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SOLUTION THERMODYNAMICS: PHARMACEUTICAL SIGNIFICANCE AND INTERPRETATION OF QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIPS *

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ABSTRACT

Following a survey of the standard states used to describe the thermodynamics of solution processes, the usefulness of solution thermodynamics, and of transfer processes in particular, to quantify structure activity processes is discussed. Analysis of $\Delta H/\Delta S$ correlations based on van't Hoff estimates is criticised. A brief review of the thermodynamic basis of transfer Gibbs energies is included.

Exploration of the literature reveals that many different standard states have been employed to define standard-state Gibbs energies and entropies of solution and to express solubilities of solutes in liquids. Abraham [1] has calculated the effect on values of $\Delta_{sln}G^0$ for various choices of standard state as is shown in Table 1. However, it should be noted that whilst comparison of Gibbs energies of solution where different standard states have been employed is certain to lead to confusion, the confusion may be reduced by use of the $\Delta_{sln}G^0$ values described in Table 1 and that differences between, say, two solutes in a given liquid solvent are independent of these standard states. These situations are the same in the case of entropies of solution.

Further confusion exists in the literature relating to solution processes in that even more, and different, standard states have been used [2,3] and advocated [4], especially in discussions of quantitative structure relationships (QSAR). The standard state adopted [4] was the pure liquid solute and the ideal solution (unit mole fraction solute). Scheme 1 indicates the relationship involved and, thus

$$\Delta_{sln}G^0(g \rightarrow aq) + \Delta_{vap}G^0(liq \rightarrow g) = \Delta_{sln}G^0(liq \rightarrow aq)$$

$\Delta_{vap}G^0$ (and other thermodynamic parameters of interest here, $\Delta_{vap}H^0$ and $\Delta_{vap}S^0$) will differ from solute to solute; the conversion $\Delta_{sln}G^0(liq \rightarrow aq)$ to

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TABLE 1

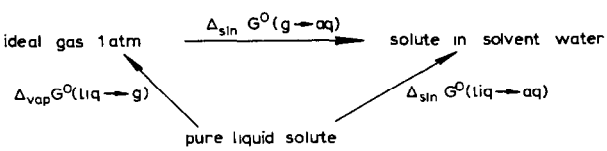
Correction parameters for standard state differences

Standard states		$\delta\Delta_{sln}G^0$ (kJ mol^{-1}) [a]		
gas	solvent	water	methanol	hexane
1 atm	unit mol fraction	0	0	0
1 atm	1 mol l^{-1}	9.95	7.93	5.02
1 atm	1 mol kg^{-1}	9.96	8.53	6.06
1 mol l^{-1}	1 mol l^{-1}	17.87	15.86	12.95
1 kPa	1 mol l^{-1}	15.62	13.61	10.70
	solvent relative molecular mass (M_r)	18.015	32.04	86.18
	solvent density	0.9971	0.7865	0.6548

[a] Defined so that: $\Delta_{sln}G^0$(1 atm → unit mole fraction) = $\Delta_{sln}G^0$ (any other standard state) + $\delta\Delta_{sln}G^0$.

$\Delta_{sln}G^0$(g → aq) will differ for all solutes no matter how closely related. Abraham [5], in a previous paper, also demonstrated that the choice of such a standard state assigns a different standard state to each solute. These different standard states arise because of solute–solute interactions in the liquid phase: a difficulty not encountered when the choice of standard state is that of the gas phase at a pressure of 1 atm. In this case the measured quantities (e.g., for $\Delta_{sln}G^0$(g → solution)) are interpreted through consideration of only solute–solute interactions.

It has been argued [6] that the use of the vapour phase state as the standard state for solution processes involving drugs is inappropriate. The claim is that interest in drugs requires that the properties of dilute solution be known and that the properties of the gas phase are not particularly relevant. Furthermore, molecules of moderate to long chain length may often exist in quite different conformational states in the vapour phase compared to their conformations in solution—thus making more complex the interpretation of data. Thus, Rytting et al. [6] propose that the universal standard state for drug molecules be a hypothetical 1 molal, molar or 1 mole fraction solution acting as if it were infinitely dilute (where the solvent is a suitable aliphatic hydrocarbon such as cyclohexane or iso-octane; water is not here [6] regarded as the best common solvent because of its highly complex and



Scheme 1.

