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Solvent effects on solution enthalpies of adamantyl derivatives

A multiparametric approach

Filomena Martins · Luís Moreira · Nélson Nunes ·
Ruben E. Leitão

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Abstract Solution enthalpies of 1-bromoadamantane, 1-adamantanol, and 2-adamantanone in a large set of protic and aprotic solvents are reported at 298.15 K. Solvent effects on the solution processes of these solutes are analyzed in terms of a modified TAKA equation, involving $\delta_{\mathrm{cav}}h^{\mathrm{s}}$ as the cavity term. The nature and magnitude of the major interactions which influence these processes are assessed and discussed in terms of the solutes' characteristics. New insights on the solution processes under scrutiny are presented.

Keywords 1-Bromoadamantane · 1-Adamantanol · 2-Adamantanone · Solution enthalpy · Multiparametric equation · Solvent effects

Introduction

Solvents outstandingly influence the majority of media driven physicochemical processes. Thermodynamic data comprise the macroscopic measurable evidences which reflect the variety of microscopic interactions taking place at a molecular level. The deep understanding of such interactions is one of the ultimate goals for researchers in the field of solution chemistry. This is achieved, for instance, through a systematic study of the differences observed for a given process in various solvents and by the rationalization of those differences in terms of particular solvent properties. This approach has been followed by several authors, for example in the study of solution processes involving tertiary halogenated compounds in hydroxylic media [1–5].

Recently, our research team has focused its attention on adamantyl derivatives. Besides their recognized pharmaceutical interest [6–8], these bulky compounds have long been attracting the physical chemists' interest. Given the importance of the knowledge of certain physicochemical properties, namely the solubility in water, in the screening process of potential new drugs, a procedure was devised to obtain the solution enthalpy value of 1-bromoadamantane in water [9] which is not possible to measure directly due to this compound's insolubility. This value together with solution enthalpies of the same compound in a series of monoalcohols allowed a comparison with the corresponding *tert*-butyl bromide's values and a first evaluation of the observed differences in protogenic media [10]. More recently, three different solutes, 1-bromoadamantane (1-AdBr), 1-adamantanol (1-AdOH), and 2-adamantanone (2-AdO) were studied in aprotic solvents [11] and a method proposed by Solomonov et al. [12] was applied to obtain the specific interaction component of their solvation processes.

In this study, we present the solution enthalpies at infinite dilution ($\Delta_{\mathrm{sol}}H$) of the previously studied solutes, 1-AdBr, 1-AdOH, and 2-AdO, in a more comprehensive set of both protic and aprotic solvents. The purpose of this project is to

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F. Martins (✉) · L. Moreira
Department of Chemistry and Biochemistry, Faculty of Sciences,
University of Lisbon, CQB, Ed. C8, Campo Grande,
1749-016 Lisbon, Portugal
e-mail: filomena.martins@fc.ul.pt

L. Moreira
Instituto Superior de Educação e Ciências, CQB, Alameda das
Linhas de Torres, 174, 1750 Lisbon, Portugal

N. Nunes · R. E. Leitão (✉)
Department of Chemical Engineering, Engineering Institute
(ISEL), Polytechnic Institute of Lisbon, CQB, R. Conselheiro
Emídio Navarro 1, 1950-062 Lisbon, Portugal
e-mail: rleitao@deq.isel.ipl.pt

assess the nature and magnitude of the solute–solvent and solvent–solvent interactions involved in the studied processes through the use of a suitable multiparametric linear regression (MLR) model equation.

MLR is a widely used and powerful technique to study solvent effects. The method consists of considering a given thermodynamic quantity, derived from a physicochemical process occurring in solution (in this case $\Delta_{\mathrm{sol}}H$), as a sum of several independent inputs which result both from the solvent properties and from the solute's sensitivity to those properties. Solvent properties, also called descriptors, can be either macroscopic or microscopic depending on whether they model the bulk solvent's behavior or the solvent's behavior in the vicinity of the solute (cybotatic region). Microscopic descriptors are based on reference processes involving molecular probes which ideally respond to changes in a single solvent property. Regardless of the nature of solvent descriptors, the solute's sensitivity to each solvent effect is evaluated through the model equation adjusted coefficients.

Formally, the solution enthalpy of a given solute (A) in a solvent (S) can be partitioned in three major energetic contributions (Eq. 1): (i) the process of creating a suitable cavity to accommodate the solute, with the corresponding breaking of solvent–solvent interactions ($\Delta_{\mathrm{cav}}H^{\mathrm{A/S}}$); (ii) the process of disrupting the solute structure, usually taken as its vaporization or sublimation enthalpy ($\Delta_{\mathrm{vap/subl}}H^{\mathrm{A}}$) depending on the solute's standard state at the working temperature; (iii) the process of accommodating the solute in the formed cavity thus creating new solute–solvent interactions ($\Delta_{\mathrm{int}}H^{\mathrm{A/S}}$), both specific and non-specific interactions:

$$\Delta_{\mathrm{sol}}H^{\mathrm{A/S}} = \Delta_{\mathrm{cav}}H^{\mathrm{A/S}} + \Delta_{\mathrm{vap/subl}}H^{\mathrm{A}} + \Delta_{\mathrm{int}}H^{\mathrm{A/S}}. \qquad (1)$$

