Solution enthalpies of hydroxylic compounds

Study of solvent effects through quantitative structure property relationships

**Marina Reis · Luís Moreira · Nelson Nunes ·
Ruben Leitão · Filomena Martins**

Abstract Solution enthalpies of adamantan-1-ol, 2-methyl-butan-2-ol, and 3-methylbutan-1-ol have been measured at 298.15 K, in a set of 16 protogenic and non-protogenic solvents. The identification and quantification of solvent effects on the solution processes under study were performed using quantitative-structure property relationships. The results are discussed in terms of solute–solvent–solvent interactions and also in terms of the influence of compound's size and position of its hydroxyl group.

Keywords QSPR · Solution enthalpy · Solvent effects ·
Adamantan-1-ol · 2-Methylbutan-2-ol ·
3-Methylbutan-1-ol

Introduction

Quantitative structure–property relationships (QSPR) are one of the most powerful techniques used to study solvent effects on media driven physicochemical processes. A multiparametric linear regression (MLR) performed between a solute related energetic quantity and a set of properly chosen solvent properties or descriptors allows the computation of several regression coefficients which measure the solute's sensitivity to those solvent properties. The method is based on a cause–effect relationship which allows the perception of how particular variations on solutes' molecular features influence the solvents' intervention in the process.

Multiparametric linear regression methodology is part of a vast field of mathematical tools which go from the widely used simple extrapolation procedures to more sophisticated approaches such as neural networks [1]. Devising QSPR models using MLR analyses is an increasingly widespread practice due to the accessibility of computational packages for personal computers [2]. However, its use should be thoroughly scrutinized to insure that sound statistical criteria are met throughout the whole modeling process [3, 4]. The misuse of MLR techniques can lead to misleading conclusions and contributes to the erroneous idea that they may provide less solid results, as pointed out by some authors [2].

Thermochemical data stand among macroscopic measurable quantities which help disclosing the nature of molecular interactions in solution. As such, they enclose valuable information that can be unraveled using QSPR techniques.

Formally, the solution enthalpy of a given solute A in a solvent S ($\Delta_{sol}H^{A/S}$) can be partitioned into three energetic contributions, namely: (i) the disruption of the solute structure, usually taken as its vaporization or sublimation enthalpy ($\Delta_{vap/subl}H^{A}$); (ii) the creation of a suitably sized cavity to accommodate the solute, which results in the breaking of solvent–solvent interactions ($\Delta_{cav}H^{A/S}$); and, finally, (iii) the accommodation of the solute in the formed cavity thus creating new non-specific ($\Delta_{int(nonsp)}H^{A/S}$) and

M. Reis · L. Moreira · F. Martins (✉)
Departamento de Química e Bioquímica, CQB, Faculdade de
Ciências, Universidade de Lisboa, 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. Leitão
Área Departamental de Engenharia Química, Instituto Superior
de Engenharia de Lisboa, Instituto Politécnico de Lisboa, CQB,
R. Conselheiro Emídio Navarro 1, 1950-062 Lisbon, Portugal

specific ($\Delta_{\text{int(sp)}}H^{\text{A/S}}$) solute–solvent interactions. $\Delta_{\text{sol}}H^{\text{A/S}}$ can thus be expressed by Eq. 1:

$$\Delta_{\text{sol}}H^{\text{A/S}} = \Delta_{\text{vap/subl}}H^{\text{A}} + \Delta_{\text{cav}}H^{\text{A/S}} + \Delta_{\text{int(nonsp)}}H^{\text{A/S}} + \Delta_{\text{int(sp)}}H^{\text{A/S}} \quad (1)$$

On the other hand, as depicted by Eq. 2, a MLR analysis applied to the study of solvent effects is based on the assumption that an energetic property measured for a certain physicochemical process of a solute A occurring in a solvent S ($E^{\text{A/S}}$), can be hypothetically obtained by adding up energetic terms corresponding to a reference solvent ($E^{\text{A/S}_0}$) and several independent energetic contributions relative to different solvent effects. The latter are computed form the product of a given solvent descriptor (d_i)—which reflects the solvent's ability to interact with the solute—and the solute's complementary capacity to undergo such interaction (a_i).