TABLE 2

Propagation of errors in ΔH^0, ΔS^0 and ΔC_p^0 at 298 K

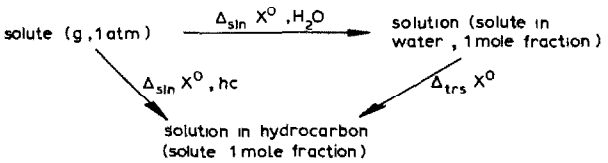
T range (K)	293–303		273–323		278–323	
T interval (K)	2		10		5	
	pK ±0.02	pK ±0.001	pK ±0.02	pK ±0.001	pK ±0.02	pK ±0.001
SD in ΔH^0 (kJ mol^{-1})	±4.06	±0.21	±0.84	±0.04	±0.79	±0.04
SD in ΔS^0 (J mol^{-1} K^{-1})	±13.81	±0.67	±2.72	±0.14	±1.33	±0.07
SD in ΔC_p^0 (J mol^{-1} K^{-1})	±2768	±138.1	±113.0	±5.44	±117.2	±5.86

structured nature leading to a significant solute–solvent and solvent–solvent interaction).

The two principal methods for the determination of $\Delta_{sol}G^0$ are (i) vapour pressure measurements when $\Delta_{vap}G^0 = -RT \ln p$, in combination with Henry's Law constants, $\Delta_{sln}G^0(g \rightarrow aq) = -RT \ln K^H$, allow the determination of $\Delta_{sln}G^0(liq \rightarrow aq)$; (ii) from solubilities of sparingly soluble solutes, $\Delta_{sln}G^0(liq \rightarrow aq) = -RT \ln X$, where X is expressed on the mole fraction scale.

Values of the corresponding enthalpies may again be determined in two different ways (i) from the variation of Henry's Law constants with temperature and (ii) by direct calorimetric determination. The determination of ΔH values from the variation of equilibrium constants with temperature is subject to great difficulty. Biltonen [7] has claimed, for example, that for reaction involving macromolecules it is unlikely that K can be known to be better than ±30%. Indeed King [8] has calculated the errors in the derived values of ΔH, ΔS and ΔC_p from such K/T data. Table 2 shows an extract of King's results where it is apparent that the calorimetric method is to be preferred particularly when equilibrium constants for reactions involving macromolecules and for partitioning processes of sparingly soluble species (often the case for drug substances) are used as the basis for determining enthalpies of reaction.

Abraham [1] has discussed the thermodynamics of solution for many solutes in water and has shown that for most homologous series of solutes investigated that the parameters for the process g → aq are linear in the number of carbon atoms in the solute and that from such linear equations methylene and group contributions are obtained. These methylene and group contributions are, however, not constant but vary from one homologous series to another. In a few homologous series (the alkan-1-ols and *n*-alkanes) the methylene increment is not constant. Abraham has further analysed [5] $\Delta_{sln}G^0$ data for solution of rare gases and alkanes in water and in 16 non-aqueous solvents to attempt a quantitative assessment of the



Scheme 2.

hydrophobic effect [9]. Following this analysis of $\Delta_{sln}G$, at 298.15 K, it was shown that solution of alkanes, but not the rare gases, in water is quite anomalous. The methylene contribution for partition of hexane, for example, between hexane and water is 3.85 kJ mol^{-1} in favour of hexane and that this can be separated into a favourable gas → hexane contribution of 3.10 kJ mol^{-1} and an unfavourable gas → water contribution of 0.75 kJ mol^{-1}. The latter quantity is shown to result from a true hydrophobic contribution of 2.26 kJ mol^{-1} and a favourable normal solvent effect of 1.151 kJ mol^{-1}. The partition "experiment" referred to is shown in Scheme 2, where $\Delta_{trs}X^0 = \Delta_{sln,hc}X^0 - \Delta_{sln}X^0$, H_2O, X represents the appropriate thermodynamic parameter, and $\Delta_{trs}X^0$ represents the value of that parameter for transfer of the solute from water to hydrocarbon solution.

