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# Determination of the thermodynamics of the methyl group in solutions of drug molecules

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The contribution of the $CH_3$ group to the solution thermodynamics of drug molecules is dependent on whether it is attached to a ring system or is in the terminal position in an aliphatic chain. In the former case group contributions for $CH_3$ are very similar to those found for the $CH_2$ group. For instance, in partition, the $CH_3$ group contribution (log $F_{CH_3}$) is in the range 0·65 to 0·28 ($\Delta G = 2{\cdot}303$ RT log $F_{CH_3}$) and is dependent on the polarity of the organic solvent. The contribution for the terminal aliphatic $CH_3$ is not equivalent to the mid chain $CH_2$ and a $CH_3$ correction factor or 1·14 to 1·34 kcal $mol^{-1}$ (4·77 to 5·61 kJ $mol^{-1}$), has been calculated from alkane solubility data and partition studies. The additivity of group contributions and the correct choice of reference state are also discussed.

Davis, Higuchi & Rytting (1972) have previously showed that the methylene group contribution to the thermodynamics of solutions of drug molecules could be obtained from activity coefficients, Henry's law constants and partition coefficient data. The free energy of transfer of the $CH_2$ group from water to organic solvent ranged from −850 to −450 cal $mol^{-1}$ (1 cal $mol^{-1}$ = 4·186 kJ $mol^{-1}$) depending on the nature of the solvent and differences in group values could be rationalized in terms of solvent polarity. In this paper the methyl group is considered.

Many authors have assumed that the $CH_2$ and $CH_3$ contributions are identical (Hansch & Anderson, 1967; Kakovsky, 1957; Hersh, 1971). So that for an alkanol ($C_nH_{2n+1}OH$)

$$\Delta G_{ROH} = \Delta(\Delta G)_{OH} + n\,\Delta(\Delta G)_{CH_2} \quad .. \quad .. \quad .. \quad (1)$$

This is unjustified because in some cases $\Delta(\Delta)G_{CH_3}$ is twice as large as $\Delta(\Delta)G_{CH_2}$ (Nemethy, Steinberg & Scheraga, 1963; Krishnan & Friedman, 1969).

Firstly the difference between the various $CH_3$ groups must be considered. The $CH_3$ group can have a number of different positions on a drug molecule and the attention of this paper is directed towards the $CH_3$ attached to an aromatic or saturated ring system and $CH_3$ in the terminal position in an alkyl chain.

## RESULTS AND DISCUSSION

### (i) *The methyl group attached to a ring system*

*Substituted benzenes.* Aromatic compounds containing methyl substituents have been studied extensively and group contributions can be calculated from literature data (Table 1). The contributions of the methyl and methylene groups to solution and partition behaviour are very similar and the assumption that $\Delta(\Delta G)_{CH_3} \cong \Delta(\Delta G)_{CH_2}$ is valid for ring substituted $CH_3$ groups. (The scatter in the results can be attributed

Table 1. *Group contributions for $CH_3$ and $CH_2$ calculated from data on alkyl and methyl substituted benzenes* (25°).

| Solute | Molar volume (*a*) | Group volume | | $\log\gamma_w^{\infty}$ (*b*) | $\Delta\log\gamma_{CH_2}^{\infty}$ | $\Delta\log\gamma_{CH_3}^{\infty}$ | log K$_D$ (*c*) octanol–water | log $F_{CH_2}$ | log $F_{CH_3}$ |
|---|---|---|---|---|---|---|---|---|---|
| | cm$^3$ mol$^{-1}$ | $CH_2$ | $CH_3$ | | | | | | |
| Benzene .. .. | 89 | — | — | 3·40 | — | — | 2·14 | — | — |
| Toluene .. .. | 107 | — | 18 | 3·98 | — | 0·58 | 2·71 | — | 0·57 |
| Ethylbenzene .. | 123 | 16 | — | 4·54 | 0·56 | — | 3·15 | 0·44 | — |
| *o*-Xylene.. .. | 121 | — | 16 | 4·46 | — | 0·53 | 2·77 | — | 0·31 |
| *m*-Xylene .. | 123 | — | 17 | 4·50 | — | 0·55 | 3·20 | — | 0·53 |
| *p*-Xylene.. .. | 124 | — | 17·5 | 4·49 | — | 0·55 | 3·15 | — | 0·50 |
| n-Propylbenzene | 140 | 17 | — | 5·08 | 0·54 | — | 3·62 | 0·47 | — |
| Mesitylene .. | 140 | — | 17 | 4·83 | — | 0·48 | — | — | — |
| Mean .. .. | — | 16·5 | 17·1 | — | 0·55 | 0·54 | — | 0·45 | 0·46 |

(*a*) 25° from Hildebrand & Scott (1950).
(*b*) From Tsonopoulos (1970)—mean values.
(*c*) From Leo & others (1971)—mean or preferred values.

to the experimental difficulties in measuring low water solubilities and high partition coefficients rather than to specific inductive effects.) Indeed, on the basis of group molar volume (Table 1) one would expect that $CH_2$ and $CH_3$ would yield similar contributions.