For a series of solution enthalpies of a solute in several solvents the $\Delta_{\mathrm{vap/subl}}H^{\mathrm{A}}$ term will be the same and therefore a suitable multiparametric equation to study these processes should comprise descriptors which account both for the energy requirements related to cavity formation ($\Delta_{\mathrm{cav}}H^{\mathrm{A/S}}$) and also for those associated with the establishment of solute–solvent interactions ($\Delta_{\mathrm{int}}H^{\mathrm{A/S}}$). The TAKA equation [13] fulfills these requisites and has been one of the most used multiparametric equations to study solvent effects, seeming therefore appropriate to use in this type of studies.

According to the TAKA equation, solvents are characterized by their dipolarity/polarizability (π^*), taken as a measure of non-specific solute–solvent interactions related to the capacity of the solvent to generate a spread of charges in the cybotatic region of the solute; their hydrogen bond donor (HBD) acidity (α) and hydrogen bond acceptor (HBA) basicity (β) abilities, regarded as measures of specific solute–solvent interactions of the Lewis type and their structuredness, given by the cohesive energy density parameter, C, which accounts for solvent–solvent interactions determining the disruption and reorganization of the solvent structure associated with the formation of a cavity to accommodate the solute. The application of the TAKA equation to the study of calorimetric data can be formulated through Eq. 2 where the a_i coefficients are the complementary solute-dependent coefficients of the solvent parameters.

$$\Delta_{\mathrm{sol}}H = a_0 + a_1\pi^* + a_2\alpha + a_3\beta + a_4C \qquad (2)$$

Experimental

Measurements were carried out at 298.15 K using a Thermometric precision solution calorimeter. Experimental details have been previously described [9]. This calorimeter has a resolution in temperature in the order of 1 μK, corresponding to a resolution in enthalpy of 1–4 mJ. The calorimeter was tested for the solution process of tris(hydroxymethyl)aminomethane (TRIS) in NaOH 0.05 mol dm^{-3} and HCl 0.1 mol dm^{-3}. Experimental and literature values agree within experimental uncertainty [10].

All solvents were supplied by Aldrich and Merck (min. 99.5%), with a water content below 0.1% and were used without further drying or purification. 1-bromoadamantane was supplied by Sigma–Aldrich (min. 99%) and 1-adamantanol and 2-adamantanone were supplied by EGA-CHEMIE (min. 98%). Solutes were weighed in a Mettler H35 analytical balance with a precision of ±0.1 mg and their concentration ranged from 0.01 to 0.02 mol dm^{-3}. Cylindrical ampoules were filled with solute and sealed. Heats of empty ampoule breaking were found to be negligible. Each enthalpy value results from an average of at least three independent experiments, with an average relative standard deviation less than 2%.

Results and discussion

Solution enthalpies at 298.15 K and infinite dilution of 2-chloro-2-methylpropane (*t*-BuCl), 2-bromo-2-methylpropane (*t*-BuBr), 1-AdBr, 1-AdOH, and 2-AdO in several solvents are presented in Table 1, together with the solvent descriptors to be used in the multiparametric analyses. Associated standard deviations for the experimental data determined in this study as well as those of previously reported data [10, 11], are also shown. The latter were re-calculated using a more demanding criterion.

The obtained values for the five solutes in the hydroxylic subset (solvents 1–8 in Table 1) are plotted in Fig. 1.

Table 1 Solution enthalpies at 298.15 K and infinite dilution of 2-chloro-2-methylpropane (*t*-BuCl), 2-bromo-2-methylpropane (*t*-BuBr), 1-bromoadamantane, 1-adamantanol and 2-adamantanone in several solvents, associated standard deviations for solutes 3–5 and solvent descriptors

