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Application of correlation analysis to solvolytic reactions of tertiary haloalkanes and Menschutkin reactions[†]

Raquel M. C. Gonçalves* **and Lídia M. P. C. Albuquerque**

Departamento de Química e Bioquímica, CECUL – Centro de Electroquímica e Cinética da Universidade de Lisboa, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisbon, Portugal

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ABSTRACT: We present a selection of our studies concerning solvent, substrate and temperature effects in solvolytic and Menschutkin reactions, by means of multiparametric equations and, more recently, by the use of factor analysis. Important steps in this development are recapitulated: (i) the application of correlation relationships relating rate constants to the properties of the solvents and of the solvents, substrates and temperature, simultaneously; (ii) the dissection of solvent effects into contributions from the initial state and the transition state; (iii) the split of intermolecular forces through the application of linear solvation energy relationships to the enthalpies of solution; and (iv) recent developments including the use of target factor analysis. The parametric descriptions reveal the dominant interaction mechanisms. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: solvolytic reactions; Menschutkin reactions; enthalpies of solution; linear solvation energy relationships (LSER); target factor analysis (TFA)

INTRODUCTION

The influence of solutes and solvents on the rate of chemical reactions has been studied for more than a century. Several attempts to express it quantitatively involve various scales of solute and solvent properties. It starts with the famous Hammett equation (1937)[1] for the study of substituent effects, and with the Grunwald–Winstein equation (1948)[2] for the correlation of solvent effects. Since the appearance of these uniparametric expressions, there has been an enormous evolution in this field of research.

It is now clear that reactivity values obtained with a wide range of solvents and substrates can only be satisfactorily correlated if multiple linear correlation analysis is used. However, any multiparametric treatment must combine solvent or/and solute parameters, which have to be independent but complementary, according to a physico-chemical model envisaged to connect these parameters to the relevant details of the chemical processes under study.[3–12]

During the last decade, our attention has been centred on the behaviour of solvolytic and Menschutkin reactions in order to identify the main solute–solvent–solvent interactions, which cause the differential solvation of the initial and transition states of these reactions. Multiple linear regression procedures, according to consistent physico-chemical models and, more recently, the use of target factor analysis (TFA), have shown to be powerful approaches.

The aim of this paper is to give an overview of the systematic studies that have been undertaken in our laboratory in order to interpret the kinetic and thermochemical results through the understanding of solute–solvent–solvent interaction mechanisms. Details of the equipment, calibration, tests and operating procedures have been described previously.[11–15]

The reacting systems under study were the unimolecular solvolysis of tertiary haloalkanes (from C_4 to C_7) in a large number of hydroxylic solvents, mainly mono- and dialcohols. We have also investigated the bimolecular Menschutkin reaction between triethylamine and iodoethane in a variety of alcohols. The chosen solvent-dependent kinetic property was the logarithm of the rate constant, log k, or the Gibbs function of activation, $\Delta^{\ddagger}G$, within the transition-state theory. The thermodynamic function of solution under analysis was the solution enthalpy, $\Delta_s H^{\infty}$, or the corresponding solvation enthalpy $\Delta_{solv}H^{\infty}$, at infinite dilution. Statistical treatments relat-

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**Correspondence to:* R. M. C. Gonçalves, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Rua Ernesto de Vasconcelos, 1749-016 Lisbon, Portugal.
E-mail: rmcgonc@clix.pt

[†] Dedicated to Dr John Shorter on the occasion of his 75th birthday.

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ing the experimental rate constants and thermodynamic solution values to the properties of the solvents and/or of the substrates allowed us to achieve significant improvements in revealing the intermolecular forces that dominate the reaction paths under study.

MECHANISMS OF INTERACTION

Solvolytic reactions of tertiary haloalkanes and Menschutkin reactions are dominated by several interaction mechanisms. In essence, we can expect three different types of interactions, as follows:

(i) solvent–solute interactions by non-specific, long-range intermolecular forces, mainly due to the polarizability and dipolarity of the solvent;
(ii) solvent–solute interactions by specific, short-range intermolecular forces, mainly determined by the solvent hydrogen-donor bond acidity and acceptor basicity in terms of the Lewis acid–base concept; and
(iii) solvent–solvent interactions determining the disruption and reorganization of the solvent structure, measured by the energy necessary to separate solvent molecules to create a suitable cavity to accommodate the solute.