$$E^{\text{A/S}} = E^{\text{A/S}_0} + \sum_{1}^{n} a_i d_i \quad (2)$$

Considering that the disruption of the solute's structure is present for all solvents (including the reference solvent) and that the subscripts have the same meaning as before, Eqs. 1 and 2 can be combined to derive Eq. 3, where $\Delta_{\text{vap/subl}}H^{\text{A}}$ terms cancel out.

$$\Delta_{\text{sol}}H^{\text{A/S}} = \Delta_{\text{sol}}H^{\text{A/S}_0} + a_{\text{cav}}d_{\text{cav}} + a_{\text{int(nonsp)}}d_{\text{int(nonsp)}} + a_{\text{int(sp)}}d_{\text{int(sp)}} \quad (3)$$

The use of both a proper set of descriptors and a suitable reference solvent, and the strict observation of solid statistical criteria, allows the calculation of Eq. 3 regression coefficients thus providing further insights into solvent effects on solution enthalpies.

In a previous study, we have analyzed solvent effects on the solution enthalpies of three different solutes, 1-bromoadamantane, adamantan-1-ol, and 2-adamantanone, in several protogenic and non-protogenic solvents [5]. In the referred work, it was recognized that the well-established TAKA equation [6] was unable to correctly quantify solvent effects on such processes. However, a modified version of this model equation using $\delta_{\text{cav}}h^{\text{S}}$ as the cavity term [7], substantially improved the results. The established model assumes that four descriptors are required to quantify solvent effects: Solomonov's specific relative cavity formation enthalpy ($\delta_{\text{cav}}h^{\text{S}}$), a measure of the solvent energetic cavity formation requirements; π^*, regarded as a measure of non-specific solute–solvent interactions; and the specific solute–solvent descriptors α and β which measure, respectively, the solvent's hydrogen bond donor (HBD) acidity and the hydrogen bond acceptor (HBA) basicity [8–10].

Descriptors π^*, α, and β are based on reference processes involving either a single or a pair of molecular probes which ideally respond differently to changes in a single solvent property. The specific relative cavity formation enthalpy for a given solvent is 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).

In order to unambiguously define the reference process and since π^*, α, and β are computed using cyclohexane as a reference solvent (for which all three descriptors are taken as zero), the cavity term was redefined to zero cyclohexane's $\delta_{\text{cav}}h^{\text{S}}$ value. To achieve this, $\delta_{\text{cav}}h^{\text{S}}$ values reported for the solvents set used in this study were subtracted by cyclohexane's value (1.42). The redefined descriptor was labeled $\delta_{\text{cav}}h_0^{\text{S}}$ and Eq. 3 was converted into Eq. 4:

$$\Delta_{\text{sol}}H^{\text{A/S}} = \Delta_{\text{sol}}H^{\text{A/S}_0} + c\delta_{\text{cav}}h_0^{\text{S}} + p\pi^* + a\alpha + b\beta \quad (4)$$

Our formerly referenced work [5] showed that adamantan-1ol provided the soundest results when compared with the other two tested solutes. Therefore, the hydroxyl residue was considered a suitable functional group to further test other dissimilarities and clarify some aspects raised in that work. As such, the aim of this study is to apply QSPR model Eq. 4 to quantify solvent effects on the solution enthalpies of adamantan-1-ol, 2-methylbutan-2-ol, and 3-methylbutan-1-ol in 16 different solvents. The selection of these three solutes will allow a separated evaluation of the impact of changing the carbonated skeleton and the hydroxyl's group position (Fig. 1).

Experimental

Solvents were supplied by Aldrich, Merck and Riedel-de-Haën (min. 99%), with a water content below 0.1% and were used without further drying or purification. Adamantan-1-ol was supplied by Aldrich (min. 99%), 2-methylbutan-2-ol by BDH (min. 99.5%), and 3-methylbutan-1-ol by Merck (min. 98%). Solutes were weighed in a Precisa XT 120A analytical balance with a precision of
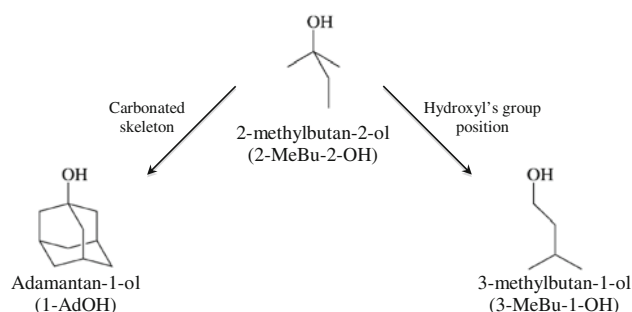
Fig. 1 Compounds analyzed in this study

±0.1 mg and their concentration ranged from 0.010 to 0.003 mol dm^{-3}.