N	Solvent	$(\Delta_{sol}H \pm s\Delta_{sol}H)$/kJ mol^{-1}					Solvent parameters				
		t-BuCl 1	*t*-BuBr 2	1-AdBr 3	1-AdOH 4	2-AdO 5	π^*	α	β	C	$10^2\delta_{cav}h^s$/ kJ cm^{-3}
1	2-Butanol	5.11^{a}	5.57^{a}	19.25 ± 0.17^{b}	12.95 ± 0.13^{d}	14.16 ± 0.10^{d}	0.54^{e}	0.54^{e}	0.91^{e}	0.511^{h}	–
2	2-Methyl-1-Propanol	3.09^{a}	3.36^{a}	16.80 ± 0.20^{b}	11.74 ± 0.20^{d}	12.82 ± 0.16^{d}	0.50^{e}	0.71^{e}	0.92^{e}	0.520^{h}	–
3	1-Pentanol	2.56^{a}	2.62^{a}	16.43 ± 0.20^{b}	11.90 ± 0.09^{d}	13.03 ± 0.26^{d}	0.50^{e}	0.73^{e}	0.88^{e}	0.501^{h}	–
4	1-Propanol	1.62^{a}	2.00^{a}	15.79 ± 0.12^{b}	12.13 ± 0.06^{d}	13.02 ± 0.04^{d}	0.53^{e}	0.79^{e}	0.85^{e}	0.597^{h}	1.5^{i}
5	2-Propanol	3.57^{a}	4.12^{a}	18.18 ± 0.06^{b}	13.00 ± 0.17^{d}	14.66 ± 0.17^{d}	0.48^{e}	0.68^{e}	0.93^{e}	0.560^{h}	2.8^{i}
6	1-Butanol	2.10^{a}	2.37^{a}	15.85 ± 0.08^{b}	12.10 ± 0.08^{d}	13.22 ± 0.05^{d}	0.54^{e}	0.74^{e}	0.84^{e}	0.542^{h}	1.6^{i}
7	Ethanol	1.50^{a}	1.75^{a}	16.26 ± 0.18^{b}	12.76 ± 0.10^{d}	12.84 ± 0.03^{d}	0.55^{e}	0.88^{e}	0.80^{e}	0.679^{h}	2.8^{i}
8	Methanol	1.56^{a}	2.20^{a}	18.09 ± 0.09^{b}	14.21 ± 0.18^{d}	11.83 ± 0.10^{d}	0.60^{e}	1.09^{e}	0.73^{e}	0.858^{h}	5.1^{i}
9	Acetonitrile	–	–	21.09 ± 0.11^{c}	27.27 ± 0.26^{c}	10.40 ± 0.09^{c}	0.75^{f}	0.19^{f}	0.37^{f}	0.576^{h}	10.66^{j}
10	Dimethylformamide	–	–	18.22 ± 0.08^{c}	18.29 ± 0.37^{c}	9.68 ± 0.21^{c}	0.88^{f}	0.00^{f}	0.69^{f}	0.582^{h}	8.62^{j}
11	Dimethylsulfoxide	–	–	20.71 ± 0.36^{c}	20.74 ± 0.06^{c}	12.51 ± 0.04^{c}	1.00^{f}	0.00^{f}	0.76^{f}	0.707^{h}	13.87^{j}
12	Propylene Carbonate	–	–	19.31 ± 0.36^{c}	25.62 ± 0.39^{c}	9.91 ± 0.06^{c}	0.83^{f}	0.00^{f}	0.40^{f}	0.737^{g}	10.14^{j}
13	Nitromethane	–	–	24.13 ± 0.00^{c}	32.77 ± 0.14^{c}	11.61 ± 0.15^{c}	0.85^{f}	0.22^{f}	0.25^{f}	0.663^{h}	13.74^{j}
14	Ethyl Acetate	–	–	15.83 ± 0.22^{c}	22.89 ± 0.21^{c}	8.32 ± 0.13^{c}	0.55^{f}	0.00^{f}	0.45^{f}	0.336^{h}	5.98^{j}
15	1,4-Dioxane	–	–	17.46 ± 0.02^{c}	22.63 ± 0.04^{c}	9.42 ± 0.08^{c}	0.49 ^{g}	0.00 ^{g}	0.37 ^{g}	0.388^{g}	7.57^{j}
16	Toluene	–	–	12.63 ± 0.03^{c}	27.85 ± 0.29^{c}	5.82 ± 0.14^{c}	0.54^{f}	0.00^{f}	0.11^{f}	0.332^{h}	2.65^{j}
17	Cyclohexane	–	–	13.19 ± 0.25^{c}	29.10 ± 1.35^{c}	11.37 ± 0.13^{c}	0.00^{f}	0.00^{f}	0.00^{f}	0.280^{h}	1.42^{j}
18	Dimethylacetamide	–	–	17.52 ± 0.13^{c}	17.27 ± 0.05^{c}	9.98 ± 0.03^{c}	0.88^{f}	0.00^{f}	0.76^{f}	0.502^{h}	7.66^{j}
19	Acetone	–	–	18.02 ± 0.13^{c}	22.90 ± 0.19^{c}	9.25 ± 0.14^{c}	0.71^{f}	0.08^{f}	0.48^{f}	0.389^{h}	7.65^{j}
20	Carbon tetrachloride	–	–	12.06 ± 0.01^{c}	28.35 ± 0.17^{c}	4.45 ± 0.07^{c}	0.28^{f}	0.00^{f}	0.00^{f}	0.308^{h}	1.91^{j}
21	*n*-Hexane	–	–	14.74 ± 0.29^{c}	32.39 ± 1.13^{c}	12.48 ± 0.27^{c}	−0.08^{f}	0.00^{f}	0.00^{f}	0.221^{h}	–
22	Aniline	–	–	18.80 ± 0.18^{c}	19.45 ± 0.15^{c}	4.20 ± 0.09^{c}	1.08^{g}	0.26^{g}	0.50^{g}	0.583^{h}	–

[a] Ref. [3], [b] Ref. [10], [c] Ref. [11], [d] This work, [e] Ref. [14], [f] Ref. [15], [g] Ref. [16], [h] Ref. [17], [i] Ref. [18], [j] Ref. [12]

Table 2 Application of Eq. 2 to the three adamantyl solutes in the full set of solvents