In order to identify and quantify the main interactions that take place between solvent and solute molecules during the reaction paths, we chose the empirical equation proposed by Taft, Abboud, Kamlet and Abraham (TAKA):[6,7]

$$P = a_0 + a_1\pi^* + a_2\alpha + a_3\beta + a_4{\delta_H}^2 \qquad (1)$$

where P is the reactivity property under study, π^*, α and β are the well-known molecular–microscopic solvatochromic parameters related to the solvent dipolarity/polarizability, hydrogen-bond donor (HBD) acidity and hydrogen-bond acceptor (HBA) basicity, respectively, and ${\delta_H}^2$ is the Hildebrand cohesive energy density of the solvent.

Based on the available values of solvent parameters, a different equation, also suitable for the evaluation of medium influences, was proposed and tested by Gonçalves, Albuquerque and Simões (GAS):[9,12,13]

$$P = a_0 + a_1 f(\varepsilon) + a_2 g(\eta) + a_3 {E_T}^N + a_4{\delta_H}^2 \qquad (2)$$

where $f(\varepsilon)$ is the Kirkwood function of the dielectric constant, $(\epsilon - 1)/(2\epsilon + 1)$, $g(\eta)$ is the refractive index function $(\eta^2 - 1)/(\eta^2 + 2)$ and ${E_T}^N$ is the normalized $E_T(30)$ parameter;[16] $f(\varepsilon)$ is related to the dipolarity of the solvent and $g(\eta)$ to the polarizability, and ${E_T}^N$ provides a measure of the solvent's HBD acidity of protic solvents. Some contribution of solvent dipolarity was also included in this last parameter.

Data concerning several solvolytic reactions were also analysed using a 'hypothesis-free' methodology, namely target factor analysis (TFA).[12] The application of TFA allows a better understanding of interaction mechanisms and has the advantage of not assuming any prior model or kind of behaviour.[17]

In addition, a general quantitative formulation of the reactivity problem did not avoid the simultaneous treatment of solvent and substrate effects.[10] An even more sophisticated and ambitious formulation involved three variables, *viz.* solvent, substrate and temperature.[18]

The dissection of solvent effects on solvolytic and Menschutkin reactions into contributions from the initial state and the transition-state solvation was achieved through the combination of transfer energies of activation and multiple linear correlations,[19,20] according to the unified approach proposed and first applied by Abraham.[21]

The acquisition of solution enthalpy values and their treatment in terms of linear solvation energy relationships (LSER) were also relevant in understanding the change of solvent and substrate in the initial state.[22]

Solvent, substrate and temperature effects

This study started with solvolytic reactions of 2-bromo-2-methylpropane (*t*-BuBr) and 2-iodo-2-methylpropane (*t*-BuI) in water, measured in 12 mono- and 10 dialcohols at 25.00 °C.[9] Rate constants were correlated with solvent parameters through the complete and truncated versions of the GAS equation, Eqn. (2). In our earlier work, the best equations fitting the data were achieved by considering Ehrenson's criterion for relative fitting.[23] Later, the decision for the selection and elimination of variables was performed taking into account, simultaneously, the significance level of each regression coefficient, the multiple linear correlation coefficient, the standard deviation of the fit and the Fisher statistical parameter.

The results show that the solvent influence on both solvolytic reactions is dominated by (i) the non-specific solvent–solute interactions due to the polarizability; (ii) the non-specific dipolarity and the specific hydrogen-bond acidity interactions of the solvent, both represented by the ${E_T}^N$ term, and (iii) the solvent–solvent interactions that are related to the work of creation a cavity for the substrate molecule.

