The Use of Characteristic Volumes to Measure Cavity Terms in Reversed Phase Liquid Chromatography

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Key Words

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Summary

In the correlation of reversed-phase liquid chromatography capacity factors through the equation,

$$\log k' = \log k'_0 + mV/100 + s\pi_2^* + b\beta_2 + a\alpha_2$$

the use of McGowans characteristic volume, V_x, which can be trivially calculated, is entirely equivalent to the use of Leahy's computer-calculated intrinsic volumes, V_I, for the cavity term mV/100. It is shown that for 209 gaseous, liquid, and solid solutes, the two sets of volumes are related through the equation,

$$V_I = 0.597 + 0.6823\,V_x$$

with a standard deviation of only 1.24 $cm^3\,mol^{-1}$, and a correlation coefficient of 0.9988.

Introduction

A very large number of physiochemical processes in condensed phases can be discussed [1, 2] in terms of a general linear solvation energy relationship (LSER) of the form of eq. (1):

$$SP = SP_0 + mV + s\pi_2^* + b\beta_2 + a\alpha_2 \quad (1)$$

SP is a solubility or solvent-dependent property such as the logarithm of the solubility of a series of solutes in a given solvent, or the logarithm of the partition coefficient for the distribution of a series of solutes between two given solvent phases, SP_0 is a constant, and the parameters V, π_2^*, β_2, and α_2 characterise the solutes. The coefficients m, s, b, and a characterise the solvent(s), and are determined by the method of multiple regression analysis. The solvatochromic parameters π_2^*, β_2, and α_2 measure the solute dipolarity, hydrogen-bond basicity, and hydrogen-bond acidity respectively and serve as markers of the exoergic solute-solvent interaction terms. The volume term, mV, arises through the endoergic work of separating solvent molecules to provide a cavity of suitable size for the solute molecule. Originally, V was defined in terms of the solute bulk molar volume, $\overline{V}$, taken as the solute molecular weight divided by the liquid density at 20°C. It was found necessary to add 10 $cm^3\,mol^{-1}$ to $\overline{V}$ for aromatic and acyclic compounds, giving an adjusted molar volume $\overline{V}_{adj}$ for use in eq. (1) [3, 4]. Normally, values of $\overline{V}_{adj}/100$ were used for convenience but this is of no significance. Apart from the theoretical difficulty of the above adjustment to $\overline{V}$, there are other disadvantages of using $\overline{V}$ or $\overline{V}_{adj}$ as a measure of the cavity term. First of all, because $\overline{V}$ is a bulk property, associated with compounds such as alcohols which have a network-like hydrogen-bond structure, it will always give rise to a molar volume that reflects not only the 'intrinsic molecular volume' but also the bulk structure. Thus for pairs of structural isomers (e.g. n-butanol and diethylether) the associated compound always has an appreciably lower molar volume, whereas this is not the case for measures of intrinsic volume (Table I). Secondly, as pointed out before [5], the use of $\overline{V}$ or $\overline{V}_{adj}$ is very inconvenient when dealing with solutes that are solids. Because of these considerations, attention has focussed on other measures of intrinsic solute volume that could be used as the volume (V) term in eq. (1).

Leahy [6] has recently published a set of computer-calculated intrinsic volumes, V_I, calculated for specific solute conformations as derived from X-ray structures. These intrinsic volumes do not have the theoretical disadvantages of molar volumes, and have the practical advantage that

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Table I. Calculated volumes in $cm^3 mol^{-1}$ for structural isomers

isomer	V_{adj}	V_I	V_x
dimethylether	69.3	30.8	44.9
ethanol	58.4	30.5	44.9
diethylether	104.6	50.5	73.1
n-butanol	92.0	49.9	73.1
anisole	118.6	63.0	91.6
benzyl alcohol	116.9	63.7	91.6
p-cresol	116.3	63.6	91.6
n-propylbenzene	149.4	76.9	113.9
isopropylbenzene	149.4	76.8	113.9
mesitylene	148.9	76.9	113.9
cyclohexane	118.0	59.8	84.5
1-hexene	125.0	62.1	91.1

they can be calculated for any solute, no matter whether liquid or solid. Leahy [6] showed that use of intrinsic volumes instead of V_{adj} led to rather better constants in regressions of octanol-water partition coefficients through eq. (1). More recently, Leahy et al. [5] have shown that if V_I values are used instead of V_{adj} in the correlation of reversed phase liquid chromatography capacity factors ($\log k'_{75}$ and $\log k'_{50}$), not only is the quality of the regression maintained or slightly improved, but the coefficients s, b, and a in eq. (1) are much more easily interpreted. There seems no doubt that these computer-calculated V_I values are to be preferred to values of V_{adj} in LSER equations such as eq. (1).

