Thermodynamic Group Contributions for Hydroxyl, Amino, and Methylene Groups

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Abstract □ The hydroxyl, amino, and methylene group contributions to the free energy of transfer from water to the organic phase, from water to the vapor phase, and from heptane to the vapor phase were determined from the Henry constants of aliphatic series of hydrocarbons, alcohols, and amines in dilute aqueous and heptane solutions. The Henry constant of each solution was measured using a vapor headspace GLC method with very dilute aqueous and organic solutions. Plotting the log of the Henry constant *versus* carbon number yielded a straight line from which the methylene group contribution was calculated. This value was −150 cal/mole for water to vapor, 760 cal/mole for heptane to vapor, and −910 cal/mole for water to the organic phase. The hydroxyl contribution was 6890 cal/mole for water to vapor, 1320 cal/mole for organic to vapor, and 5570 cal/mole for the transfer of a hydroxyl group from water to the organic phase. For the amino group, the free energy of transfer was 6470 cal/mole for water to vapor, 1490 cal/mole for heptane to vapor, and 4980 cal/mole for water to the organic phase. The values determined were in reasonable agreement with literature data. Such data can be used to predict the effects of various functional groups on the distribution and transport tendencies of drugs.

Keyphrases □ Thermodynamic group contributions—hydroxyl, amino, and methylene, free energy of transfer from one phase to another □ Hydrocarbons, aliphatic series—methylene group contribution to free energy of transfer from one phase to another □ Alcohols, aliphatic series—hydroxyl group contribution to free energy of transfer from one phase to another □ Amines, aliphatic series—amino group contribution to free energy of transfer from one phase to another

Over the years, considerable effort has been directed toward understanding the relationship between molecular structure and the distribution–transport characteristics of chemical and drug species. Although distribution is an equilibrium process and transport is a rate process, transport is subject to distribution for all passive diffusion processes and for most active transport phenomena in their presaturation phase. For example, a substantial portion of drug absorption involves partitioning into the rate-controlling membrane. The lipophilic–hydrophilic balance of ophthalmic drugs, for instance, largely determines their transcorneal absorption rate. Similarly, the GI absorption rate of passively absorbed drugs usually depends on their ability to partition into the rate-determining barrier membrane. This condition is also true for dermal agents.

BACKGROUND

Such basic considerations can be used to design and develop more effective drugs and form the rationale for the use of structure–activity relationships. Over the years, several *a priori* methods for predicting the thermodynamics of organic molecules in solution have been proposed. However, no single approach has been completely satisfactory. The thermodynamic parameters that define solution behavior provide a basis for predicting solubility and the distribution properties of molecules. A method that allows *a priori* estimation of solution behavior should have application in understanding the distribution and transport of drug molecules in the body.

Ideally, it is preferable to be able to predict how a particular solute will behave in a given solvent simply from the physical properties of the pure components (*e.g.*, molar volume, solubility parameter, dipole moment, and polarizability). However, rigorous methods based on this approach are limited almost entirely to mixtures of nonpolar species. The extension of statistical thermodynamics to binary systems has yet to provide good estimates of nonideal behavior, and often the derived equations are based on mathematically convenient approximations that have little physical significance. Consequently, a semiempirical group contribution approach appears to be an acceptable alternative.

In this approach, a molecule is considered to be composed of groups acting independently of the rest of the molecule and having certain associated thermodynamic properties. Therefore, the activity coefficient, free energy, or partition coefficient can be found from the sum of the values for the different groups comprising the molecule. In contrast to the more theoretical approaches, this method is derived solely from an analysis of empirical data. However, the results frequently assume a form similar to those mathematically derived from statistical mechanics. In cases where two polar groupings are close to each other on a solute molecule, some modification of the additive concept is necessary. However, there is no reason why such correction factors could not be calculated. This concept was originally introduced by Langmuir (1) as the "principle of independent surface action." It was refined and verified by Butler and coworkers in papers on the thermodynamics of hydration (2, 3).

The group contribution approach has been applied to the transfer of whole molecules from one phase to another (4). Its application to the transfer of various hydrocarbon groups from water to nonpolar solvents was reported (5). In this study, the group contribution approach is extended to polar groups. The hydroxyl, amino, and methylene group contributions to the free energy of transfer from water to the organic phase, from water to the vapor phase, and from heptane to the vapor phase were determined from the Henry constants of aliphatic series of hydrocarbons, alcohols, and amines in dilute aqueous and heptane solutions.

EXPERIMENTAL

Equipment and Reagents—All analyses were carried out on a gas chromatograph[1] with a dual hydrogen flame detector using helium as the carrier gas. For the alcohol studies, matched stainless steel dual columns[2] were used. For the amines, columns packed with acid-washed Chromosorb W[3] were used.