*Detailed partition results.* $CH_3$ group contributions (log $F_{CH_3}$) obtained from partition studies on methyl substituted aromatic solutes and other ring systems, are listed in Table 2. The original partition experiments were examined critically as before (Davis & others, 1972). For most solvents, preferred values of log $F_{CH_3}$ were selected from consistent data in accurate partition studies and where the $CH_3$ is not "masked" or next (*ortho*) to a polar grouping on the ring. For instance, when the $CH_3$ group is next to a polar function (e.g. 2-methylaniline) the group contribution is usually larger than when removed from the polar group (3 or 4-methylaniline) (Golumbic & Goldbach, 1951; Lien, Koda & Tong, 1971). Similarly, a $CH_3$ group itself can be masked by the presence of the ring system and give a much smaller contribution, e.g. 2-methyl-8-hydroxyquinoline.

The preferred log $F_{CH_3}$ values for a given solvent are essentially constant. A similar conclusion was reached by Fujita, Iwasa & Hansch (1964) who studied only the octanol–water partition system. The mean preferred values of log $F_{CH_3}$ (Table 3)

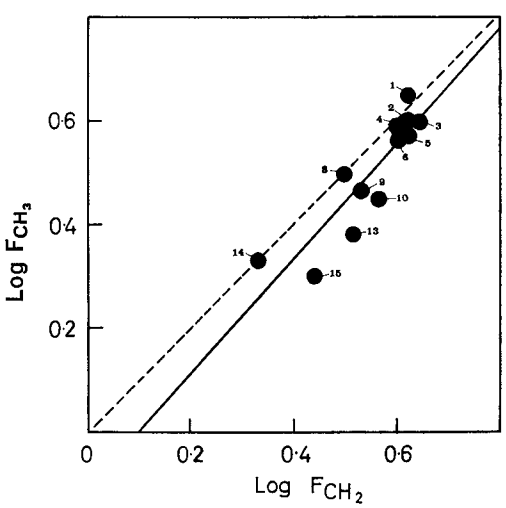


FIG. 1. Correlation between $CH_3$ and $CH_2$ group contributions from partition studies. Abscissa log $F_{CH_2}$. Ordinate log $F_{CH_3}$. Numbers refer to solvents listed in Table 3. Solid line: Regression line (eqn 2). Dotted line: log $F_{CH_3}$ = log $F_{CH_2}$.

Table 2. *The methyl group contribution (ring systems) to partition between water and organic solvent.*

| Solvent | log $F_{CH_3}$ | Solute system | Reference |
|---|---|---|---|
| Cyclohexane | 0·85 | 2-Methylphenol | Golumbic & others (1949) |
| | 0·76 | Alkylbenzenes | Currie & others (1966) |
| | 0·74 (a) | 2,5-Methylphenol | Golumbic & others (1949) |
| | 0·74 (a) | 2,4-Methylphenol | |
| | 0·73 | 2-Methylsalicylaldehyde | Burton & others (1964) |
| | 0·71 | 4-Methylphenols | Higuchi & others (1969) |
| | 0·70 | 3-Methylsalicylaldehyde | Burton & others (1964) |
| | 0·68 | 4-Methylchlorophenol | Golumbic & others (1949) |
| | 0·66 (a) | 2,6-Methylaniline | Golumbic & Goldbach (1951) |
| | 0·65 | 2-Methylaniline | Golumbic & Goldbach (1951) |
| | 0·65 | 2-Methyl conjugated compounds | Currie & others (1966); Lough & others (1968) |
| | 0·65* | 4-Methyl conjugated compounds | Currie & others (1966); Lough & others (1968) |
| | 0·63 (a) | 3,5-Methylphenol | Golumbic & others (1949) |
| | 0·62* | 4-Methylphenol | |
| | 0·61 (a) | 2,5-Methylaniline | Golumbic & Goldbach (1951) |
| | 0·61 (a) | 2,4-Methylaniline | |
| | 0·61* | 3-Methylaniline | Golumbic & Goldbach (1951) |
| | 0·60 | 2-Methylnitrostyrenes | Currie & others (1966); Lough & others (1968) |
| | 0·60* | 4-Methylnitrostyrenes | |
| | 0·59 (a) | 3,5-Methylaniline | Golumbic & Goldbach (1951) |
| | 0·57* | 3-Methylphenol | Golumbic & others (1949) |
| | 0·54* | 4-Methylaniline | Golumbic & Goldbach (1951) |
| | 0·48 | 3-Methylbenzaldehyde | Burton & others (1964) |
| | 0·16 | 2-Methylbenzaldehyde | |
| Heptane | 0·57* | 3-Methylphenol | De Ligny & others (1966) |
| | 0·57* | 3-Methylaniline | |
| Carbon tetrachloride | 0·66* | 4-Methyl-8-hydroxyquinoline | Mottola & Freiser (1966); Fresco & Freiser (1964) |
| | 0·65* | | |
| | 0·61 | 2-Methyl-8-hydroxyquinoline | Fresco & Freiser (1964); Mottola & Freiser (1966) |
| | 0·58 | | |
| Chloroform | 0·76 | 3-Methylhydrobromides | Quintana & Smithfield (1967) |
| | 0·70 | 2-Methylsulphonamides | Kakeya & others (1969) |
| | 0·64 | 2-Methyl-8-hydroxyquinoline | Stary (1964) |
| | 0·63* | 4-Methyl-8-hydroxyquinoline | Fresco & Freiser (1694) |
| | 0·63* | | Mottola & Freiser (1966) |
| | 0·62* | 5-Methyl-8-hydroxyquinoline | Stary (1964) |
| | 0·50 | 2-Methyl-8-hydroxyquinoline | Mottola & Freiser (1966); Fresco & Freiser (1964) |
| | 0·58 | | |
| | 0·57* | 4-Methylsulphonamides | Kakeya & others (1969) |
| | 0·56* | 3-Methylsulphonamides | |
| | 0·53 | 4-Methylbenzylpyridine | Quintana & Smithfield (1967) |
| | 0·33 | Alkyl sulphates of methyl quinolinium derivatives | Plakogiannis & others (1970) |
| Methylene dichloride | 0·59* | 4-Methyl-8-hydroxyquinoline | Mottola & Freiser (1966) |
| | 0·52 | 2-Methyl-8-hydroxyquinoline | |
| Toluene | 0·57* | 4-Methyl-8-hydroxyquinoline | Mottola & Freiser (1966) |
| | 0·54 | 2-Methyl-8-hydroxyquinoline | |
| Di-ethyl ether | 0·49 | Steroids $CH_3$ in 16$\beta$, 6$\alpha$- and 16$\alpha$-positions | Flynn (1971) |
| | 0·46 | | |
| | 0·40 | | |
| Butanol | 0·30* | 4-Methyl-8-hydroxyquinoline | Mottola & Freiser (1966) |
| | 0·27 | 2-Methyl-8-hydroxyquinoline | |
| 3-Methyl-1-butanol | 0·40* | 4-Methyl-8-hydroxyquinoline | Mottola & Freiser (1966) |
| | 0·34 | 2-Methyl-8-hydroxyquinoline | |
| 4-Methyl-2-pentanol | 0·38* | 4-Methyl-8-hydroxyquinoline | Mottola & Freiser (1966) |
| | 0·36 | 2-Methyl-8-hydroxyquinoline | |