What has not been realised is that there is a set of intrinsic solute volumes already available through the work of McGowan, and it is the purpose of this paper to compare McGowan's [7–9] 'characteristic molecular volumes', denoted as V_x, with computer-calculated V_I values. McGowan's volumes are derived from consideration of the parachor [10], and like this quantity, they are additive. Indeed, McGowan was able to construct a table of atomic increments to V_x from which the latter can be calculated by trivial arithmetic [9]. A comprehensive list of atomic V_x values is given in Table II. The use of V_x volumes for the estimation of physical and biochemical properties of molecules has recently been reviewed [11]. It should be noted that in the calculation of molecular characteristic volumes, $6.56 cm^3 mol^{-1}$ is subtracted for each bond, no matter whether single, double or triple. Thus V_x for benzene is calculated as $V_x = 6 \times 16.35 + 6 \times 8.71 - 12 \times 6.56 = 71.64 cm^3 mol^{-1}$, an example of how trivial the calculation is. In most cases V_x is the same for structural isomers (which contain not only identical atoms but also the same total number of bonds). This seems not to be any disadvantage, because V_I values for structural isomers are also almost identical (Table I). Since single and double bonds are counted the same in the calculation of V_x, values of V_x will not be the same for structural isomers that differ in the number of double bonds, for example cyclohexane and 1-hexene in Table I.

Table II. Characteristic atomic volumes, V_x in $cm^3 mol^{-1}$

C	16.35	N	14.39	O	12.43	F	10.48	H	8.71
Si	26.83	P	24.87	S	22.91	Cl	20.95	B	18.32
Ge	31.02	As	29.42	Se	27.81	Br	26.21		
Sn	39.35	Sb	37.74	Te	36.14	I	34.53		

For each bond between atoms, $6.56 cm^3 mol^{-1}$ is to be subtracted

Results and Discussion

We follow exactly the procedure of Leahy et al. [5] in the application of eq. (1) to the 29 liquid solutes and the 40 (liquid plus solid) solutes given in their Table I. The V_x values we have used are in Table III, and the π_2^*, β_2, and α_2 values are the same as those used before [5]. The experimental constants to be regressed are the capacity factors of Hafkenscheid and Tomlinson [12] with eluents 75:25 methanol:water and 50:50 methanol:water. The values of $\log k'_{75}$ and $\log k'_{25}$ are also exactly as used by Leahy et al. [5].

A summary of the regression equations is in Table IV, where the coefficients of V/100, π_2^*, β_2, and α_2 are given together with the standard deviation, *sd*, and the correlation coefficient *r*. For regressions with $V_{adj}/100$ and $V_I/100$ our computed coefficients are exactly the same as these of Leahy et al. [5]. In a number of cases, the term in α_2 is statistically not significant, and we have repeated the correlations using only three explanatory variables instead of four. Because the conclusions to be drawn from results in Table IV are completely unambiguous, they can be detailed very simply:

(a) The regressions with V_I, V_x, and V_{adj} for the liquid solutes are all equally as good, there being hardly any difference in *sd*, and *r* for the four parameter equations.

(b) Whereas, as found by Leahy et al. [5], there are significant differences in the coefficients of the parameters (especially of π_2^* and α_2) when V_I and V_{adj} are used, the equations with V_x yield identical coefficients to those with V_I.

(c) In the case of V_x and V_I all the equations, both for the liquid solutes and for the 40 total solutes, are absolutely identical except for the coefficient of V. Hence any interpretations of solute-solvent effects will also be exactly the same using V_x or V_I.

Thus for the 40 solutes in Table III, there is no advantage to be gained by the use of computer-calculated V_I values over McGowan's V_x values. Indeed, for these 40 solutes, the two sets of volumes are very well correlated by eq. (2), so that any correlations involving V_I and V_x will lead to exactly the same coefficient of all the terms, except that the coefficients for the volume term will be in the ratio of 0.68:1, as observed.

$$V_I = (0.706 \pm 0.008) + (0.6827 \pm 0.0086)\, V_x \qquad (2)$$

$$n = 40 \quad sd = 1.11 \quad r = 0.9970$$

Table III. Characteristic Volumes, in $cm^3 mol^{-1}$, used in this work

	Liquid Solutes	V_x		Solid Solutes	V_x
1.	Methylene chloride	49.4	30.	Phenol	77.5
2.	Chloroform	61.7	31.	p-Cresol	91.6
3.	Carbon tetrachloride	73.9	32.	p-Chlorophenol	89.7
4.	n-Butanol	73.1	33.	p-Dichlorobenzene	96.1
5.	n-Pentanol	87.2	34.	p-Chloronitrobenzene	101.3
6.	n-Hexanol	101.3	35.	p-Dinitrobenzene	106.5
7.	Cyclohexane	84.5	36.	Durene	128.0
8.	Cyclohexanol	90.4	37.	Benzoic acid	93.2
9.	Cyclohexanone	86.1	38.	p-Chlorobenzoic acid	105.4
10.	2-Methylpropanoic acid	74.7	39.	Pentamethylbenzene	142.1
11.	Hexanoic acid	102.8	40.	p-Toluic acid	107.3
12.	Octanoic acid	131.0			
13.	Diethyl ether	73.1			
14.	Ethyl acetate	74.7			
15.	Benzene	71.6			
16.	Toluene	85.7			
17.	Ethylbenzene	99.8			
18.	Isopropylbenzene	113.9			
19.	n-Propylbenzene	113.9			
20.	sec-Butylbenzene	128.0			
21.	p-Xylene	99.8			
22.	Mesitylene	113.9			
23.	Chlorobenzene	83.9			
24.	p-Chlorotoluene	98.0			
25.	Nitrobenzene	89.1			
26.	Methylbenzoate	107.3			
27.	Ethyl benzoate	121.4			
28.	n-Propylbenzoate	135.4			
29.	Benzyl alcohol	91.6			