Gastight syringes[4] (2.5 or 10 ml) were used for injections. Serum vials[5], 30 ml, and rubber stoppers were used for solution equilibration. All amines and alcohols[6] had a purity of at least 99.5% as determined by GLC. These compounds were redistilled and stored over molecular sieves to remove possible traces of water.

Aqueous solutions were prepared with water distilled a second time from acid permanganate in an all-glass apparatus. Organic solutions were prepared with heptane[7] with a purity of at least 99.5% as ascertained by GLC.

To overcome the turbidity encountered during solution of the amines in distilled water and to reduce the proportion of ionized species present, 0.01 *N* NaOH was used as the aqueous phase for amines. To exclude carbon dioxide as much as possible, the distilled water was boiled before use.

Procedure—Dilute solutions (0.001–0.01 mole fraction) of either al-

[1] Beckman GC-45.
[2] Beckman 96670W, 1.830 m × 0.635 cm o.d., packed with C-22 Firebrick, 42–60 mesh, which had been coated with 30% (w/w) of a mixture consisting of (v/v): polyethylene glycol 600, three parts; diisodecyl phthalate, 10 parts; and Flexol 8N8, 15 parts.
[3] DMCS 80–100 mesh containing 5% (w/w) dc 550 as the liquid phase.
[4] Hamilton.
[5] Fisher.
[6] Polyscience Corp.
[7] Phillips Petroleum Co.

Table I—Henry Constants and γ_i^∞ Values in Water

Compound	Henry Constants: mm Hg/mole Fraction	Henry Constants: mm Hg/mole	P_i^{0a}, mm Hg	Measured γ_i^∞	Literature γ_i^∞
		Alcohols			
Methanol	187	3.37	122.2	1.53	4.51[b], 2.29[c], 1.51[d]
Ethanol	220	3.96	59.0	3.73	3.48[d], 3.69[e], 4.68[c]
1-Propanol	283	5.09	20.1	14.1	14.4[e], 12.5[b], 10.6[c]
2-Propanol	335	6.03	44.0	7.61	11.0[c], 6.54[d], 7.7[f]
1-Butanol	358	6.45	6.78	52.8	52.9[f]
2-Butanol	424	7.64	17.1	24.8	25.1[f], 24.7[d]
2-Methyl-1-propanol	516	9.29	11.6	44.5	43.2[f]
2-Methyl-2-propanol	547	9.85	42.4	12.9	11.8[f], 10.1[d]
1-Pentanol	461	8.30	2.17	212.5	214[f], 169[d]
1-Hexanol	600	10.8	0.72	834	903[f]
		Amines			
Butylamine	800	14.4	103.9	7.70	7.7[g]
Amylamine	1030	18.5	34.5	29.7	30.4[g]
Hexylamine	1310	23.6	11.4	114.5	109[g]
Heptylamine	1700	30.5	3.95	429	—
Octylamine	2170	39.1	1.34	1621	—
		Alkanes			
Pentane	5.33×10^7	9.61×10^5	513	1.04×10^5	—
Hexane	7.62×10^7	1.37×10^6	151	5.04×10^5	—
Heptane	8.63×10^7	1.56×10^6	45.7	1.89×10^6	—
Octane	1.35×10^8	2.42×10^6	14.0	9.61×10^6	—

[a] Vapor pressures for the alcohols are from Ref. 6, p. 384; those for the alkanes are from G. A. Riddick and W. G. Bunger, "Techniques of Chemistry, vol. II, Organic Solvents," A. Weissberger, Ed., Wiley-Interscience, New York, N.Y., 1970. [b] Reference 2. [c] Reference 11. [d] Reference 12. [e] Reference 13. [f] Reference 14. [g] Reference 15.

cohol or amine in water and heptane were prepared by weight in 25-ml glass-stoppered erlenmeyer flasks.

In the alcohol study, 2 ml of these solutions was then placed into 30-ml serum vials. The vials were tightly stoppered and placed in a constant-temperature water bath (25 ± 0.05°). The stoppers were punctured for approximately 15 sec to equalize vial pressure with atmospheric room pressure. The samples were allowed to equilibrate for a minimum of 15 min before analysis. Equilibration times of 5 min or more were satisfactory.

Samples of headspace gas ranging generally between 0.2 and 1.0 ml (dependent on the specific vapor pressure of the alcohol under study) were removed and injected into the gas chromatograph for analysis along with an equal amount of room air. An amount of air (equal to the total amount of sample removed) was replaced into the serum vial headspace between repeated injections. All data can be considered to be obtained under conditions of infinite dilution, so the concentrations of the species under investigation are equal to their activities.