Eqs.	Solute	a_0 s (a_0) % SL[a]	a_1 s (a_1) % SL	a_2 s (a_2) % SL	a_3 s (a_3) % SL	a_4 s (a_4) % SL	sd$_{fit}^{b}$	R^{2c}	N^{d}	F^{e}
A	1-AdBr	13.2	6.9	–	–	–	2.09	0.48	22	18
		1.1	1.6	–	–	–				
		>99.99	99.96	–	–	–				
B	1-AdOH	27.8	–	−5.6	−19.2	9.2	1.95	0.94	22	89
		1.5	–	1.6	1.9	3.3				
		>99.99	–	99.71	>99.99	98.80				
C	2-AdO	6.8	−11.8	−4.5	8.7	14.4	1.68	0.73	22	12
		1.3	2.6	2.1	2.0	4.5				
		99.99	99.97	95.30	99.95	99.48				

[a] Significance level

[b] Standard deviation of the fit

[c] Determination coefficient

[d] Number of points

[e] Fisher statistics

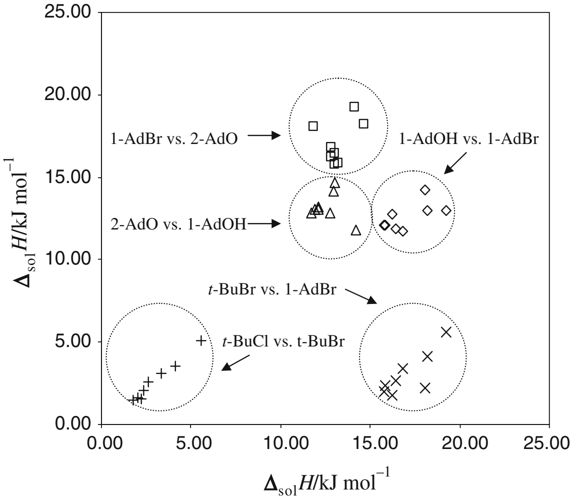

Fig. 1 Solution enthalpies, in solvents 1–8 (Table 1), of: *t*-BuCl versus *t*-BuBr (*plus*), *t*-BuBr versus 1-AdBr (*cross*), 1-AdBr versus 2-AdO (*open square*), 2-AdO versus 1-AdOH (*open triangle*) and 1-AdOH versus 1-AdBr (*open diamond*)

Comparing selected pairs of solutes, Fig. 1 shows that the two *t*-butyl solutes with different halogen atoms (*t*-BuCl vs. *t*-BuBr) make up an almost perfect straight line. On the other hand, a size increase (*t*-BuBr *vs.* 1-AdBr) leads to a more complex behavior and the observed deviations for ethanol, and especially for methanol, have been attributed to the degree of structuring of these two solvents and therefore to larger energetic requirements to form a cavity of suitable size to accommodate the solute [10]. Moreover, substitution of a 1-bromide by a 1-hydroxy or a 2-ketone in the adamantyl compounds leads to the most significant deviations from a linear trend. These comparisons clearly show that very different solute–solvent–solvent interactions must be involved in the adamantyl cage derivatives' solution processes.

The TAKA equation (Eq. 2) was then applied to the full set of solvents shown in Table 1 for each of the three adamantyl solutes, after a careful evaluation of the intercorrelations among solvent parameters which were all found to be negligible ($R^2 < 0.5$), thus assuring absence of redundancy. The selection, by elimination, of the solvent descriptors relevant to model the enthalpic process was performed according to the criterion that a descriptor should be kept if the significance level of its regression coefficient was ≥95%. The results are summarized in Table 2. The global quality of the fits was assessed through several statistical criteria, such as the standard deviation of the fit, $\mathrm{sd_{fit}}$, the determination coefficient, R^2, and Fisher's F value.

The obtained results were considered unsatisfactory. The overall poor statistical outputs, especially those obtained for 1-AdBr (where only 48% of the variability in $\Delta_{sol}H$ is explained by the best found regression), were considered evidences of an incorrect evaluation of the solvent effects on these thermodynamic processes. Even for the best regression—regression B for 1-AdOH—the standard deviation of the fit is rather high. A small number (1 or 2) of apparent outliers (i.e., points for which differences between expected and experimental values deviate more than 2 sd) was detected in all cases. However, given the small relative uncertainties of the corresponding experimental $\Delta_{sol}H$ values and, especially, the general poor quality of the model equations, we found no reason to discard these data points, and their nature as possible outliers will be re-evaluated further on.