It is this process of transfer which has been most discussed in relation to drug QSAR [10,11]. The majority of the correlations of drug structure with activity have centred around "Hansch" analysis [10] or some variant [11]. The majority of workers have published data on the values of partition coefficients for partitioning of drug substances between water and a variety of non-aqueous solvents [10]; the most commonly used non-aqueous or lipid-like solvent being octan-1-ol. However, little attention has been devoted to the analysis of the thermodynamic parameters which describe this process and, consequently, to the thermodynamics of solution of such solutes in water and in a variety of non-aqueous solvents. It would appear from the analysis of the data presented by Abraham [1] that there should be regular increments in $\Delta_{trs}G^0$ per methylene group within homologous series since, for most homologous series, the $\Delta_{sln}G^0$ (see scheme 1) values are each linear with carbon number in the solute. Recent evidence presented by Beezer et al. [2,12,13] suggests that such linearity is not always the case. Experiments to determine the thermodynamic parameters for solution of a series of *m*-alkoxy phenols, in water, octan-1-ol and the mutually saturated solvents indicated an oscillation in $\Delta(\Delta_{trs}G^0)$ values on ascending the homologous series. Similar valued oscillations were detected for solution in water and in octan-1-ol-saturated water. Inspection of other data to be found in the literature suggested that other series (alkanols and alkanoic acids [14,15]) may also show similar valued oscillations in $\Delta_{trs}G^0$. The existence of such oscillations in the thermodynamic parameters for solution and transfer processes is important since it has long been assumed that in partition

coefficients (P), (and, hence, $\Delta_{trs}G^0 = -RT \ln P$) for transfer of solutes, in particular drugs, between water and a non-aqueous, lipid-like phase are linearly related to chain length for a homologous series. "Hansch" analysis, referred to earlier, has been used for some years to correlate biological activity for a series of drugs with π values ($\pi = \log P/P_0$ where P is the partition coefficient for a member of an homologous series and P_0 is that for the "parent" member of the series). The values of P for many of such drug compounds are now calculated from group contributions [10], fragmental constants [16] or other molecular connectivity schemes [17]. Clearly, the basis for such calculations is that there exists a linear Gibbs energy relationship similar to the Hammett equation [18]. Such linearity has also been invoked by Gill and Wadsö [19] in their derivation of a "hydrophobic equation of state" which attempts to show the dependence of $\Delta_{trs}G^0$ upon the number of hydrogen atoms in a hydrocarbon molecule (two hydrogen atoms are equivalent to one methylene group). Indeed the existence of a linear relationship between X and carbon number in the solute molecule is the basis of linear free (Gibbs) energy relationships (LFER). The first instance of such relationships was carefully described by Hammett [18]. Tomlinson [20] has described and reviewed in great detail the application of LFERs in pharmaceutical, biochemical and biological systems. This review draws attention to the statistical basis of the results used to correlate ΔH with ΔS and, hence, to the determination of isokinetic–isoequilibrium relationships. Following Krug et al. [21–24] it is emphasised that in order for thermodynamic data to show "chemical causality" then the data which must be linearly related are the ΔG^0 and ΔH^0 values determined for the harmonic mean of the experimental temperatures. Thus, if, for a homologous series, a linear plot of ΔH versus ΔS was observed, this could not be taken as evidence of chemical causality. In contrast, since the errors associated with ΔG and ΔH determined at the harmonic mean temperature are not correlated, then a linear plot of ΔG versus ΔH is a demonstration of the chemical basis of the variation in these thermodynamic parameters. The existence of these LFERs and their chemical causality is important in biological sciences since they are at the heart of all structure–activity relationships.

It is apparent from the above that direct determination of ΔH values, by microcalorimetry, is to be preferred. These data, in combination with ΔG data derived from partition coefficients, will also allow a satisfactory thermodynamic description of the transfer process. The ΔH values are most usefully determined by measurements of the enthalpies of solution of solutes in the two individual solvents.