Table 2—*continued.*

| Solvent | log $F_{CH_3}$ | Solute system | Reference |
|---|---|---|---|
| 1-Octanol | 0·68 | 2-Methylphenoxyacetic acid | Fujita & others (1964) |
| | 0·57* | 3-Methylphenol | |
| | 0·57* | 3-Methylnitrobenzene | |
| | 0·56* | Methylbenzenes | |
| | 0·54* | 3-Methylsulphonamides | Kakeya & others (1969) |
| | 0·53 | 2-Methylsulphonamides | |
| | 0·52* | 4-Methylphenoxyacetic acid | Fujita & others (1964) |
| | 0·52* | 3-Methylbenzoic acid | |
| | 0·52* | 4-Methylnitrobenzene | |
| | 0·52* | 4-Methylethers | Fuller & others (1968) |
| | 0·52 (a) | 3,4-Methylethers | |
| | 0·51 (a) | 3,5-Methylethers | |
| | 0·51 (a) | 3,4,5-Methylethers | |
| | 0·51* | 4-Methylsulphonamide | Kakeya & others (1969) |
| | 0·51* | 3-Methylphenoxyacetic acid | Fujita & others (1964) |
| | 0·50 (a) | 3,4-Methylphenoxyacetic acid | |
| | 0·50* | 3-Methylbenzyl alcohol | |
| | 0·50* | 3-Methylaniline | |
| | 0·49* | 3-Methylphenylacetic acid | |
| | 0·49* | 4-Methylaniline | |
| | 0·48* | 4-Methylbenzyl alcohol | |
| | 0·48* | 4-Methylphenol | |
| | 0·47* | 3-Methylphenol | Machleidt & others (1972) |
| | 0·47* | 4-Methylphenol | |
| | 0·45 | 3,5-Methylphenol | |
| | 0·45* | 4-Methylphenylacetic acid | Fujita & others (1964) |
| | 0·44* | 4-Methyl-8-hydroxyquinoline | Mottola & Freiser (1966) |
| | 0·42* | 4-Methylbenzoic acid | Fujita & others (1964) |
| | 0·37 | 2-Methyl-8-hydroxyquinoline | Mottola & Freiser (1966) |
| | 0·30 | 2,6-Methylphenol | Machleidt & others (1972) |
| | 0·24 | Methyl substituted analgesics | Dearden & Tomlinson (1971) |
| Dodecanol | 0·40 | 3-Methylsalicylaldehyde | Burton & others (1964) |
| Oleyl alcohol | 0·61 | 2-Methylsalicylaldehyde | Burton & others (1964) |
| | 0·56 | 3-Methylsalicylaldehyde | |
| n-Butyl acetate | 0·61 | 3-Methylphenols | Ivanov & Makeikina (1964) |
| iso-Pentyl acetate | 0·45* | 4-Methyl-8-hydroxyquinoline | Mottola & Freiser (1966) |
| | 0·37 | 2-Methyl-8-hydroxyquinoline | |
| Methyl dodecanoate | 0·72 | 2-Methylsalicylaldehyde | Burton & others (1964) |
| | 0·62 | 3-Methylsalicylaldehyde | |
| 3-Pentanone | 0·34 | 2-Methyl-8-hydroxyquinoline | Mottola & Freiser (1966) |
| | 0·33* | 4-Methyl-8-hydroxyquinoline | |
| Cyclohexanone | 0·28* | Methylphenoxyacetic acids | Leo & others (1971) |
| *o*-Dichlor-benzene | 0·53* | 4-Methyl-8-hydroxyquinoline | Mottola & Freiser (1966) |
| | 0·52 | 2-Methyl-8-hydroxyquinoline | |
| Olive oil | 0·46* | Alkylbenzenes | Brancha & O'Brien (1966) |