Solution enthalpies were measured at 298.15 ± 0.01 K using a Thermometric 2225 precision solution calorimeter. [5, 11–14] This equipment operates under semiadiabatic conditions and has a temperature resolution in the order of 1 μK, corresponding to a resolution in enthalpy of (1–4) mJ.

Cylindrical ampoules were filled with solute and sealed. Each sealed ampoule was immersed into 100 mL of solvent, inside the glass reaction vessel, and stirred at (500–600) rpm. Two electrical calibrations were performed before and after breaking each ampoule. Each reported enthalpy value in a given solvent, results from the average of at least three independent experiments, with a relative standard deviation always less than 5%. Heats of empty ampoule breaking, measured in the solvent with the higher vapor pressure (acetone), were found to be negligible [14].

The performance and accuracy of the calorimetric system was tested by measuring the solution enthalpy of tris(hydroxymethyl)aminomethane (TRIS) in both 0.05 mol dm^{-3} NaOH and 0.1 mol dm^{-3} HCl. Experimental and literature values agree within experimental uncertainty [13].

Results and discussion

Experimental solution enthalpies ($\Delta_{sol}H_{exp}$) at 298.15 K and infinite dilution of adamantan-1-ol (1-AdOH), 2-methylbutan-2-ol (2-MeBu-2-OH), and 3-methylbutan-1-ol (3-MeBu-1-OH) in the chosen solvents set, corresponding standard deviations ($s\Delta_{sol}H_{exp}$) and solvent descriptors used in the subsequent analyses are presented in Table 1.

Data preparation is considered a crucial task in the development of suitable QSPR models [3, 4]. In studies such as these, standard statistical requirements comprise: (i) the selection of a set of independent descriptors reflecting major solute–solvent and solvent–solvent interactions; (ii) the inclusion of a sufficient number of data points (solvents)—usually more than three times the number of descriptors; (iii) and a judicious choice of solvent media so that the set includes several solvent classes reflecting, as much as possible, the full descriptors' space, and has no leverage points. The performed choice of solvents and the use of a modified version of the well-established TAKA model equation insured the compliance with the above mentioned requirements.

Moreover, to further test the obtained models, the reference solvent (cyclohexane) was withdrawn from the solvents' set. This procedure allowed, on one hand, to test the models' ability to predict the solution enthalpy of the solutes in the reference solvent and, on the other hand, to gain a deeper insight into the solution process, as it will be detailed later on in the text.

To thoroughly guarantee the independency of the chosen parameters, the determination coefficient, r^2, for each pair of descriptors should always be smaller than 0.5, and for a given descriptor against all others, one should have, $R^2 < 0.8$. These requirements were not totally fulfilled since for the pair $\delta_{cav}h_0^S/\pi^*$, $r^2 = 0.70$. This intercorrelation deters the simultaneous use of both descriptors in the analysis and implies a clear-cut choice. Our previous work [5] pointed out that the inclusion of a cavity descriptor was always important to achieve sound results, whereas the dipolarity/polarizability term was only relevant for solutes with a carbonyl residue such as 2-adamantanone. Therefore, for the three solutes under analysis, π^* was removed from the model equation, and Eq. 4 assumed the form expressed by Eq. 5. The statistical figures in Table 2 now reflect the absence of redundancy for the remaining descriptors, for the 15 solvents.

$$\Delta_{sol}H^{A/S} = \Delta_{sol}H^{A/S_0} + c\delta_{cav}h_0^S + a\alpha + b\beta \qquad (5)$$