For the amines in water and heptane, 4 ml of solution was placed into 30-ml serum vials. The vials were tightly stoppered with care to ensure that the amine solutions did not directly contact the rubber stoppers. The stoppers were punctured for approximately 30 sec to equalize vial pressure with atmospheric pressure. The vials were placed in a 25° water bath controlled to ±0.05°. The samples were allowed to equilibrate for 30 min before analysis. Less than 2-ml samples of headspace gas were removed and injected into the gas chromatograph for analysis along with an equal amount of room air.

RESULTS AND DISCUSSION

An ideal solution is defined as one that obeys Raoult's law and in which the activity of a component is equal to its mole fraction over the entire concentration range:

$$a_i = X_i \qquad \text{(Eq. 1)}$$

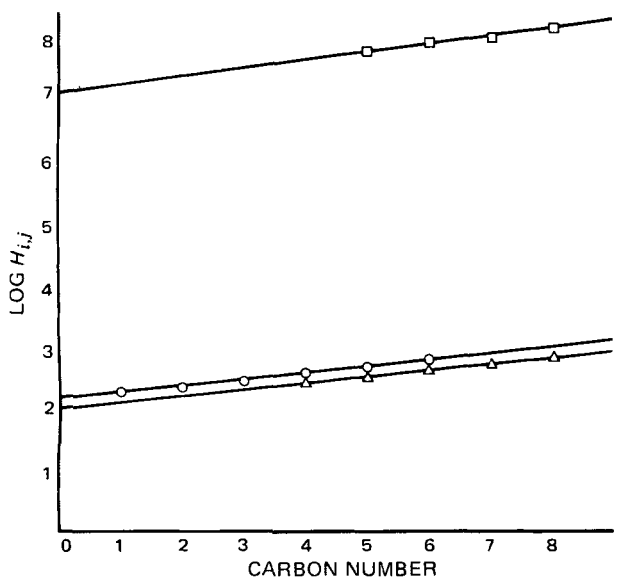

Figure 1—*Log Henry constants* versus *carbon number for homologous series of alkanes (□), alcohols (○), and amines (△) in water.*

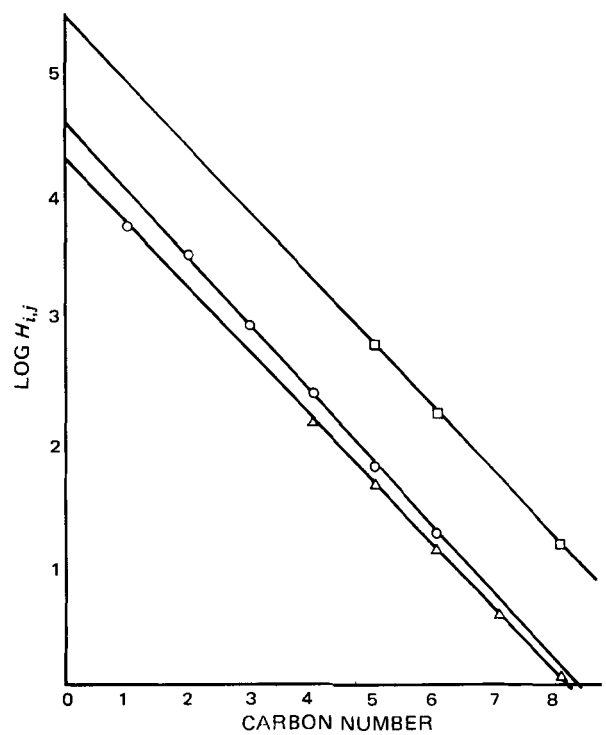

Figure 2—*Log Henry constants* versus *carbon number for homologous series of alkanes (□), alcohols (○), and amines (△) in heptane.*

Table II—Group Contribution to the Free Energy of Transfer, $\Delta(\Delta G)_x$, at 25°

Group	Process	System Studied	$\Delta(\Delta G)$, cal/mole: Measured	$\Delta(\Delta G)$, cal/mole: Literature
Methylene	Water to vapor phase	Alcohols and amines in water	−148	—
Methylene	Heptane to vapor phase	Alcohol in heptane	759	—
		Amines in heptane	703	—
		Alkanes in heptane	729	—
Methylene	Water to heptane phase	Alcohols	−907	−917[a], −877[b], −872[c], −850[d]
		Amines	−851	−849[e], −880[e]
Hydroxyl	Water to vapor phase	Alcohol in water	6880	—
Hydroxyl	Heptane to vapor phase	Alcohol in heptane	1320	—
Hydroxyl	Water to heptane phase	—	5570	5280[f], 5650[g]
Amino	Water to vapor phase	Amines in water	6470	—
Amino	Heptane to vapor phase	Amines in heptane	1490	—
Amino	Water to heptane phase	—	4980	5140[f]

[a] Reference 5. [b] Reference 17. [c] Reference 18. [d] Reference 19. [e] Reference 4, Table 21. [f] Reference 20. [g] Reference 21.