Since the studied solutes were chosen so that they had similar molecular sizes, the differences in solution enthalpies between pairs of solutes should be mainly sensitive to the energy differences associated with the establishment of solute–solvent interactions ($\Delta_{int}H^{A/S}$ in Eq. 1) after the solute's introduction into the formed cavity. The TAKA equation was therefore applied to the three $\Delta_{sol}H$ differences (1-AdOH − 1-AdBr, 1-AdBr − 2-AdO, and 1-AdOH − 2-AdO) and results are summarized in Table 3. These

Table 3 Application of Eq. 2 to $\Delta_{sol}H$ differences for the three adamantyl solutes in the full set of solvents

Eqs.	Solute	a_0 s (a_0) % SL	a_1 s (a_1) % SL	a_2 s (a_2) % SL	a_3 s (a_3) % SL	a_4 s (a_4) % SL	$\mathrm{sd_{fit}}$	R^2	N	F
D	1-AdOH − 1-AdBr	16.92	−3.42	−3.82	−19.46	–	1.18	0.98	22	298
		0.65	1.13	1.09	1.37	–				
		>99.99	99.26	99.75	>99.99	–				
E	1-AdBr − 2-AdO	3.14	12.03	–	−6.68	–	1.26	0.88	22	70
		0.68	1.05	–	0.92	–				
		99.98	>99.99	–	>99.99	–				
F	1-AdOH − 2-AdO	19.99	9.09	−2.87	−27.06	–	1.06	0.99	22	495
		0.58	1.02	0.98	1.23	–				
		>99.99	>99.99	99.10	>99.99	–				

results show in all three cases that when C is excluded as a descriptor, differences in solution enthalpies are in fact well explained by the remaining descriptors, i.e., those describing solute–solvent interactions. Even Eq. E, apparently not as good as Eq. B in Table 2, in terms of R^2 or F, shows a significant reduction in sd_{fit}.

So the good quality of regressions D–F (without C) confirms that the TAKA equation describes well the solute–solvent interactions involved in these processes, and lay bare that C is indeed the parameter responsible for the bad performance of Eq. 2 in regressions A–C. Therefore, this descriptor clearly seems not to explain conveniently the energetics of cavity formation and another descriptor is sought to fulfill that purpose.

The correct assessment of the energy requirements for cavity formation has long been recognized as a central issue in the evaluation of solvent effects in solution enthalpies and several methods have been proposed to obtain this energetic term [2, 3, 19–24]. In a recent paper, Solomonov et al. [12] suggested the introduction of a new quantity, the specific relative cavity formation enthalpy for a given solvent ($\delta_{cav}h^s$) which could be correctly determined by dividing the solution enthalpy of a linear alkane in the same solvent by the alkane's McGowan characteristic volume (or averaging this quotient for a series of alkanes' values). Several $\delta_{cav}h^s$ have since been computed and reported [12, 18] and are available for solvents 4–20 (Table 1). We have therefore tested the effect of replacing C by this parameter in the regressions for each individual solute using a modified TAKA equation which assumes now the following formulation:

$$\Delta_{sol}H = a_0 + a_1\pi^* + a_2\alpha + a_3\beta + a_5\delta_{cav}h^s. \qquad (3)$$

Results of the application of Eq. 3 to the referred 17 solvents are shown in Table 4 and Fig. 2. 2-PrOH was the only data point identified as an outlier ($|\Delta_{sol}\ H_{exp} - \Delta_{sol}\ H_{calc}| > 2\ sd_{fit}$), in the 1-AdBr regression, and the model was therefore refitted with the exclusion of this solvent, leading to a regression with higher statistical quality. For comparative purposes, we have also applied the original TAKA equation (Eq. 2) to the same set of 17 solvents, as illustrated in Table 5. Worth of notice is the observation that the figures of merit in regressions A′ to C′ did not improve with the reduction of the number of solvents (compare with equations A–C) and that relevant descriptors are now different from those appearing in Table 2, thus confirming the non-robustness of Eq. 2.

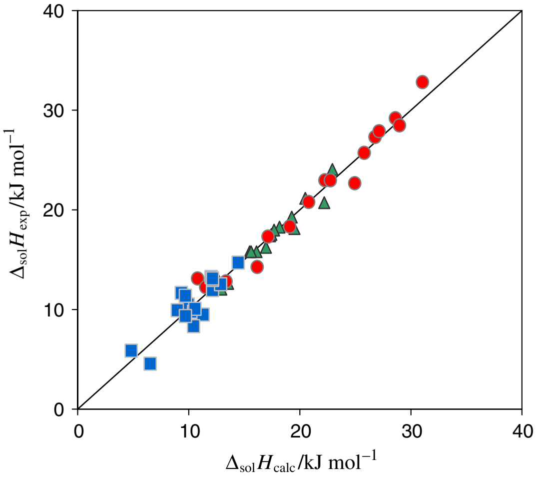

Fig. 2 Plot of $\Delta_{sol}\ H_{exp}$ versus $\Delta_{sol}\ H_{calc}$ according to Eq. 3 (*filled diamond*)—1-AdBr, 1-AdOH, and 2-AdO

Figure 2 shows a very good agreement between experimental and calculated values in all three cases. The standard deviations of the fits improve significantly when we compare the results obtained from Eq. 2 and Eq. 3 for the same set of solvents (1-AdBr: from 2.11 (if we also exclude 2-PrOH) to 0.80, 1-AdOH: from 1.71 to 1.20 and 2-AdO: from 1.89 to 1.43) and R^2 is also systematically higher for Eq. 3.