The modeling procedure was initiated by testing Eq. 5 for all solvents shown in Table 1, except cyclohexane as mentioned earlier. Selection, by elimination, of solvent descriptors relevant to model the enthalpic process was then performed, and descriptors whose significance level (SL) was <95% were excluded. According to this criterion, α was discarded for all three solutes (SL = 7% for 1-AdOH, 84% for 2-MeBu-2-OH, and 45% for 3-MeBu-1-OH). Results are presented in Eqs. 5a, 5b, and 5c. The global quality of the models was assessed through several statistical criteria, namely standard deviation of the fit, sd_{fit}, determination coefficient, R^2, and Fisher's F value. Figure 2 shows a very good agreement between calculated ($\Delta_{sol}H_{calc}$) and experimental ($\Delta_{sol}H_{exp}$) values in all three cases. No significant outliers (i.e., $\left|\Delta_{sol}H_{exp} - \Delta_{sol}H_{calc}\right| > 2sd_{fit}$), were identified. The overall results demonstrate that the derived models are adequate to identify and quantify solvent effects on the analyzed thermochemical processes. It is therefore established that the solution enthalpies of these three solutes are influenced by the solvents HBA basicity and the specific relative cavity formation enthalpy.

$\Delta_{sol}H^{1-AdOH/S}$

$= 28.02_{\pm 1.04} + 0.64_{\pm 0.08}\delta_{cav}h_0^S - 19.39_{\pm 1.31}\beta$

$\quad (100.00\%) \qquad (100.00\%) \qquad (100.00\%)$

$\quad (sd_{fit} = 1.254, R^2 = 0.969, N = 15, F = 188) \qquad (5a)$

$\Delta_{sol}H^{2-MeBu-2-OH/S}$

$= 14.76_{\pm 1.17} + 0.38_{\pm 0.09}\delta_{cav}h_0^S - 20.86_{\pm 1.46}\beta$

$\quad (100.00\%) \qquad (> 99.84\%) \qquad (100.00\%)$

$\quad (sd_{fit} = 1.400, R^2 = 0.959, N = 15, F = 140) \qquad (5b)$

Table 1 Experimental solution enthalpies at 298.15 K and infinite dilution of adamantan-1-ol, 2-methylbutan-2-ol, and 3-methylbutan-1-ol in the chosen solvents set, corresponding standard deviations and solvent descriptors

Solvent	$(\Delta_{sol}H_{exp} \pm s\Delta_{sol}H_{exp})$/kJ mol^{-1}			Solvent parameters[a]			
	Adamantan-1-ol[a]	2-methylbutan-2-ol[b]	3-methylbutan-1-ol[b]	α	π^*	β	$10^2\delta_{cav}h_0^s$/kJ cm^{-3}[d]
Cyclohexane	30.78 ± 0.67[b]	19.19 ± 0.11	22.10 ± 0.04	0	0	0	0
Acetonitrile	27.27 ± 0.26	9.96 ± 0.14	11.57 ± 0.10	0.19	0.75	0.37	9.24
Dimethylformamide	18.29 ± 0.37	2.76 ± 0.08	3.70 ± 0.04	0.00	0.88	0.69	7.2
Dimethylsulfoxide	20.74 ± 0.06	4.67 ± 0.10	5.36 ± 0.03	0.00	1.00	0.76	12.45
Propylene carbonate	25.62 ± 0.39	10.19 ± 0.15	11.98 ± 0.02	0.00	0.83	0.40	8.72
Nitromethane	32.77 ± 0.14	14.97 ± 0.24	17.24 ± 0.12	0.22	0.85	0.25	12.32
Ethyl acetate	22.89 ± 0.21	7.64 ± 0.17	8.73 ± 0.14	0	0.55	0.45	4.56
1,4-Dioxane	22.63 ± 0.04	7.63 ± 0.11	9.11 ± 0.12	0	0.49	0.37	6.15
Dimethylacetamide	17.27 ± 0.05	1.45 ± 0.02	1.67 ± 0.03	0.00	0.85	0.76	6.24
Acetone	22.90 ± 0.19	6.75 ± 0.11	7.67 ± 0.19	0.08	0.71	0.48	6.23
Carbon tetrachloride	28.35 ± 0.17	16.07 ± 0.21	18.62 ± 0.19	0	0.28	0	0.49
Propan-1-ol	12.13 ± 0.06	-2.63 ± 0.02	0 ± 0[c]	0.79	0.53	0.85	0.08
Propan-2-ol	13.00 ± 0.17	-1.60 ± 0.02	$0.03 \pm 0.00_2$	0.680	0.480	0.930	1.38
Butan-1-ol	12.10 ± 0.08	-2.55 ± 0.07	$-0.03 \pm 0.00_2$	0.74	0.54	0.84	0.18
Ethanol	12.76 ± 0.10	-2.40 ± 0.03	0.42 ± 0.02	0.88	0.55	0.80	1.38
Methanol	14.21 ± 0.18	-2.07 ± 0.06	1.56 ± 0.02	1.09	0.60	0.73	3.68