Other methods of calorimetric determination of $\Delta_{trs}H$ have been proposed including simultaneous determination of P and $\Delta_{trs}H$ in one calorimetric titration experiment [25] and direct measurement of $\Delta_{trs}H$ via a flow microcalorimeter [26]. Thus, much work remains to be done to establish the real existence of LFERs for use in QSAR and to establish the thermody-

namic properties of lipoid solvents which accurately reflect the properties of the cell membrane. A start has been made in this direction by attempts to provide a thermodynamic analysis of the transfer process and of the Collander equation [27] by Beezer et al. [28]. Furthermore, the results suggest the possibility of the development of Cratin's treatment [29] to include a scaling factor which is descriptive of the non-aqueous solvent and relates its behaviour to that of a "standard" solvent. Preliminary results [30] also suggest the possibility (given some fairly large assumptions) of direct determinations of $\Delta_{trs}H$ for transfer of drugs from water to cells themselves.

REFERENCES

1 M.H. Abraham, J. Chem. Soc., Faraday Trans. 1, 80 (1984) 153.
2 A.E. Beezer, W.H. Hunter and D.E. Storey, J. Pharm. Pharmacol., 35 (1983) 350.
3 A.E. Beezer and W.H. Hunter, J. Med. Chem., 26 (1983) 757.
4 C. Tanford, The Hydrophobic Effect: Formation of Micelles and Biological Membranes, Wiley Interscience, New York, 1980.
5 M. Abraham, J. Am. Chem. Soc., 101 (1979) 5477.
6 J.H. Rytting, S.S. Davis and T. Higuchi, J. Pharm. Sci., 61 (1972) 816.
7 R.L. Biltonen, in A.E. Beezer (Ed.), Biological Microcalorimetry, Academic Press, London, 1980.
8 E.J. King, Acid Base Equilibria, Pergamon Press, Oxford, 1965.
9 M. Abraham, J. Am. Chem. Soc., 104 (1982) 2085.
10 A. Leo, C. Hansch and D. Elkins, Chem. Rev., 71 (1971) 525.
11 J.C. Dearden (Ed.), Quantitative Approaches to Drug Design, Elsevier, Amsterdam, 1983.
12 A.E. Beezer, W.H. Hunter and D.E. Storey, J. Pharm. Pharmacol., 32 (1980) 815.
13 A.E. Beezer and W.H. Hunter, J. Med. Chem., 26 (1983) 757.
14 R. Aveyard and R.W. Mitchell, Trans. Faraday Soc., (1969) 2645.
15 R. Aveyard and R.W. Mitchell, Trans. Faraday Soc., (1970) 37.
16 G.G. Nys and J. Kekker, Eur. J. Med. Chem., 9 (1974) 361.
17 J.C. Boyd, J.S. Millership and A.D. Woolfson, J. Pharm. Pharmacol., 34 (1982) 158.
18 L.P. Hammett, Physical Organic Chemistry, McGraw-Hill, New York, 1940.
19 S.J. Gill and I. Wadsö, Proc. Natl. Acad. Sci. U.S.A., 73 (1976) 2955.
20 E. Tomlinson, Int. J. Pharm., 13 (1983) 115.
21 R.R. Krug, W.G. Hunter and R.A. Grieger, J. Phys. Chem., 80 (1976) 2335.
22 R.R. Krug, W.G. Hunter and R.A. Grieger, J. Phys. Chem., 80 (1976) 2341.
23 R.R. Krug, W.G. Hunter and R.A. Grieger, Nature (London), 261 (1976) 566.
24 R.R. Krug, W.G. Hunter and R.A. Grieger-Block, Am. Chem. Soc., Symp. Ser., 52 (1977) 192.
25 R. De Lisi, M. Goffredi and V.T. Liveri, J. Chem. Soc., Chem. Commun., (1980) 380.
26 W. Riebesehl and E. Tomlinson, J. Chem. Soc., Faraday Trans. 1, 79 (1983) 1311.
27 R. Collander, Acta Chem. Scand., 4 (1950) 1085.
28 A.E. Beezer, P.L.O. Volpe and W.H. Hunter, in preparation.
29 P.D. Cratin, Ind. Eng. Chem., 60 (1968) 14.
30 A.E. Beezer, P.L.O. Volpe and W.H. Hunter, in preparation.