Table 4 Application of the modified TAKA equation (Eq. 3) to the three adamantyl solutes in the 17 solvent's set

Eqs.	Solute	a_0 s (a_0) % SL	a_1 s (a_1) % SL	a_2 s (a_2) % SL	a_3 s (a_3) % SL	a_5 s (a_5) % SL	sd_{fit}	R^2	N	F
G	1-AdBr	11.3	–	3.5	–	0.8	0.80	0.94	16	112
		0.5	–	0.6	–	0.1				
		>99.99	–	>99.99	–	>99.99				
H	1-AdOH	27.8	–	–	−20.1	0.6	1.20	0.97	17	249
		0.7	–	–	1.0	0.1				
		>99.99	–	–	>99.99	>99.99				
I	2-AdO	8.9	−12.5	–	10.6	0.6	1.43	0.76	17	14
		1.0	3.5	–	1.7	0.2				
		>99.99	99.69	–	>99.99	99.48				

Table 5 Application of Eq. 2 to the three adamantyl solutes in the 17 solvent's set

Eqs.	Solute	a_0 s (a_0) % SL	a_1 s (a_1) % SL	a_2 s (a_2) % SL	a_3 s (a_3) % SL	a_4 s (a_4) % SL	sd$_{\text{fit}}$	R^2	N	F
A′	1-AdBr	11.1	11.8	–	–	–	2.44	0.42	17	11
		2.0	3.6	–	–	–				
		>99.99	99.49	–	–	–				
B′	1-AdOH	27.2	10.1	–	−23.6	–	1.71	0.94	17	118
		1.2	1.9	–	1.5	–				
		>99.99	99.99	–	>99.99	–				
C′	2-AdO	7.3	–	–	6.2	–	1.89	0.52	17	16
		0.9	–	–	1.5	–				
		>99.99	–	–	99.89	–				

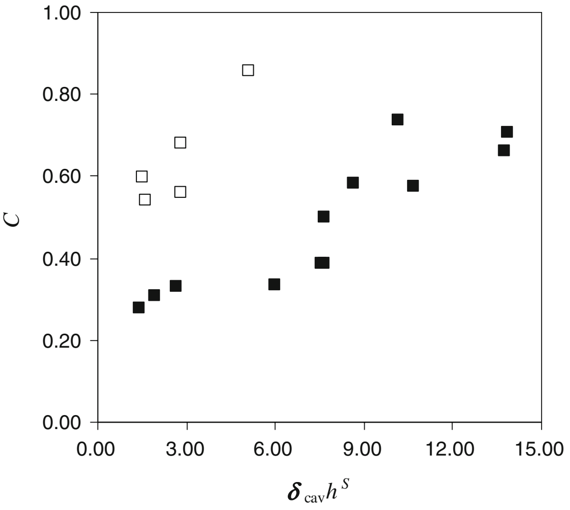

Fig. 3 C versus $\delta_{\text{cav}}h^{\text{s}}$ values for hydroxylic, *open square* (4–8) and aprotic solvents, *filled square* (9–20)

Since C and $\delta_{\text{cav}}h^{\text{s}}$ are both supposed to measure solvent–solvent interactions, the observed improvements resulting from the use of Eq. 3 must be related to some difference between these two descriptors. The plot in Fig. 3 of C values against $\delta_{\text{cav}}h^{\text{s}}$ shows that hydroxylic solvents rank higher in terms of C when compared to $\delta_{\text{cav}}h^{\text{s}}$ than do aprotic solvents. This might be related to the definition of these two quantities. Whereas C measures the energy required to bring all molecules contained in a unit volume of solvent to infinite distances from one another [16], $\delta_{\text{cav}}h^{\text{s}}$ simply measures the amount of energy needed to form a cavity. One can then assume from the observation of the data in this plot, that in the case of alcohols there seems to be an incomplete breaking of solvent–solvent interactions when a given cavity is formed and thus, for similar $\delta_{\text{cav}}h^{\text{s}}$ values, C is always much higher for the hydroxylic solvents. Unlike aprotic solvents, hydroxylic media appear to have the capacity to rearrange around a formed cavity without loosing its structuring degree to an extent comparable to that of aprotic solvents.

In processes fairly energetically dependent on cavity formation, such as the ones studied in this work, this different behavior is important, especially if there is only a small contribution from solute–solvent interactions, as is the case for 1-AdBr (see Table 4). For 1-AdOH and 2-AdO, the statistical improvement is not as good because these solutes show comparatively larger solute–solvent interactions.

The use of $\delta_{\text{cav}}h^{\text{s}}$ to describe the process of cavity formation seems therefore to allow a better perception of all involved interactions and a better modeling of the solution process as a whole.