* Preferred value
(a) Value per $CH_3$

fall as the solvent becomes more polar and there are broad qualitative correlations relating group contribution values to dielectric constant, dipole moment and solubility parameter.

Christian, Johnson & others (1966) noted that the solubility of water in various solvents was a good measure of their relative solvation ability and, Leo, Hansch & Elkins (1971) have found that partitioning solvents could be ordered sensibly according to the amount of water they contained at saturation. Hence, the inability of a particular solvent to accommodate water is a good measure of its lipophilic behaviour to a wide range of solutes. The present work shows that this is also the

Table 3. *Group contributions for the methyl group.*

| | Solvent | log $F_{CH_3}$ (*a*) | log $F_{CH_3}$ (*b*) | Solvent solubility parameter (*d*) (Cal $^{1/2}cm^{-3/2}$) | Solvent dielectric constant (*e*) | Solvent dipole moment (*e*) | Solubility of water in solvent (molar) (*e*) |
|---|---|---|---|---|---|---|---|
| 1. | Carbon tetrachloride | 0·65 | 0·62 | 8·6 | 2·24 | 0 | 0·0088 |
| 2. | Chloroform | 0·60 | 0·62 | 9·3 | 4·81 | 1·15 | 0·060 |
| 3. | Cyclohexane | 0·60 | 0·64 | 8·2 | 2·02 | 0 | 0·0044 |
| 4. | Methylene dichloride | 0·59 | 0·60 | 9·7 | 8·93 | 1·14 | 0·14 |
| 5. | Heptane | 0·57 | 0·62 | 7·5 | 1·92 | 0 | 0·0035 |
| 6. | Toluene | 0·57 | 0·60 | 8·9 | 2·37 | 0·31 | 0·015 |
| 7. | *o*-Dichlorbenzene | 0·53 | — | 10·0 | 9·93 | 2·37 | 0·22 |
| 8. | 1-Octanol | 0·50 | 0·50 | 10·3 | 10·34 | 1·7 | 2·3 |
| 9. | Olive oil | 0·46 | 0·53 | — | — | — | — |
| 10. | Diethyl ether | 0·45 | 0·56 | 7·4 | 4·34 | 1·15 | 0·57 |
| 11. | Isopentyl acetate | 0·45 | — | 8·5 | 4·60 | 1·82 | 0·77 |
| 12. | 3-Methyl-1-butanol | 0·40 | — | 11·1 | 14·7 | 1·82 | 4·32 |
| 13. | 4-Methyl-2-pentanol | 0·38 | 0·51 (*c*) | 10·0 | — | — | 2·85 |
| 14. | 3-Pentanone | 0·33 | 0·33 | 8·8 | 17·0 | 2·82 | 1·15 |
| 15. | 1-Butanol | 0·30 | 0·44 | 11·4 | 17·5 | 1·75 | 9·2 |
| 16. | Cyclohexanone | 0·28 | — | 10·4 | 18·3 | 3·01 | 3·59 |

(*a*) Mean of preferred values in Table 2.
(*b*) Mean of preferred values from Table 5 (Davis & others, 1972).
(*c*) Earlier a value of 0·54 was given (Davis & others, 1972). Further experimental values suggest a value of 0·51.
(*d*) Hildebrand & Scott (1950, 1962), Rheineck & Lin (1968).
(*e*) Riddick & Burger (1970).

case for the functional groups $CH_2$ and $CH_3$ for as the solubility of water in the solvent increases, the contributions fall. (A detailed statistical analysis of the relation between group contributions and solvent properties using regression analysis will be published elsewhere.)

