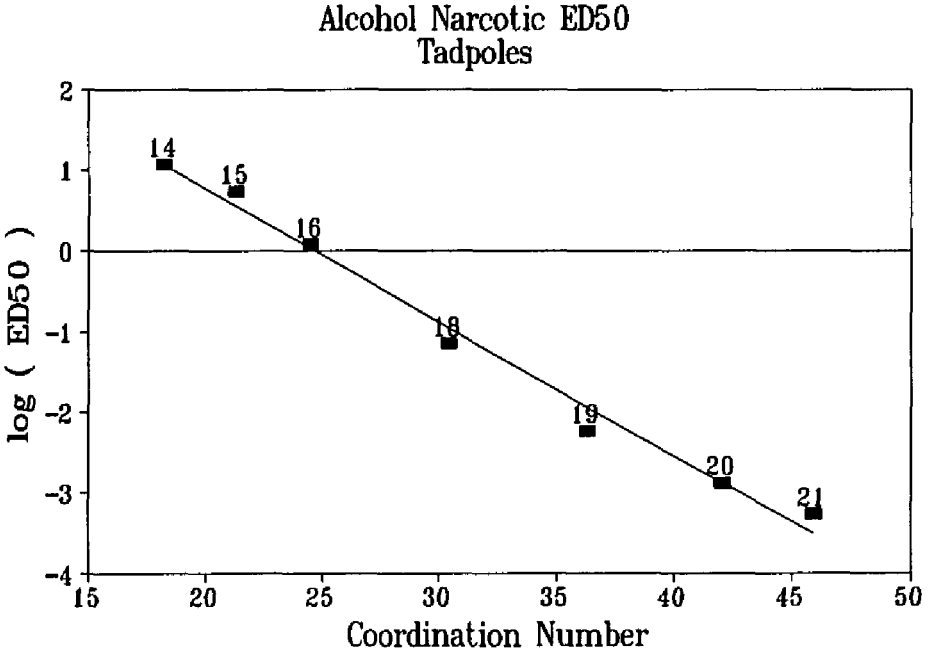

Figure V.12 Alcohol narcotic effect on tadpoles. Solid line represents least squares fit of ED_{50} and total coordination number for alcohols. Table V.1 contains associated data.

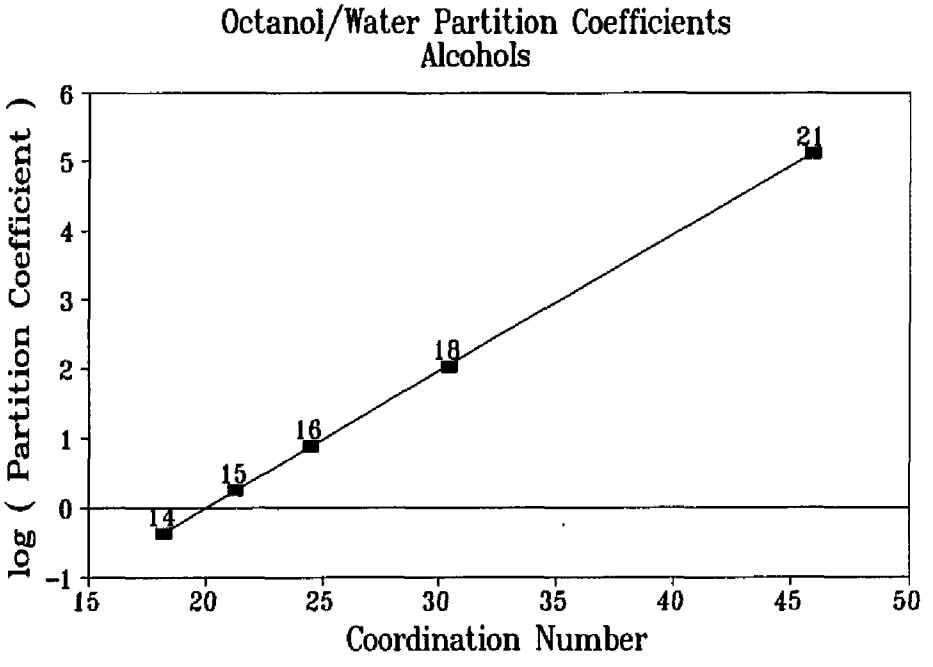

Figure V.13 Alcohol partition coefficients. Solid line represents least squraes fit of log (octanol/waterP partition coefficient and total coordination number for alcohols. Table V.3 contains associated data.

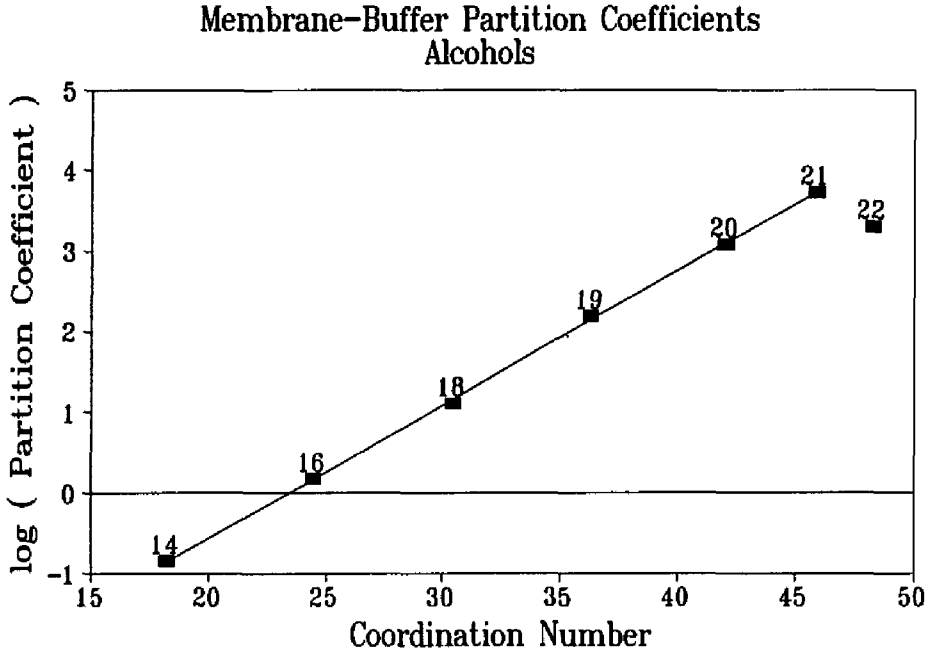

Figure V.14 Membrane-buffer partition coefficients. Solid line represents least squares fit of log partition coefficient and total coordination number for alcohols. Table V.1 contains associated data.

Chapter VI

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