In a previous study, we have shown that, in hydroxylic solvents, differences in solution enthalpies between 1-AdBr and *t*-BuBr, due to different energetic requirements for cavity formation, were adequately accounted for by C [10]. This conclusion could at first sight seem awkward vis-à-vis our present findings. However, Fig. 3 shows a fairly linear trend between C and $\delta_{\text{cav}}h^{\text{s}}$ if one considers separately the protic and the aprotic subsets. Considering hydroxylic solvents 4–8, for which data is available for $\Delta_{\text{sol}}H$, C, and $\delta_{\text{cav}}h^{\text{s}}$ for 1-AdBr and *t*-BuBr, correlations between differences in the solution enthalpies for both solutes with either C ($R^2 = 0.95$; sd$_{\text{fit}} = 0.24$) or $\delta_{\text{cav}}h^{\text{s}}$ ($R^2 = 0.95$; sd$_{\text{fit}} = 0.25$) show equivalent statistical quality. Hence, these results clear out any apparent contradiction with our earlier observations.

Further insights into the solution processes of the adamantyl derivatives can also be achieved by analyzing the resulting a_i coefficients from Eq. 3, in Table 4. The term associated with $\delta_{\text{cav}}h^{\text{s}}$ is significant in all regressions and the corresponding coefficients (a_5) are all positive (as expected) showing that the cavity formation step is endothermic. On the other hand, these values would be expected

Table 6 McGowan characteristic volumes, sublimation enthalpies and $a_0 - \Delta_{\mathrm{subl}}H$ values for 1-AdBr, 1-AdOH, and 2-AdO

	1-AdBr	1-AdOH	2-AdO
$10^{-2}V_x^{\mathrm{A}}/\mathrm{cm^3mol^{-1}}$	1.3668[a]	1.2505[a]	1.2075[a]
$\Delta_{\mathrm{subl}}H \pm s\Delta_{\mathrm{subl}}H/\mathrm{kJ\ mol^{-1}}$	71.60 ± 1.10[b]	86.73 ± 0.22[c]	66.38 ± 0.25[d]
$a_0 - \Delta_{\mathrm{subl}}H \pm s(a_0 - s\Delta_{\mathrm{subl}}H)/\mathrm{kJ\ mol^{-1}}$	−60.28 ± 1.19	−58.91 ± 0.77	−57.48 ± 1.04

[a] Calculated from data on Ref. [16]

[b] Ref. [25]

[c] Ref. [26]

[d] Ref. [27]

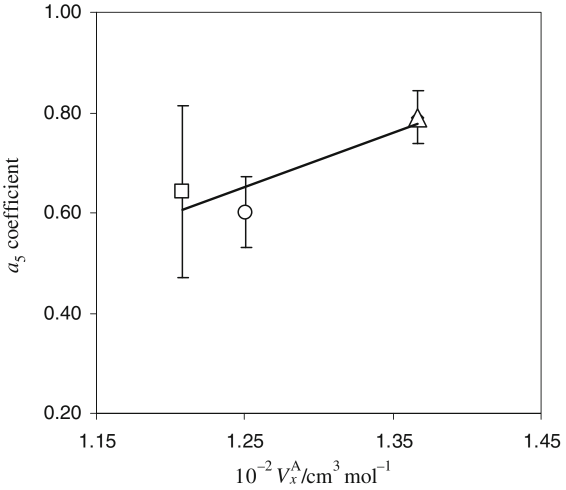

Fig. 4 a_5 versus V_x^{A} values for 1-AdBr (*open triangle*), 1-AdOH (*open circle*), and 2-AdO (*open square*)

to be linearly related to the relative sizes of the solutes. To test this supposition, the McGowan characteristic volumes, V_x^{A}(considered a reliable calculation of an isolated molecule's volume [16]) for the three solutes were determined and are presented in Table 6. A plot of a_5 versus V_x^{A} for 1-AdBr, 1-AdOH, and 2-AdO is shown in Fig. 4 and does reveal a fairly linear trend.

Analyzing the results in terms of the solute–solvent interaction coefficients (a_1–a_3) which prevail for each solute's solution process, the simplest to interpret seems to be the one obtained for 1-AdOH. This process is influenced by an exothermic contribution arising from the solvent's HBA basicity, β. This result is in line with our previous study [11] and is explained by the acid characteristics of the solute's hydroxyl group. Figure 5 illustrates this type of interaction, here exemplified with an ethanol solvent molecule.

Results obtained for 1-AdBr may seem at first glance more difficult to analyze. According to Table 4, its solution process is dependent on a single solute–solvent endothermic contribution due to the solvents' HBD acidity, α. The role of α is not unexpected since the bromide atom is an electro-attractive residue and is therefore able to interact with the solvent's acidic characteristics, measured by α. Figure 6 illustrates this type of interaction also with an ethanol solvent molecule.

The most striking aspect is, however, the positive sign associated with the α coefficient (a_2). From an enthalpic point of view, it seems that in this case solvent molecules prefer to interact with each other rather than with the solute, since the latter represents an energy-consuming interaction. The reason for the occurrence of this solution process lies ultimately in the lowering of the solution process driving force, the Gibbs energy, which results from the increase in solution entropy due to the disruption of the solute and solvent structures. It seems therefore that although the solvent's HBD acidity is an energetically unfavorable process in terms of enthalpy, the system's entropic gain is sufficient to compensate this outflow.