The log $F_{CH_3}$ values are in general slightly smaller than the corresponding log $F_{CH_2}$ values (Fig. 1). The interrelation is represented by the regression equation

$$\log F_{CH_3} = 1{\cdot}12 \log F_{CH_2} - 0{\cdot}113 \quad .. \quad .. \quad .. \quad (2)$$

The correlation coefficient = 0·887; standard deviation = 0·057; and for 95% confidence limits the slope has a range 0·709 to 1·53 and the intercept a range −0·340 to 0·115. In assuming that log $F_{CH_3}$ = log $F_{CH_2}$ the error will be small for the $CH_3$ group attached to a ring system provided that there is no interaction between functional groups. The slight differences between log $F_{CH_3}$ and log $F_{CH_2}$ values, where they occur, can be attributed to inductive effects (Marcinkiewicz, Green & McHale, 1963).

It is unfortunate that results, such as those above for the $CH_3$ group attached to a ring system, have been extrapolated to aliphatic compounds and in particular to the $CH_3$ group in the terminal position. In this situation log $F_{CH_2} \gg$ log $F_{CH_3}$.

(ii) *The methyl group in the terminal position in an alkyl chain*

The terminal $CH_3$ contribution is difficult to calculate as it is not possible to subtract the log of an activity or partition coefficient for the parent molecule from the log of the value for the substituted derivative. Moreover, if one extrapolates a free energy versus carbon number plot to zero carbon number (Fig. 2) one must take into account not only the $CH_3$ contribution but also the contribution from the polar grouping(s) unless dealing with the unsubstituted alkanes.

If $$\Delta \log \gamma^{\infty}_{w\,CH_3} = \Delta \log \gamma^{\infty}{}_{w\,CH} \quad .. \quad .. \quad .. \quad (3)$$

a plot of the excess free energy of mixing of various homologous alkanes with water against the number of carbon atoms (Fig. 2) should pass through the origin. Instead, an intercept (some form of $CH_3$ correction) of 2·00 kcal $mol^{-1}$ is found.

A perusal of the physico-chemical data for the $CH_3$ (terminal) and $CH_2$ groups shows that in all cases the values for $CH_3$ are much larger than for $CH_2$ (Table 4) and it is difficult to see why many previous workers have ignored all the evidence to this effect. Thus, the extrapolation of activity or partition coefficient data for aliphatic compounds to zero carbon number *does not* give a group value for the functional group unless one is able to calculate, and correct for, the presence of the terminal $CH_3$. If this is not possible one must quote extrapolated values in a suitable form (*e.g.* HO . . . H) (Krishnan & Friedman, 1969).

Table 4. *Evidence that aliphatic $CH_2$ is not the same as aliphatic $CH_3$ terminal.*

| Parameter | $CH_2$ | $CH_3$ | Comments | Reference |
|---|---|---|---|---|
| *Size* | | | | |
| Volume (molar) | 10·23 | 13·67 | $cm^3\ mol^{-1}$ from models | Bondi (1964) |
| | 16·5 | 34·0 | ml $mol^{-1}$ | Rheineck & Lin (1968) |
| | 16·15 | 32·30 | " | Papadopoulos & Derr (1959) |
| | 16·261 | 32·837 | " | Hirsch (1970) |
| | 16·58 | 31·48 | " | Exner (1967a) |
| Parachor | 39·7 | 56·7 | | Exner (1967b) |
| | 40·0 | 55·7 | | Vogel (1948) |
| | 40·0 | 55·5 | | Quayle (1953) |
| | 39·0 | 56·1 | | Sugden (1924) |
| Area (surface) | 1·35 | 2·13 | $cm^2\ mol^{-1} \times 10^9$ from models | Chao & others (1967) |
| | 1·35 | 2·12 | | Bondi (1964) |
| | 0·26 | 0·46 | Relative surface area found from models by packing H atoms around groups | Harris (1971) |
| Area (cross-sectional) | 1·0 | 1·59 | Relative ($CH_2 = 1·0$) | Papadopoulos & Derr (1959) |
| | 0·05 | 0·11 | $nm^2$ from models (area occupied at interface) | Pomerantz & others (1967) |
| | 6·5 | 15·0 | Å adsorption | Values calculated from data summarized by McClellan & Harnsberger (1967) |
| | 5·0 | 11·0 | Å Van der Waals models | |
| | 6·0 | 8·5 | Å models from density | |
| | 4·6 | 11·0 | Å measurements | |
| Water neighbours | 2 | at least 8 | | Nemethy & others (1963) |
| | 2+ | 7+ | some water molecules in touch with other groups in solute molecule | Laiken & Nemethy (1970) |
| | 2 | 3 | | Butler (1962) |
| Thermodynamic quantities | 0·22 | 0·16 | kcal $mol^{-1}$ Entropy of transfer | Krishnan & Friedman (1969) |
| | −2·7 | −5·8 | kJ $mol^{-1}$ Enthalpy of adhesion | Aveyard, Briscoe & Chapman (1972) |
| Others | 133 | 214 | Molar attraction constant used in solubility parameter calculations | Small (1953) |
| | 1·83 | 2·56 | $Å^3$ molecular polarizability | Krishnan & Friedman (1969) |
| | 1·83 | 2·33 | | Padday & Uffindell (1968) |
| | 12·51 | 18·80 | Group polarizability | Moelwyn-Hughes (1964) |
| | 4·66 | 6·34 | Group refractivity | Vogel (1948) |

*The terminal $CH_3$ group correction factor from alkane solubility.* Four different approaches used to calculate the $CH_3$ correction factor will be considered with reference to data for the alkanols and the OH group contribution (Table 5). The $CH_2$ contribution (calculated from the gradient of the straight line in Fig. 2) is the same for the alkanes and the alkanols.