[a] [5]

[b] This study

[c] Taken as zero since the value is too small to be measured

[d] $\delta_{cav}h_0^S = \delta_{cav}h^S - 1.42(\delta_{cav}h^{cyclohexane})$

Table 2 R^2 values for the correlations among descriptors $\delta_{cav}h_0^S$, α, and β for the set of 15 solvents

R^2	$\delta_{cav}h_0^S$	α	β
$\delta_{cav}h_0^S$	–	0.34	0.09
α	–	–	0.35
all	0.35	0.53	0.35

$$\Delta_{sol}H^{3-MeBu-1-OH/S}$$
$$= 17.54_{\pm1.17} + 0.26_{\pm0.09}\delta_{cav}h_0^S - 21.47_{\pm1.38}\beta$$
$$(100.00\%) \quad (>98.75\%) \quad (100.00\%)$$
$$(sd_{fit} = 1.315, R^2 = 0.962, N = 15, F = 154) \quad (5c)$$

In a QSPR study, the analysis of the coefficients of the model equation provides new insights into the process under investigation. In this case, the first result to be scrutinized refers to $\Delta_{sol}H^{A/S_0}$. Ideally, this coefficient should be identical (within uncertainty's range) to the solution enthalpy of the corresponding solute in cyclohexane. However, in all three cases, a closer examination of the obtained values shows a clear deviation from this assumption. Figure 3 illustrates differences between the expected and experimentally determined $\Delta_{sol}H^{A/S_0}$ values

for the three solutes. This figure includes error bars related to the dominant source of uncertainty which is that resulting from the coefficients' computation. It is clear that all three results are equal and non-zero, within experimental uncertainty.

This result might be related with the simultaneous exclusion of π^* and cyclohexane from the analysis. As was already mentioned, the $\delta_{cav}h_0^S/\pi^*$ pair intercorrelation is very high. However, the most striking aspect is the even stronger dependence of π^* from both $\delta_{cav}h_0^S$ and β. In fact, for the same solvent set, π^* values can be obtained with a precision of ±0.073 using Eq. 6, as depicted in Fig. 4.

$$\pi^* = 0.227_{\pm0.061} + 0.046_{\pm0.005}\delta_{cav}h_0^S - 0.324_{\pm0.077}\beta$$
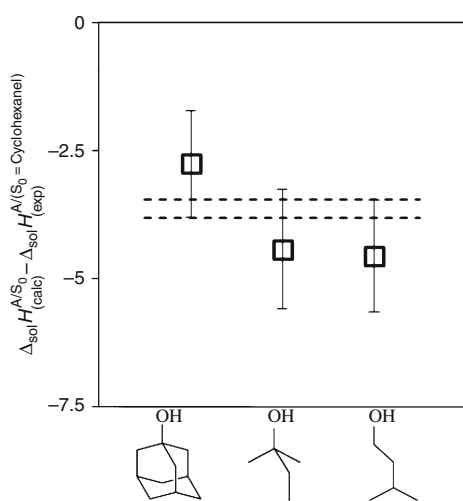$$(>99.71\%) \quad (100.00\%) \quad (>99.88\%)$$
$$(sd_{fit} = 0.073, R^2 = 0.881, N = 15, F = 44)$$
$$(6)$$

The referred dependency implies therefore that a non-specific interaction contribution evaluated by the p coefficient in Eq. 4 is indeed spread between computed coefficients b and c in Eq. 5.