Deviations from ideal behavior are, therefore, reflected in the degree to which the value of the activity coefficient, γ_i, differs from unity, where:

$$\gamma_i = \frac{a_i}{X_i} \qquad \text{(Eq. 2)}$$

A disadvantage of a correlation based on γ_i values is that the standard state, the pure solute, is itself a complex environment. The choice of a pure solute as the standard state was criticized previously (6, 7). Rytting *et al.* (8) considered the choice of the standard state and concluded that the infinitely dilute solute in a reference hydrocarbon solvent is preferable for drug systems; *i.e.*, drug solution behavior should be examined on the basis of Henry's limiting law rather than Raoult's law, *i.e.*:

$$H_{i,j} = \frac{P_i}{X_i \gamma_i^*} \qquad \text{(Eq. 3)}$$

where $H_{i,j}$ is Henry's constant and γ_i^* is an activity coefficient that has a value of unity at infinite dilution.

Prausnitz (9) and Miller and Prausnitz (10) discussed the relationship between activity coefficients based on Raoult's law ($\gamma_i \rightarrow 1$ as $X_i \rightarrow 1$) and those based on Henry's law ($\gamma_i^* \rightarrow 1$ as $X_i \rightarrow 0$).

In the limit as $X_i \rightarrow 0$:

$$H_{i,j} = \gamma_i^\infty P_i^0 \qquad \text{(Eq. 4)}$$

where γ_i^∞ is the activity coefficient of the solute at infinite dilution in the solvent and the pure solute is taken as the standard state.

Table I shows the γ_i^∞ values and the Henry constants in both a mole fraction and molar scale for the alcohols and amines in water found in this study at 25° along with the P_i^0 values of the pure substances as recorded in the literature at 25°.

The values for the Henry constants of alkanes in water, also listed in Table I, were obtained by calculation from the solubility data of McAuliffe (16). He determined the solubilities in water at room temperature of various alkanes by direct injection of hydrocarbon-saturated water into a gas chromatograph and reported the solubilities in grams of hydrocarbon per 10^6 g of water.

The Henry constants for the alkanes in water were determined by converting the solubility data of McAuliffe into mole fraction, X_i, solubility. The following assumptions were made:

1. The activity of alkane must be the same in both phases that are in equilibrium with each other.
2. The miscibility of the two liquids being slight, the activity, a_i, of the alkane in the alkane-rich phase will be practically one, while the activity in the dilute aqueous phase will be equal to $X_s \gamma_i^\infty$, where X_s is the solubility expressed as a mole fraction. Thus, $X_s \gamma_i^\infty = 1$; and for a saturated solution of mole fraction X_s of pure alkane, one may write:

$$\gamma_i^\infty = \frac{1}{X_s} \qquad \text{(Eq. 5)}$$

Similarly, Henry constants are obtained as described earlier in Eq. 4. The calculated values for the γ_i^∞ and the Henry constants for the alkanes in water are listed in Table I. Although there is a lack of agreement among literature values, a relatively constant methylene group contribution is often observed within individual studies.

Figure 1 shows a plot of the log $H_{i,j}$ values *versus* carbon number for the alcohols and amines studied in water as well as for alkanes in water. The free energy of the methylene group is calculated from the slope of the line:

$$\Delta(\Delta G) = -RT \ln (\text{slope}) \qquad \text{(Eq. 6)}$$

The result was −148 cal/mole for the transfer of a methylene group from water to the vapor phase. Also, from Fig. 1, the hydroxyl and amine group contributions may be obtained by subtracting the alkane in water values from the alcohol in water and amine in water values for each corresponding carbon number:

$$\Delta(\Delta G)_X = -RT (\ln H_{i,jRX} - \ln H_{i,jRH}) \qquad \text{(Eq. 7)}$$