A mean $CH_3$ (terminal) correction of 1·14 kcal $mol^{-1}$ can be calculated from the values under methods 3 and 4. [Method 4 will give similar values to method 3 but will be limited by the accuracy of the alkane datum. Reliable alkane solubility (and partition data) are difficult to obtain, especially for the higher chain length compounds. Furthermore, above $C_{10}$ the linear relation between $\Delta G$ and carbon number appears to fall off due to a probable aggregation of the alkane molecules (Franks, 1966; McAuliffe, 1969)]. This indicates that $\Delta(\Delta G)_{CH_3} = 2{\cdot}00$ kcal $mol^{-1}$; a value more than twice that for $CH_2$ (850 cal $mol^{-1}$). Further verification of this value can be obtained from Tanford's (1962) studies on the solubility of proteins.

*The terminal $CH_3$ group correction factor from partition studies.* The correction values listed in Table 5 were determined from values of the excess free energy of solutes at infinite dilution in water. In partitition studies the differences between the $CH_3$ and $CH_2$ groups in the organic phase must also be considered. In general, both groups will behave in a more or less ideal manner in all but very polar solvents and the limited evidence available would suggest that, as a first approximation (Ratcliff & Chao, 1969)

$$\Delta \log \gamma^{\infty}_{o CH_3} \simeq \Delta \log \gamma^{\infty}_{o CH_3} \quad .. \quad .. \quad .. \quad .. \quad (4)$$

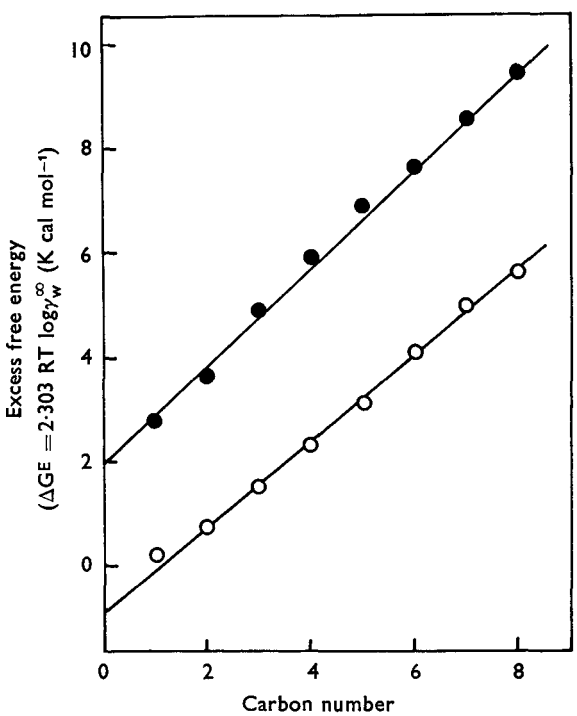


FIG. 2. The change in free energy with chain length for alkanes and alkanols in water (25°). Abscissa, carbon number. Ordinate, excess free energy ($\Delta G^E = 2{\cdot}303$ RT log $\gamma^{\infty}_{w}$ ) kcal $mol^{-1}$. ●, alkanes—values calculated from data of McAuliffe (1966), Nelson & De Ligny (1968). ○, Alkanols—values calculated from data of Pierotti & others (1959a), Butler (1962), Kinoshita & others (1958). log $\gamma^{\infty}_{w}$ = −log x where x is mol fraction solubility.

Table 5. *Group contributions for the free energy of mixing of the hydroxyl group with water and the terminal $CH_3$ correction.*

| Method | $\Delta(\Delta G^E)_{OH}$ (kcal mol$^{-1}$) | Correction for Terminal $CH_3$ (kcal mol$^{-1}$) | Comments | Author |
|---|---|---|---|---|
| | | | *Incorrect* | |
| 1 | −0·90 | nil | Simple extrapolation | Hansch & Anderson (1967)<br>Copp & Everett (1953) |
| | | | *Incorrect* | |
| 2 | −3·0 | 2·0 | Alkane intercept (fig. 1), i.e. $2CH_3$ groups | Nelson & de Ligny (1968)<br>Brown & others (1968)<br>Hansch & Fujita (1964) |
| | | | *Correct* | |
| 3 | −1·95 | 1·00 | ½ alkane intercept | Fig. 1 |
| | −1·81 | 0·90 (a) | Preference given to higher alkanes | Nemethy & others (1963) |
| | −2·21 | 1·33 | | Molyneux & others (1965) |
| | | 1·43 (a) | | Mukerjee (1967) |
| | | | *Correct* | |
| 4 | −2·20 | 1·19 | EtOH − ½ butane | Alexander & Hill (1969) |
| | −2·00 | 0·99 | PrOH − ½ hexane | |
| Mean | Methods 3 and 4 | 1·14 | | |
| Protein solubility studies | | 1·15 | Transfer of lysine and norleucine side chains from water to ethanol and butanol | Tanford (1962) |

(a) Value not quoted by original authors; calculated from the experimental data that they provided.