From this analysis, also emerges an opportunity to evaluate the non-specific interaction contribution for the solution process. Equation 6 predicts cyclohexane's π^*
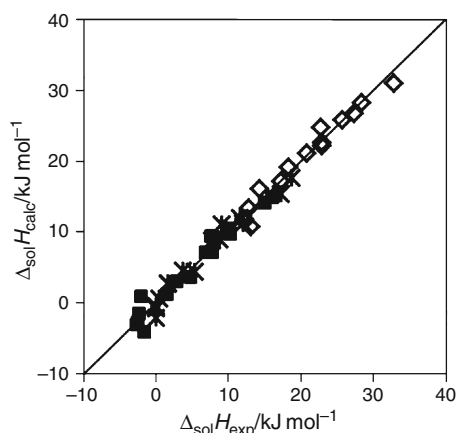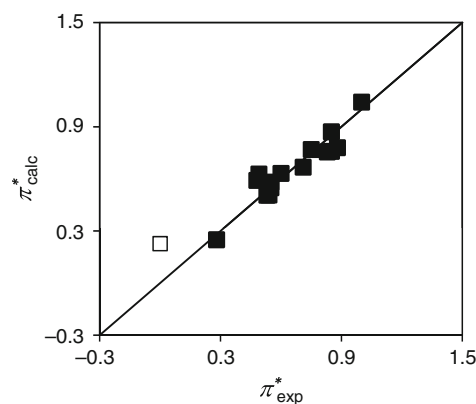
Fig. 2 Plot of $\Delta_{sol}H_{calc}$ versus $\Delta_{sol}H_{exp}$ according to equations: 5a (*open diamond* 1-AdOH), 5b (*filled square* 2-MeBu-2-OH), and 5c (*asterisk* 3-MeBu-1-OH)

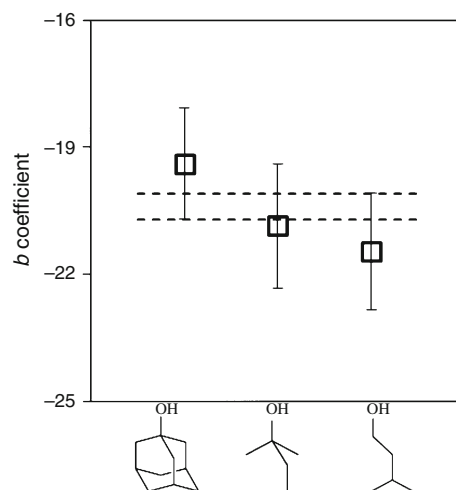**Fig. 4** Plot of calculated versus experimental π^* values obtained from Eq. 6 for the 15 solvents used to determine the 5a, 5b, and 5c model equations (*filled square*), and for cyclohexane (*open square*)

Fig. 3 $\Delta_{sol}H^{A/S_0}_{(calc)} - \Delta_{sol}H^{A/(S_0=cyclohexane)}_{(exp)}$ values and associated errors for 1-AdOH, 2-MeBu-2-OH and 3-MeBu-1-OH

Fig. 5 b coefficients' values and associated errors for 1-AdOH, 2-MeBu-2-OH, and 3-MeBu-1-OH

value as $0.227_{\pm 0.061}$ which is substantially higher than the true (zero) value. The predicted solution enthalpies for the reference solvent surely reflect this overestimated assumption. Consequently, the $\Delta_{sol}H^{A/S_0}_{(calc)} - \Delta_{sol}H^{A/(S_0=Cyclohexane)}_{(exp)}$ values can be considered directly proportional to this non-zero non-specific interaction term since the other descriptors ($\delta_{cav}h_0^S$ and β) rank zero for cyclohexane. Unfortunately, the associated error for cyclohexane's predicted π^* value inhibits a further detailed quantitative analysis. In view of this, one can assume that Fig. 3 supports the fact that an exothermic non-specific solute–solvent interaction, equivalent for all three solutes, is present in the corresponding solution processes. The exothermic character of the non-specific interaction is reflected by the negative sign of the difference $\Delta_{sol}H^{A/S_0}_{(calc)} - \Delta_{sol}H^{A/(S_0=Cyclohexane)}_{(exp)}$.

