Quantitative Formulation of Reactivity in Terms of Solvent and Substrate Properties. Solvolysis of *tert*-Butyl Halides in Hydroxylic Solvents

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Experimental rate constant values for the solvolysis of *tert*-butyl chloride in 12 alcohols at 25 °C are presented. These results, together with previous data, are well correlated through the linear solvation energy relationship $\log k = a_0 + a_1\, g(\eta) + a_2\, E_T^N + a_3\, C$ where $g(\eta)$ is a function of the refractive index, E_T^N is the normalized Dimroth and Reichardt parameter and C is the solvent cohesive energy density. The same is true for *tert*-butyl bromide and iodide.

A statistical treatment relating the experimental values of the solvolytic rate constants of the three halides in the same set of hydroxylic solvents (water, 8 monoalcohols and 10 dialcohols) to the properties of the solvents [$g(\eta)$, E_T^N and C] and of the substrate [molar volume (V) and dipole moment (μ)] simultaneously was performed.

The effect of solvent on the rates of chemical reactions has been studied for more than a century. Some attempts to express it quantitatively involve various solvent scales and multiparameter treatments. The same aspects are also of importance in the context of substrate effects. In addition, it is interesting to note that Koppel and Palm[1] proposed a correlation analysis of solvent effects by means of appropriate substituent constants and, as pointed out previously, modifications of substrate molecules by substituent changes may be considered equivalent, in thermodynamic terms, to solvent effects, the solvation being equivalent to loosely attached substituents.[2]

A general quantitative formulation of the reactivity problem should not avoid the simultaneous treatment of solvent and substrate effects. Although it is not known how the two effects are interrelated, some studies have been carried out concerning this matter.[3–5] A similar approach has been used by Koppel[6] employing two variables; the nature of one component of the binary solvent mixtures (the Taft induction constant of its radical) and its mole fraction in the mixtures. The system studied was 2-chloro-2-methylpropane (Bu^{t}Cl) in several alcohol–aprotic solvent media. A more ambitious formulation, proposed by Palm,[7] involved the simultaneous quantitative treatment of the effect of three variables (substituent, solvent and temperature) on the reactivity. Several treatments of solvent effects on the solvolytic reactions of *tert*-butyl halides have been previously attempted in terms of linear solvation energy relationships with excellent results.[1,8–10] Furthermore, we found that an approach relating the experimental values of the rate constants of the three halides, chloride, bromide and iodide, in the same set of solvents to the properties of the solvents and of the substrates, in order to arrive at one parametric description of the involved quantities, could help in the interpretation of chemical phenomena.

In this paper we wish to present a new collection of experimentally determined rate constants, k, for the solvolysis of Bu^{t}Cl in several mono- and di-alcohols, at 25 °C. Multiple correlation analysis of these results (together with previously obtained data) with solvent parameters confirm the available information about the dominant solute–solvent–solvent mechanistic interactions.[9,10] The rate constant values for the solvolytic reactions of Bu^{t}Cl, Bu^{t}Br and Bu^{t}I in the same set of solvents (water, 8 monoalcohols and 10 dialcohols) are submitted to a multiple regression statistical analysis based on that proposed by Glikberg and Marcus.[5] This enables us to obtain a common relationship to relate log k to selected properties of the solvents and of the substrates, simultaneously.

Experimental

The conductimetric technique, and the Kezdy–Swinbourne method of analysis of the conductance data, used to obtain the rate constants of the solvolytic reactions of Bu^{t}Cl in the various alcohols have been described previously.[10]

All the observed kinetics were first-order, with experimental errors of 1–2% in k, using no more than 75% of the increasing conductance values.

Results and Discussion

The observed mean rate constants for the solvolytic reactions of Bu^{t}Cl in two monoalcohols (butan-2-ol and pentan-1-ol) and ten dialcohols (ethane-1,2-diol, propane-1,2- and -1,3-diol, butane-1,2-, -1,3-, -1,4- and -2,3-diol, pentane-1,5-diol, diethylene glycol and triethylene glycol) are presented in Table 1. Also presented in Table 1 are the previously obtained rate constants for the solvolysis of the three *tert*-butyl halides in the same set of nineteen hydroxylic solvents.