Table III—Henry Constants and γ_i^∞ Values in Heptane

Compound	Henry Constants: mm Hg/mole Fraction	Henry Constants: mm Hg/mole	P_i^{0a}, mm Hg	Measured γ_i^∞	Literature γ_i^∞
		Alcohols			
Methanol	4970	733	122.2	40.6	29.6[b], 92.6[c]
Ethanol	2800	414	59.0	47.5	16.5[b], 49[c]
1-Propanol	810	119.5	20.1	40.3	14.2[b]
2-Propanol	1550	229	44.0	35.3	32.4[c]
1-Butanol	226	33.4	6.78	33.4	13.6[b], 37.1[c]
2-Butanol	511	75.3	18.29	27.9	27.9[c]
2-Methyl-1-propanol	332	49.0	10.22	32.5	32.5[c]
2-Methyl-2-propanol	775	114	43.0	18.0	18.0[c]
1-Pentanol	59.0	8.71	2.17	27.2	—
1-Hexanol	17.1	2.52	0.72	23.8	—
		Amines			
Butylamine	132	19.5	104	1.27	—
Amylamine	41.8	6.16	34.5	1.21	—
Hexylamine	12.9	1.91	11.4	1.13	—
Heptylamine	3.79	0.56	3.95	0.96	—
Octylamine	1.17	0.17	1.34	0.87	—
		Alkanes			
Pentane	554	81.65	513.6	1.08	—
Hexane	156	23.0	151	1.03	—
Octane	13.9	2.04	14	0.99	—

[a] See footnote *a*, Table I. [b] Reference 22. [c] Reference 12.

The results are shown in Table II.

Figure 2 shows a plot of the log $H_{i,j}$ values (Table III) *versus* the carbon number for the alcohols, amines, and alkanes in heptane. The free energy of the methylene group was about 730 cal/mole for the transfer of a methylene group from organic to vapor phases. The hydroxyl and amino group contributions also may be obtained from Fig. 2 by subtracting the alkane in heptane values for each corresponding carbon number as in Eq. 7. These values were 1320 cal/mole for the hydroxyl group and 1490 cal/mole for the amino group from organic to vapor phases (Table II).

The group contribution to the free energy of transfer for the methylene group from water to organic phases was −851 cal/mole based on the data for the amines. The value found for the methylene group in the alcohol studies was −907 cal/mole. Both of these values agree with reported literature values for the methylene group (Table II).

The group contribution to the free energy of transfer for the amino group from water to the organic phase was 4980 cal/mole. Pescar and Martin (20) used GLC to study the thermodynamic solution properties of two-component volatile nonelectrolyte solutions at infinite dilution. Their method for the determination of γ_i^∞ was based on chromatographic retention volumes, and the value reported for the free energy contribution of transfer of the amino group from water to the organic phase was 5140 cal/mole.

The group contribution to the free energy change for the hydroxyl group from water to the organic phase was 5570 cal/mole, which is in reasonable agreement with the literature values shown in Table II.

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Spectrophotometric Determinations of 3-Dimethylaminomethylkhellin Hydrochloride and Khellin

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Received October 7, 1976, from the **Pharmaceutical Chemistry Department, Faculty of Pharmacy, Cairo University, Cairo, Egypt*, and the ‡*Stability Research Department, The Nile Company for Pharmaceuticals and Chemical Industries, El-Ameria, Cairo, A.R. Egypt.*
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Abstract □ Spectrophotometric assays are proposed for the determination of 3-dimethylaminomethylkhellin hydrochloride and khellin in bulk chemical and dosage forms. The acid dye method, using methyl orange at pH 5, is applied to assay the amine in the form of an ion-pair extractable in chloroform with maximum absorbance at 420 nm. The perchloric acid method, depending on formation and extraction of the oxonium salts of both compounds, is used to assay the amine and khellin at 333 or 430 nm and at 325 or 410 nm, respectively. The reineckate method can be used to assay the amine as the reineckate derivative in acetone with maximum absorbance at 530 nm. However, small amounts of the amine (1.5–3 mg) can be determined as the reineckate in methanol with maximum absorbance at 245 nm. Stability determination of the two compounds can be done by the acid dye and perchloric acid methods. The three methods are sufficiently accurate, sensitive, and precise.

Keyphrases □ 3-Dimethylaminomethylkhellin—spectrophotometric analyses in bulk drug and dosage forms, various methods compared □ Khellin—spectrophotometric analyses in bulk drug and dosage forms, various methods compared □ Spectrophotometry—analyses, 3-dimethylaminomethylkhellin and khellin in bulk drug and dosage forms, various methods compared □ Spasmolytic agents—3-dimethylaminomethylkhellin and khellin, spectrophotometric analyses in bulk drug and dosage forms, various methods compared

3-Dimethylaminomethylkhellin hydrochloride (I) possesses approximately three times the spasmolytic activity of khellin and is only half as toxic (1). Clinical trials showed that I is well tolerated for the treatment of acute renal colics with negligible side effects (2).

For the quantitative determination of I, either the basic