Figure 5 discloses the existence of an exothermic (notice the negative coefficients' sign in Eqs. 5a–5c) specific solute–solvent HBA basicity contribution measured by the b coefficient which is also equivalent for all three solutes. Considering the above references to the existence of an intercorrelation between terms, it is worth pointing out that the computed b coefficient is, in absolute terms, overestimated by the non-specific term's contribution. Hence, although the input might not be correctly quantified, it still gives rise to a strong exothermic effect. This result was already explained in previous works as a consequence of the acidic characteristics of the solutes' hydroxyl group [5, 13]. In addition, the present work demonstrates that this particular solute–solvent interaction

$$c = -0.41_{\pm 0.28} + 0.83_{\pm 0.28}(10^{-2}V_x^A)$$
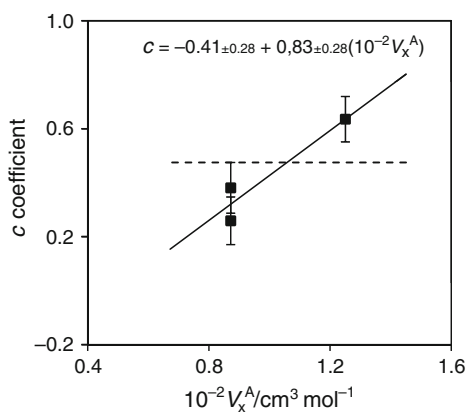
Fig. 6 c coefficients' values and associated errors versus $10^{-2} V_x^A$ values for 1-AdOH, 2-MeBu-2-OH, and 3-MeBu-1-OH

is in this case similar in extent for the primary, tertiary and bulky hydroxylic solutes.

Lastly, the cavity term (c coefficient) should be related to the solutes' size. Equations 5a, 5b, and 5c show that, as expected, smaller solutes (2-MeBu-2-OH and 3-MeBu-1-OH) exhibit a smaller c coefficient than the bulky 1-AdOH compound. Also, the coefficients' positive sign reveals an endothermic contribution reflecting the solvent–solvent interactions which are necessary to be broken to form a suitable cavity to accommodate the solute.

Due to the $\delta_{cav}h_0^s$ definition, the c coefficient should be related to the McGowan volume for each solute. However, owing to the already referred non-specific exothermic contribution, this coefficient should be smaller than expected in all three cases. Also, and since the exothermic non-specific contribution is similar for all solutes, as seen before, a linear relationship should be perceptible from a plot of c versus the McGowan volume for each solute ($10^{-2}V_X^A/cm^3 \ mol^{-1}$: 1-AdOH = 1.2505; 2-MeBu-2-OH and 3-MeBu-1-OH = 0.8718) [15]. Moreover, the slope of this linear trend should be equal to one and the intercept consistently negative, reflecting the previously mentioned non-specific exothermic contribution. The lack of a sufficient number of tested solutes (only three and two of them with the same V_X^A values) hampers the possibility to evaluate this hypothesis rigorously. However, Fig. 6 shows that the observed trend does not conflict with the expected outcome.

Conclusions

The complete analysis of all results can be summarized as follows:

(i)   The pursued strategy was adequate to identify and quantify solvent effects on the solution enthalpies of three hydroxylic compounds with different sizes and substitution patterns.

(ii)   QSPR models were developed using a wide variety of solvents including alcohols. Results do not seem to indicate any singular solvation behavior regarding protogenic media. However, no further attempt was made to disclose any differences in behavior between dissimilar sets of solvents.

(iii)   HBD acidity was found not to have any particular influence on the solution process of any of the analyzed solutes.

(iv)   The cavity term appears to be linearly related to the solutes' McGowan volume, further substantiating that $\delta_{cav}h_0^s$ is a suitable descriptor to quantify solvent–solvent interactions disrupted during the cavity formation process.

(v)   Both non-specific and HBD basicity solute–solvent interactions were found to be important, exothermic and their extent similar, for the solution processes of all studied solutes.

(vi)   Hydroxyl group's position did not influence the mentioned specific and non-specific interactions. This feature was particularly evident when comparing 2-MeBu-2-OH and 3-MeBu-1-OH solutes.

(vii)   Different structural characteristics of the carbonated skeleton also did not show any significant influence on the identified specific and non-specific interactions.

It is worth noticing that kinetic studies performed on the heterolysis reactions of adamantyl and t-butyl compounds seemed to suggest that differences in the observed kinetic behavior had to do with different magnitudes of specific solute–solvent interactions, favoring the adamantyl compound [16, 17]. The referred authors explain these facts based on the assumption that the different steric environments of both compounds are responsible for a dissimilar development of a specific (and thus oriented) hydrogen bond interaction. This paper provides evidences that support the fact that, at least outside the reactivity context, no significant differences are observed in the magnitude of solute–solvent interactions between caged and uncaged compounds.