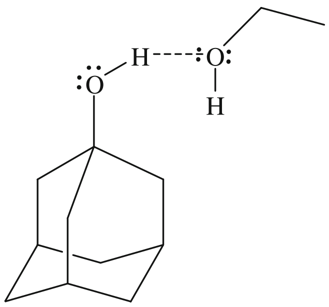

Fig. 5 Solvent's β interaction with 1-AdOH

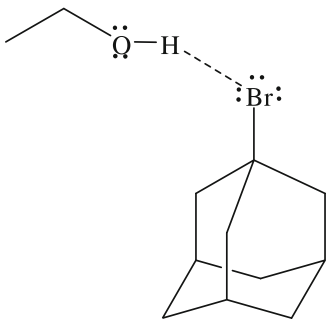

Fig. 6 Solvent's α interaction with 1-AdBr

For 2-AdO, two solute–solvent contributions were found to influence the solution process. An exothermic contribution arising from the solvent's dipolarity/polarizability ability measured by π^* and due to the solute's carbonyl residue which most certainly originates an appreciable dipolar moment, and an endothermic contribution due to the solvent's basicity, β. The endothermicity of this interaction may be similarly explained in terms of an entropic gain. It is well known that in a ketone the hydrogen atoms of the carbonyl adjacent carbon atoms are moderately acidic, and Bistričić et al. [28] have recently demonstrated the existence of a larger charge deficit in these hydrogen atoms when compared to that of the remaining hydrogen atoms in the molecule. Therefore, these two acidic sites in the AdO molecule are probably responsible for the emergence of such β interactions, as Fig. 7 illustrates.

One last significant issue regards the magnitude of the obtained a_0 coefficients. In a first approximation, one would expect that a_0 coefficient values should be close to the solutes' $\Delta_{\text{subl}}H$ values, within computed uncertainties. However, this would only be true if all other descriptors' coefficients were zero in the gas phase, which is not the case (e.g., π^* in the gas phase $= -1.1$ [29]). In fact, there are considerable differences between both quantities and this can be further attributed to some sort of non-specific contributions not accounted for by any other parameter in the regression but which could be switched on according to the solutes' size. As such, $(a_0 - \Delta_{\text{subl}}H)$ also presented in Table 6 were plotted against V_x^{A} in Fig. 8 confirming, within computed uncertainties, the existence of the anticipated relation.

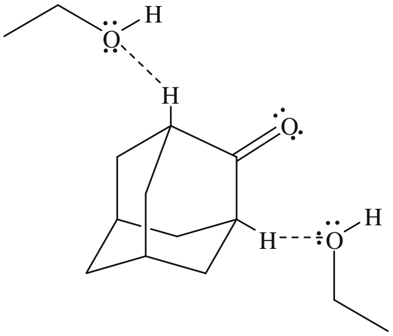

Fig. 7 Solvent's β interaction with 2-AdO

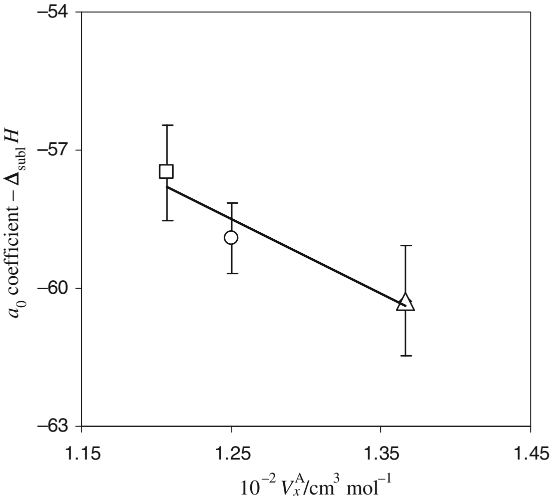

Fig. 8 $(a_0 - \Delta_{\text{subl}}H)$ versus V_x^{A} values for 1-AdBr (*open triangle*), 1-AdOH (*open circle*), and 2-AdO (*open square*)

Conclusions

Solvent effects on solution enthalpies were shown not to be properly evaluated via the well-established TAKA equation (Eq. 2) for the studied adamantyl derivatives. The same equation applied to differences in $\Delta_{\text{sol}}H$ between pairs of solutes was able to explain successfully these differences in terms of the equation solute–solvent descriptors, giving therefore an indication that cavity formation was not well accounted for by C. A new multiparametric equation was then devised by replacing C by Solomonov's $\delta_{\text{cav}}h^{\text{s}}$. This change lead to statistical improved regressions and allowed the assessment of the nature and magnitude of the major solute–solvent–solvent interactions influencing the solution processes addressed in this study.

An analysis of the coefficients of the best regressions clearly showed the significance of an endothermic contribution related to $\delta_{\text{cav}}h^{\text{s}}$ in all cases, and pinpointed the involvement of different solute–solvent interactions in these compounds' solution processes, which were attributed to their particular acid/base and dipolarity characteristics.

The unexpected solute–solvent endothermic contribution due to the α coefficient in the solution process of 1-AdBr was explained in terms of an enthalpic/entropic balance between newly formed solute–solvent and broken solvent–solvent interactions.

Solutes' size relations, anticipated for coefficients a_0 and a_5, should be further investigated with properly chosen solutes.

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