Shortly after our first attempts to study solvent effects in solvolytic reactions, we arrived to a parametric description relating reactivity and parameters with solvent and substrate, simultaneously.[10] Although it is not known how the two influences are interrelated, some studies concerning this matter have been carried out. One of them, the Gilkberg and Marcus approach,[24] was used by us. First, log k values were expressed in terms of the most statistically relevant solvent parameters. Second,

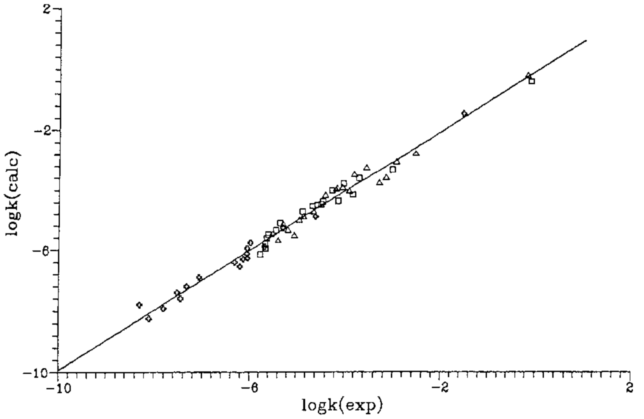

Figure 1. Plot of log*k* values calculated according to Eqn. (3) against the experimental log *k* values for tertiary halobutanes solvolysis

the regression coefficients, a_0 and a_i, were submitted to a single regression in terms of various properties of the substrates in order to identify the relevant interdependencies. In this sense, it was interesting that the coefficients of the dipolarity term depend on the polarity of the solute as represented by the dipole moment μ_2 and that those of the polarizability and the cavity terms depend on the molar volume of the substrate V_2 ($\mathrm{cm^3\,mol^{-1}}$). The result of applying this procedure is given by

$$\log k = -102.4 - 38.46g(\eta) + 65.67E_T{}^N + 3.988 \times 10^{-3}\delta_H{}^2 + 39.96\mu_2 + 48.21g(\eta)V_2 - 26.71E_T{}^N\mu_2 - 2.092 \times 10^{-3}\delta_H{}^2V_2 \quad (3)$$

The fit achieved with this final equation describes very well the solvolysis of *t*-BuX (X = Cl, Br, and I) in 19 hydroxylic solvents[10] ($N = 57$ log *k* values) with a confidence level >99.99% ($\sigma = 0.24$), as shown in Fig. 1. In Fig. 1, log *k* values calculated according to Eqn. (3) are plotted against the corresponding experimental values. The straight line represents a perfect fit.

The results of an equivalent treatment concerning solution enthalpies are summarized later (see Enthalpies of solution).

Correlation analysis was also applied to the rate constants for the solvolytic reactions of tertiary halobutanes, at temperatures ranging from 0 to 60 °C in 5 °C steps.[18] To perform this analysis we chose the parameter τ of Charton and Charton[25] as a variable independent of solvent and substrate effects, to account for the effect of temperature; this is given by $\tau = 1000/T - 1000/298.15$ (T in kelvin). Rate constant values were from different sources ($N = 220$) and, again, a method based on the Glikberg and Marcus approach was used. Equation (4) was then obtained ($\sigma = 0.24$), as follows:

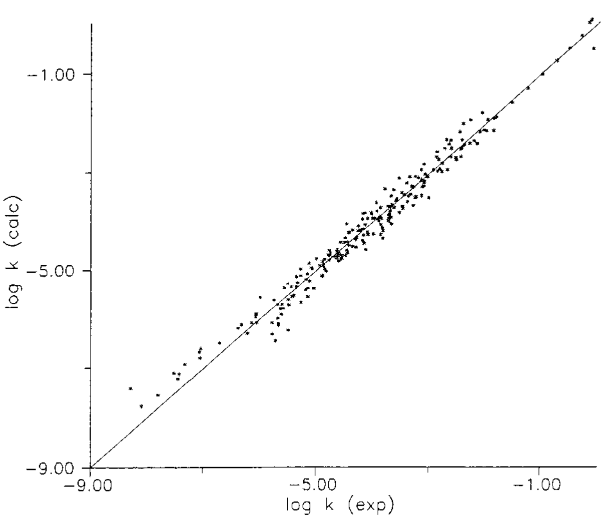

Figure 2. Plot of log*k* values calculated according to Eqn. (4) against the experimental log *k* values for tertiary halobutanes solvolysis

$$\log k = -71.42 - 35.02g(\eta) + 25.12E_T{}^N + 3.648 \times 10^{-3}\delta_H{}^2 - 5.085\tau + 25.94\mu_2 + 0.4633g(\eta)V_2 - 8.595E_T{}^N\mu_2 - 1.612 \times 10^{-3}\delta_H{}^2V_2 \quad (4)$$