Table 6. *Log $F_x$ values obtained by differences in partition coefficients (equation 5).*

| Group | Solvent | log $K^x_{D(RX)}$ (a) | log $K^x_{D(RH)}$ (a) | log $F_x$ |
|---|---|---|---|---|
| *COOH* | | | | |
| RX = β-Phenyl propionic acid | Octanol | 1·84 | 3·15 | −1·31 |
| RH = Ethyl benzene | Xylene | 1·23 | 4·54 (b) | −3·31 |
| | Chloroform | 1·74 | 4·57 (c) | −2·83 |
| *OH* | | | | |
| RX = 3-Phenyl propanol | Octanol | 2·71 | 4·55 | −1·74 |
| RH = Propyl benzene | Hexane | 0·95 | 4·83 (d) | −3·88 |

(*a*) Partition coefficient (25°) were taken from the compilation of Leo & others (1971) and corrected to mole fraction concentration scale.

(*b*) Experimental partition coefficient value not available.
log $K^x_D$ calculated as log $\gamma^{\infty}_w$ − log $\gamma^{\infty}_o$.
log $\gamma^{\infty}_w$ = 4·54 (Tsonopoulos, 1970)
log $\gamma^{\infty}_o$ = 0·00 (estimated from Hildebrand & Scott (1950) solubility parameter equation and published values of limiting activity coefficients for benzene-alkyl benzene systems.)

(*c*) As (*b*) above. log $\gamma^{\infty}_o$ = −0·03 (estimated from solubility parameters and published values of limiting activity coefficients for alkylbenzenes—chloroform systems).

(*d*) Experimental partition coefficient value not available.
log $K^x_D$ calculated as in (*b*).
log $\gamma^{\infty}_w$ = 5·08 (Tsonopoulos, 1970).
log $\gamma^{\infty}_o$ = 0·25 (calculated from data presented by Pierotti & others (1959a,b).

and a $CH_3$ correction factor of 1·14 kcal $mol^{-1}$ should be valid for partition studies provided that one is dealing with reasonably non-polar solvents. [In refined statistical thermodynamic treatments of solution behaviour the differences between $CH_2$ and $CH_3$ are taken into account even for inert solvents (Orwoll & Flory, 1967).]

It could be advanced that the calculation of a $CH_3$ correction factor from data on the alkanes is invalid as the interaction of the terminal $CH_3$ attached to a polar aliphatic compound may be different from that attached to an alkane; perhaps through an interaction of the polar function with the hydrogen bonded water 'icebergs' around the hydrocarbon moiety (Frank & Evans, 1945). Consequently, a $CH_3$ correction factor has been calculated from partition data without using information on alkanes.

We showed that there is no terminal $CH_3$ effect for the alkyl benzenes (Table 1) and that $\log F_{CH_3} \simeq \log F_{CH_2}$. Thus group contributions for polar groups (OH, COOH) can be obtained from a difference in the log of partition coefficients provided that there are at least two $CH_2$ groups between the benzene ring and the polar function to destroy any spurious effects due to resonance (Iwasa, Fujita & Hansch, 1965).

e.g. $$\log F_{COOH} = \log K_{D(C_6H_5CH_2CH_2COOH)} - \log K_{D(C_6H_5CH_2CH_3)} \quad .. \quad (5)$$

On the other hand, group values obtained from alkyl compounds by extrapolation to zero carbon will be a combination of the polar group value and the $CH_3$ correction. Therefore, a comparison of the group values obtained by the two different methods will allow one to calculate the $CH_3$ term.

First, we must consider the standard state (concentration scale) used in partition studies (Davis, unpublished). When log F values are calculated by differences in partition coefficients they will be concentration scale independent because any conversion terms will simply cancel out. However, when log F values are obtained by extrapolation they will be concentration scale dependent. It is generally agreed that, for the distribution of solutes between organic and aqueous phases, the difference in unitary free energy (calculated from the thermodynamic partition coefficient) can be considered to be additively composed of contributions from the functional groups (Mukerjee, 1967; Aveyard & Mitchell, 1969; Hersh, 1971). Therefore, in our studies it is nesessary to convert partition coefficients on the molar scale ($K_D^m$) to the mole fraction scale ($K_D^x$).