References

1. Kovalishyn V, Aires-de-Sousa J, Ventura C, Leitao RE, Martins F. QSAR modeling of antitubercular activity of diverse organic

compounds. Chemometr Intell Lab. 2011;107(1):69–74. doi:10.1016/j.chemolab.2011.01.011.

2. Bentley TW, Garley MS. Correlations and predictions of solvent effects on reactivity: some limitations of multi-parameter equations and comparisons with similarity models based on one solvent parameter. J Phys Org Chem. 2006;19(6):341–9. doi:10.1002/poc.1084.

3. Tropsha A, Gramatica P, Gombar VK. The importance of being earnest: validation is the absolute essential for successful application and interpretation of QSPR models. QSAR Comb Sci. 2003;22(1):69–77.

4. Martins F, Ventura C. Application of quantitative structure–activity relationships to the modeling of antitubercular compounds. 1. The hydrazide family. J Med Chem. 2008;51(3):612–24. doi:10.1021/jm701048s.

5. Martins F, Moreira L, Nunes N, Leitao RE. Solvent effects on solution enthalpies of adamantyl derivatives. J Therm Anal Calorim. 2010;100(2):483–91. doi:10.1007/s10973-009-0651-x.

6. Taft RW, Abboud JLM, Kamlet MJ, Abraham MH. Linear solvation energy relations. J Solut Chem. 1985;14(3):153–86.

7. Solomonov BN, Novikov VB, Varfolomeev MA, Mileshko NM. A new method for the extraction of specific interaction enthalpy from the enthalpy of solvation. J Phys Org Chem. 2005;18(1):49–61. doi:10.1002/poc.753.

8. Kamlet MJ, Taft RW. Solvatochromic comparison method.1. Beta-scale of solvent hydrogen-bond acceptor (HBA) basicities. J Am Chem Soc. 1976;98(2):377–83.

9. Taft RW, Kamlet MJ. Solvatochromic comparison method.2. Alpha-scale of solvent hydrogen-bond donor (HBD) acidities. J Am Chem Soc. 1976;98(10):2886–94.

10. Kamlet MJ, Abboud JL, Taft RW. Solvatochromic comparison method. 6. Pi-star scale of solvent polarities. J Am Chem Soc. 1977;99(18):6027–38.

11. Martins F, Nunes N, Moita ML, Leitao RE. Solution enthalpies of 1-bromoadamantane in monoalcohols at 298.15 K. Thermochim Acta. 2006;444(1):83–5. doi:10.1016/j.tca.2006.02.030.

12. Nunes N, Martins F, Leitao RE. Thermochemistry of 1-bromoadamantane in binary mixtures of water-aprotic solvent. Thermochim Acta. 2006;441(1):27–9. doi:10.1016/j.tca.2005.11.035.

13. Martins F, Nunes N, Moreira L, Leitao RE. Determination of solvation and specific interaction enthalpies of adamantane derivatives in aprotic solvents. J Chem Thermodyn. 2007;39(8):1201–5. doi:10.1016/j.jct.2006.12.002.

14. Martins F, Reis M, Leitao RE. Enthalpies of solution of 1-butyl-3-methylimidazolium tetrafluoroborate in 15 solvents at 29815 K. J Chem Eng Data. 2010;55(2):616–20. doi:10.1021/je9005079.

15. Marcus Y. The properties of solvents. Wiley series in solution chemistry, vol. 4. Chichester, New York: Wiley; 1998.

16. Abraham MH, Doherty RM, Kamlet MJ, Harris JM, Taft RW. Linear solvation energy relationships. 37. An analysis of contributions of dipolarity polarizability, nucleophilic assistance, electrophilic assistance, and cavity terms to solvent effects on tert-butyl halide solvolysis rates. J Chem Soc Perk Trans. 1987;2(7):913–20.

17. Gajewski JJ. Is the tert-butyl chloride solvolysis the most misunderstood reaction in organic chemistry? Evidence against nucleophilic solvent participation in the tert-butyl chloride transition state and for increased hydrogen bond donation to the 1-adamantyl chloride solvolysis transition state. J Am Chem Soc. 2001;123(44):10877–83.