Figure 2 shows the excellent plot of calculated log *k* values against experimental log *k* values ($T \in [0; 60\,°\mathrm{C}]$). Again, the straight line represents the perfect fit.

The detailed parametric description given above was very useful in the interpretation of chemical phenomena. Moreover, we also devised general equations that can be used to reproduce and predict rate constants of solvolytic reactions from solvent and substrate properties at any temperature within the range studies.

Our attention was also attracted by the reactions of haloalkanes with tertiary amines (S_N2 reactions of Menschutkin type) as, in general, they exhibit a high sensitivity to solvent polarity. We decided to investigate the reaction of iodoethane (EtI) with triethylamine ($\mathrm{Et_3N}$) in water, in 10 mono- and nine dialcohols.[11]

As a result of the increasing interest in the values of Kamlet–Taft solvatochromic parameters to be used in the TAKA equation, we decided to extend the available data to hydroxylic solvents. In this sense, a new collection of 25 values for π^*, α and β was obtained using four solvatochromic indicators that are sensitive to the solvent dipolarity/polarizability π^* (4-nitroanisole, 2-nitroanisole, 4-ethylnitrobenzene and *N*,*N*-diethyl-4-nitroaniline), two sensitive to the solvent's dipolarity/polarizability π^* and the hydrogen-bond acceptor capability β (4-nitroaniline and 4-nitrophenol) and one particularly sensitive to the solvent's dipolarity/polarizability π^* and the hydrogen-bond donor capability α [2,6-diphenyl-4-(2,4,6-triphenylpyridinio)phenolate].[14]

Again, the TAKA and GAS equations were applied to the rate constant values. Both equations accommodate successfully the results and allow an almost common and complementary interpretation. We observed that (i) non-specific solvent–solute interactions of the dipolarity and polarizability types are relevant, (ii) specific solvation on account of the HBD acidity and the HBA basicity of the solvent are irrelevant and (iii) solvent–solvent interactions related to disruption and reorganization of solvent molecules are important, although to a small extent.

The strong influence of the solvent's dipolarity/polarizability is exerted in stabilizing the ion-pair like activated complex and, consequently, in increasing the rate constant. The irrelevancy of the solvents such as HBD (and HBA) is presumably, as pointed out before,[8] a consequence of the counterbalance between the stabilization of the leaving halide ion in the transition state by electrophilic assistance and the stabilization of the tertiary amine in the initial state.

Initial- and transition-state solvation

For a more detailed analysis of the solvent effect, reactivity properties can first be dissected into contributions from the initial state and the transition state; then, the effect can be divided into the various mechanisms of interaction through appropriate multiple linear correlations. The preliminary studies that used this methodology were performed by Winstein and Fainberg,[26] Arnett *et al.*[27] and Abraham.[21]

We extended the study of the influence of the solvent on the Gibbs functions of activation of tertiary halobutane solvolysis and of the Menschutkin reaction of EtI with Et_3N, both in alcohols and at 25.00 °C.[19,20] The values of $\Delta^{\ddagger}G$ were calculated from rate constants using the fundamental equation of the transition-state theory. Next, by using a reference solvent, we calculated the transfer Gibbs energies of activation, $\delta\Delta^{\ddagger}G$, the transfer Gibbs energies of the reactants, δG_{i}, and the transfer Gibbs energies of the activated complex, δG_{t}. The three types of transfer functions are related through the equation

$$\delta G_{\mathrm{t}} = \delta G_{\mathrm{i}} + \Delta^{\ddagger}G_j - \Delta^{\ddagger}G_{\mathrm{r}} = \delta G_{\mathrm{i}} + \delta\Delta^{\ddagger}G \qquad (5)$$

where j refers to any solvent and r to the reference solvent. Values for the initial state were calculated using the following equation:

$$\delta G_i = RT\ln(\gamma_j{}^{\infty}/\gamma_r{}^{\infty}) \qquad (6)$$

where $\gamma_j{}^{\infty}$ and $\gamma_{\mathrm{r}}{}^{\infty}$ are the infinite dilution activity coefficients of the solute in a solvent j and in the reference solvent r, respectively. The values of activity coefficients at infinite dilution were calculated by the UNIFAC group-contribution method and ethanol was used as the reference solvent in both nucleophilic displacement reactions.