Log F values for the COOH and OH groups for four solvent systems obtained from

Table 7. *Log $F_x$ values obtained by extrapolation of log partition coefficient vs carbon number plots to zero carbon number.*

| Carbon number | Partition coefficient log $K_D^x$ (a) | | | | |
|---|---|---|---|---|---|
| | | Alkanoic acids | | Alkanols | |
| | Octanol | Xylene | Chloroform | Octanol | Hexane |
| 1 | — | — | — | 0·01 | — |
| 2 | 0·59 | −1·08 | −0·76 | 0·51 | −1·39 |
| 3 | 1·12 | −0·49 | −0·17 | 1·17 | −0·61 |
| 4 | 1·62 | 0·03 | 0·40 | 1·71 | 0·09 |
| 5 | — | 0·50 | 1·03 | 1·99 | — |
| 6 | 2·37 | 1·18 | 1·61 | 2·86 | — |
| log $F_x$ | −0·45 | −2·27 | −1·94 | −0·65 | −2·83 |

(*a*) Partition coefficient values were taken from the compilations of Landolt-Bornstein (1960) and Leo & others (1971). Where necessary reported values were corrected for effects due to ionization and association and are expressed in terms of mole fraction concentrations. When more than one value was reported a mean or weighted mean was calculated.

Table 8. *The $CH_3$ correction term (log F) calculated from partition studies.*

| Solvent | Group | log $F_x$ Difference (Table 6) | log $F_x$ Extrapolation (Table 7) | $CH_3$ correction (log F) |
|---|---|---|---|---|
| Octanol | COOH | −1·31 | −0·45 | 0·86 |
| | OH | −1·74 | −0·67 | 1·07 |
| Xylene | COOH | −3·31 | −2·27 | 1·04 |
| Chloroform | COOH | −2·83 | −1·93 | 0·90 |
| Hexane | OH | −3·88 | −2·83 | 1·05 |
| | | | Mean .. .. | 0·98 |

phenyl alkyl derivatives by difference ($CH_2$ equals $CH_3$) are given in Table 6 and from alkyl derivatives by extrapolation ($CH_2$ not equal to $CH_3$) in Table 7. The extrapolated values will be a combination of the functional group contribution (OH or COOH) and $CH_3$ correction. The latter can be found by subtracting the log F values found by difference from log F values found by extrapolation (Table 8). There is some scatter in these $CH_3$ corrections but the agreement between the different solvents is considered to be satisfactory. The mean value provides $CH_3$ free energy correction of 1·34 kcal $mol^{-1}$ which compares well with the mean value of 1·14 kcal $mol^{-1}$ given in Table 5.

As yet it is not possible to arrive at any conclusions about the effect of organic solvent on the $CH_3$ correction, nevertheless, we would predict that the $CH_3$ correction term would become smaller as the organic solvent became more polar and more similar to an aqueous environment.

## CONCLUSIONS

Studies on the thermodynamics of the solution and partitioning processes indicate that, unlike the $CH_2$ group, the $CH_3$ group cannot be ascribed a single group contribution value for a given solvent system. Its group value depends on its position in the drug molecule. If the $CH_3$ is attached to a ring system it has a group molar volume similar to the $CH_2$ group (16·5 $cm^3$ $mol^{-1}$) and has a similar thermodynamic group contribution to the solubility and partition equilibria. In partition of a drug from aqueous to organic phase the $CH_3$ group contributions (expressed as log F) are dependent on the polarity of the organic phase and there is satisfactory correlation between $CH_3$ and $CH_2$ values through the regression equation

$$\log F_{CH_3} = 1{\cdot}12 \log F_{CH_2} - 0{\cdot}113$$

The $CH_3$ group in the terminal position in an aliphatic chain is almost twice as large as the $CH_3$ group attached to a ring system and this is reflected in a much larger group contribution. The assumption, that is often made in structure-activity studies, that the aromatic and aliphatic $CH_3$ are equivalent can lead to serious errors.

An aliphatic $CH_3$ correction factor can be calculated from data on the solubility of alkanes (and proteins) and in terms of free energy is equivalent to a contribution of 1·14 kcal $mol^{-1}$. A somewhat higher value of 1·34 kcal $mol^{-1}$ can be calculated from limited data on partition and activity coefficients provided that due consideration is given to the correct choice of standard state for the partition studies.

The partition coefficient of an aliphatic compound, on the mol fraction scale, distributed between water and a more or less non-polar solvent can be written as:

$$\log K^{x}_{D\ (C_nH_{2n+1}X)} = \log F_X + n \log F_{CH_2} + \log F_{CH_2(CORRECTION)} \quad .. \quad (6)$$

and in terms of Hansch's $\pi$ constant (molar concentration scale) as

$$\log K^{m}_{D\ (C_nH_{2n+1}X)} = \pi_X + n\,\pi_{CH_2} + \pi_{CH_2\,(CORRECTION)} - \log (V_o/V_w) \quad .. \quad (7)$$

Interestingly, the term $\log (V_o/V_w) = 0{\cdot}94$ for the octanol–water system and thus *for aliphatic compounds only*

$$\log K^{m}_{D} \simeq \pi_X + n\,\pi_{CH_2} \quad .. \quad .. \quad .. \quad .. \quad (8)$$

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