Table IV. Summary of the Application of eq. (1) to the HPLC Capacity Factors of Hafkenscheid and Tomlinson [12]

	Const	V/100	π_2^*	β_2	α_2	sd	r
A. Liquid Solutes, n = 29, $\log k'_{75}$							
V_I	− 0.52	1.84 ± 0.06	− 0.44 ± 0.04	− 1.55 ± 0.05	− 0.21 ± 0.05	0.043	0.9953
V_x	− 0.50	1.25 ± 0.04	− 0.44 ± 0.04	− 1.54 ± 0.05	− 0.21 ± 0.05	0.042	0.9954
V_{adj}	− 0.67	1.04 ± 0.03	− 0.36 ± 0.04	− 1.52 ± 0.05	− 0.03 ± 0.05	0.044	0.9951
V_I	− 0.56	1.90 ± 0.08	− 0.41 ± 0.05	− 1.68 ± 0.06	–	0.057	0.9914
V_x	− 0.55	1.29 ± 0.05	− 0.41 ± 0.05	− 1.67 ± 0.06	–	0.056	0.9916
V_{adj}	− 0.67	1.05 ± 0.03	− 0.36 ± 0.04	− 1.53 ± 0.05	–	0.044	0.9950
B. Liquid Solutes, n = 29, $\log k'_{50}$							
V_I	− 0.38	3.22 ± 0.07	− 0.44 ± 0.05	− 2.38 ± 0.06	− 0.03 ± 0.05	0.048	0.9974
V_x	− 0.36	2.18 ± 0.04	− 0.43 ± 0.04	− 2.36 ± 0.06	− 0.03 ± 0.05	0.046	0.9976
V_{adj}	− 0.64	1.81 ± 0.04	− 0.30 ± 0.05	− 2.31 ± 0.07	0.28 ± 0.06	0.054	0.9967
V_I	− 0.39	3.23 ± 0.06	− 0.44 ± 0.05	− 2.40 ± 0.05	–	0.048	0.9974
V_x	− 0.38	2.18 ± 0.04	− 0.43 ± 0.04	− 2.38 ± 0.05	–	0.046	0.9976
V_{adj}	− 0.55	1.75 ± 0.05	− 0.34 ± 0.07	− 2.15 ± 0.08	–	0.073	0.9939
C. Liquid and Solid Solutes, n = 40, $\log k'_{75}$							
V_I	− 0.53	1.88 ± 0.05	− 0.47 ± 0.03	− 1.56 ± 0.05	− 0.20 ± 0.03	0.044	0.9953
V_x	− 0.54	1.29 ± 0.03	− 0.44 ± 0.03	− 1.56 ± 0.05	− 0.19 ± 0.03	0.044	0.9953
D. Liquid and Solid Solutes, n = 40, $\log k'_{50}$							
V_I	− 0.32	3.15 ± 0.07	− 0.52 ± 0.05	− 2.40 ± 0.06	–	0.063	0.9953
V_x	− 0.34	2.16 ± 0.04	− 0.47 ± 0.04	− 2.39 ± 0.06	–	0.057	0.9962

Because of the importance of eq. (2), we have collected all the published values of V_I [5, 6] and for a total of 209 gaseous, liquid, and solid solutes we find an excellent correlation almost identical to that in eq. (2):

$$V_I = (0.597 \pm 0.003) + (0.6823 \pm 0.0023)\, V_x \qquad (3)$$

$$n = 209 \quad sd = 1.24 \quad r = 0.9988$$

It is therefore now possible to use either V_I or V_x in eq. (1), instead of the adjusted molar volume. Leahy et al. [5] have suggested that the use of V_{adj} in eq. (1) might gradually be phased out in favour of V_I, particularly because the latter can be applied to solid solutes. It seems equally useful to replace V_{adj} by V_x, values of which can simply be obtained from the atomic values in Table II. Alternatively, V_x or V_I values can simply be interconverted via eq. (3), with an error of only about $1\,cm^3\,mol^{-1}$. It might be felt than an additive scheme, such as that for V_x would break down for very complicated molecules, but eq. (3) holds for quite large molecules with V_x up to $270\,cm^3\,mol^{-1}$ (e.g. 1-octadecanol, pentamethylbenzene, methyl octanoate, or benzyl benzoate). In any case, for these molecules, the necessary structural information needed to calculate V_I may not always be available, and so V_x values would still be very useful.

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