The GAS equation was successfully applied to the transfer Gibbs energies of the activation process, the initial state and the transition state of tertiary halobutanes solvolysis in 16 solvents. Meaningful correlations show conclusively that all the various factors making up the overall solvent effect, namely, polarizability, dipolarity–HBD acidity and disruption/reorganization, which dominate the activation process, are mainly due to transition-state contributions. In fact, the coefficients affecting each dependent variable in the $\delta\Delta^{\ddagger}G$ and δG_{t} correlations are very similar in sign and in magnitude; conversely, the equivalent coefficients for the $\delta\Delta^{\ddagger}G$ and δG_i correlations always show opposite numerical signs.[19]

Based on the available data, we chose the TAKA equation to correlate the transfer Gibbs energies of the Menschutkin reaction in 19 mono- and dialcohols. In this case, we found that the dominant interaction mechanisms were (i) solute–solvent interactions due to dipolarity/polarizability and (ii) solvent–solvent interactions due to disruption/reorganization. Specific interactions (acidity and basicity) seemed to be irrelevant. These conclusions were valid for the activation process and the initial state. The same treatment applied to δG_{t} values gave poor correlations and did not allow reliable information to be obtained.[20]

Enthalpies of solution

Our first steps in this field included the dissolution of 2-chloro-2-methylpropane (*t*-BuCl) and 2-bromo-2-methylpropane (*t*-BuBr) in water and in 13 monoalcohols at 25.00 °C and infinite dilution.[28] The experimental data were fitted to the complete and truncated versions of the GAS equation.

As expected, no single macroscopic physical parameter could account for the multitude of mechanisms of interaction; the same applies to any regression analysis including only either non-specific or specific intermolecular forces. The best equations fitting the data were identical for both solutes and include $f(\varepsilon)$, $E_{\mathrm{T}}{}^{\mathrm{N}}$ and $\delta_{\mathrm{H}}{}^2$ terms, which means that enthalpies for the initial state of the solvolytic reactions are very sensitive to the solute–solvent interactions of the dipole–dipole type, to the electrophilic assistance by protic solvents and to the solvent–solvent interaction mechanism on account of the solute cavity effect. Conversely, to the Gibbs function of transfer for the initial-state polarizability is relatively unimportant, probably owing to compensation effects.

Later, we extended our study relating enthalpies of solution and intermolecular forces to the solution of *t*-BuI, in connection with cavity theories of solution.[22]

Table 1. Relevant descriptors of solvents obtained using LSER (GAS and TAKA equations) and TFA multivariate analysis

Substrate	GAS	TAKA	TFA
t-BuI	$g(\eta)$, E_T^N	π^*, α	$g(\eta)$, E_T^N (monoalcohols) $g(\eta)$, E_T^N (dialcohols)
t-BuBr	$g(\eta)$, E_T^N	π^*, α	$g(\eta)$, E_T^N (monoalcohols) $g(\eta)$, E_T^N (dialcohols)
t-BuCl	$g(\eta)$, E_T^N	π^*, α, β	$g(\eta)$, E_T^N (monoalcohols) $g(\eta)$, E_T^N (dialcohols)
2-Br-2-MeBu	$g(\eta)$, E_T^N	π^*, α	$g(\eta)$, E_T^N (monoalcohols) $g(\eta)$, E_T^N (dialcohols)
2-Cl-2-MeBu	E_T^N (dialcohols)	π^*, α (dialcohols)	$g(\eta)$, E_T^N (monoalcohols) $g(\eta)$, E_T^N (dialcohols)
3-Cl-3-MeBu	E_T^N (dialcohols)	π^*, α (dialcohols)	$g(\eta)$, E_T^N (monoalcohols) $g(\eta)$, E_T^N (dialcohols)
3-Cl-3-EtPe	E_T^N (dialcohols)	π^*, α(dialcohols)	$g(\eta)$, E_T^N (monoalcohols) $g(\eta)$, E_T^N (dialcohols)

Application of LSER confirmed the previous conclusions about the relevant mechanisms of interaction.

Finally, a statistical treatment of data was carried out in terms of the properties of the solvents and those of the solutes (dipole moment, μ_2, and molar volume, V_2), simultaneously ($N = 42$; $\sigma = 0.65$). Equation (7) represents the best dependence:

$$\begin{aligned}\Delta_s H^\infty = {} & -6.418 - 11.38\, f(\varepsilon) + 1.400\, E_T^N \\ & + 2.252 \times 10^{-3} \delta_H^{\,2} + 3.032 \times 10^{-2}\, V_2 \\ & + [23.71\, f(\varepsilon) - 12.24\, E_T^N + 0.9270 \\ & \times 10^{-3} \delta_H^{\,2}]\mu_2 \end{aligned} \tag{7}$$

RECENT DEVELOPMENTS

A recently published study involving log *k* values for the solvolysis of seven substrates in 18 solvents illustrates the progress of our research in this area.[12] The solvolytic reactions were always unimolecular alcoholysis of tertiary haloalkanes (from C_4 to C_7) in mono- and dialcohols. Correlation of rate constants was performed with the TAKA equation and also with a modified version of the GAS equation, Eqn. (8); in this new version, the $f(\varepsilon)$ term was eliminated, since for the whole set of studied alcohols there is a moderate collinearity between the variables $f(\varepsilon)$ and E_T^N, and a new term was introduced to account for the possibility of nucleophilicity assistance during heterolysis:

$$\log k = a_0 + a_1 g(\eta) + a_2 E_T^N + a_3 \beta + a_4 \delta_H^{\,2} \tag{8}$$

The results of the application of both equations show conclusively that the factors that dominate the activation process are the dipolarity/polarizability and the HBD acidity of the solvent. All these influences contribute to accelerate the solvolytic process. For the particular case of *t*-BuCl, the HBA basicity should also be considered, which means that nucleophilic assistance during the reaction path has a moderate contribution, as suggested by other authors.[7,29–31]

An interesting feature is concerned with the significance of the ‘hidden’ parameter, a_0. This statistical quantity should correspond to the value of the solvent-dependent property in the gas phase or in an inert solvent. For the three tertiary halobutanes (chloro-, bromo- and iodo-) the statistical a_0 values obtained by Eqn. (8) correspond well to the values reported by Macoll[32] and by Koppel and Palm[33] for reactions in the gas phase.

The same set of reactioning, systems (seven substrates and 17 solvents) was treated by the TFA methodology.[17,34,35] As far as we know, this was an innovative application in the context of solvolysis. Once the number of abstract factors had been decided, TFA was applied to identify the nature of each one. The possible real factors or targets achieved are in good agreement with the more relevant parameters obtained by LSER, which correspond to the dominant mechanisms of interaction dipolarity/polarizability and hydrogen-bond donor acidity of the solvent. Further, the TFA methodology allowed us to differentiate between the behaviour of mono- and dialcohols.

Table 1 shows the relevant descriptors of solvent obtained when GAS and TAKA linear solvation energy relationships are applied, and also TFA multivariate analysis.[36]

The results we have obtained during the last decade involving solute–solvent–solvent interactions using correlation analysis have made, a fruitful contribution to detailing the mechanism of Menschutkin reactions and, mainly, of haloalkane solvolysis. Although the TFA treatment has already been shown to be a highly useful tool for obtaining additional information concerning reaction processes in solution, an increase in the number of columns and rows of the starting matrix is needed in order to increase the statistical meaning of the results. In this respect, kinetic studies using heavily congested tertiary haloalkane substrates with amides and binary mixtures of alcohols as solvents are in progress.

Acknowledgements

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