Solvent Effects.—In order to account for the three types of dominant solute–solvent–solvent interactions (non-specific, specific and solvent–solvent interactions from the cavity effect),[11] and considering the available values of solvent polarity parameters, we tested the application of eqn. (1) to correlate the rate constants of Bu^{t}Cl solvolysis.

$$\log k = a_0 + a_1\, f(\varepsilon) + a_2\, g(\eta) + a_3\, E_T^N + a_4\, C \quad (1)$$

In eqn. (1), $f(\varepsilon)$ is the Kirkwood function of the relative permittivity, $(\varepsilon - 1)/(2\varepsilon + 1)$, $g(\eta)$ is a function of the refractive index, $(\eta^2 - 1)/(\eta^2 + 2)$, E_T^N is the normalized Dimroth and Reichardt parameter and C is the cohesive energy density. E_T^N is defined according to the following equation, $E_T^N = [E_T(\text{solvent}) - E_T(\text{TMS})]/[E_T(\text{water}) - E_T(\text{TMS})]$, using water and tetramethylsilane (TMS) as extreme reference solvents.[12,13] E_T^N has the advantage over the primitive $E_T(30)$ of being dimensionless. The cohesive energy density is a measure of the total molecular cohesion per unit volume given by $C = (\Delta_v H - RT)/V$, where $\Delta_v H$ is the enthalpy of vaporization

Table 1 Solvolysis rate constants of *tert*-butyl halides at 25 °C (k/s^{-1})

	$-\log k$					
Solvent	Bu^{t}Cl	Ref.	Bu^{t}Br	Ref.	Bu^{t}I	Ref.
Water	1.54	18	0.12	18	0.19	18
Methanol	6.06	19	4.46	19	3.91	10
Ethanol	7.07	20	5.36	21	4.65	10
Propan-1-ol	7.33	22	5.44	10	4.86	10
Propan-2-ol	7.80	23	5.67	10	5.05	10
Butan-1-ol	7.52	24	5.61	10	4.95	10
Butan-2-ol	8.10[a]		5.78	10	5.40	10
2-Methylpropan-1-ol	8.30	23	5.68	10	5.19	10
Pentan-1-ol	7.45[a]		5.64	10	5.29	10
Ethane-1,2-diol	4.61[a,b]		3.03	10	2.55	10
Propane-1,2-diol	5.51[a]		4.03	10	3.56	10
Propane-1,3-diol	5.29[a]		3.71	10	2.95	10
Butane-1,2-diol	6.14[a]		4.57	10	4.16	10
Butane-1,3-diol	6.05[a]		4.50	10	4.05	10
Butane-1,4-diol	5.99[a]		4.27	10	3.81	10
Butane-2,3-diol	6.21[a]		4.88	10	4.48	10
Pentane-1,5-diol	6.32[a]		4.68	10	4.19	10
Diethylene glycol	5.69[a]		3.84	10	3.16	10
Triethylene glycol	6.07[a]		4.14	10	3.30	10

[a] Results obtained in this work. [b] Rudakov in ref. 25 reported the value −4.60 which is in excellent agreement with our value.

Table 2 Selected properties of the solvents[a]

Solvent	ε	η	E_T^N	C/10^{3}MPa
Water	78.30	1.3330	1.000	2.307
Methanol	32.66	1.3284	0.762	0.887
Ethanol	24.55	1.3614	0.654	0.703
Propan-1-ol	20.45	1.3856	0.617	0.590[e]
Propan-2-ol	19.92	1.3772	0.546	0.552[e]
Butan-1-ol	17.51	1.3993	0.602	0.485
Butan-2-ol	16.56	1.3971	0.506	0.488[e]
2-Methylpropan-1-ol	17.93	1.3959	0.552	0.516[f]
Pentan-1-ol	13.9	1.4100	0.568	0.497[e]
Ethane-1,2-diol	37.7	1.4318	0.790	0.887
Propane-1,2-diol	28.59[b]	1.4324[c]	0.722	0.881[g]
Propane-1,3-diol	34.98[b]	1.4398[c]	0.747	0.847[h]
Butane-1,2-diol	22.35[b]	1.4378[c]	0.676	0.60[i]
Butane-1,3-diol	28.57[b]	1.4410[c]	0.682	0.562[e]
Butane-1,4-diol	30.86[b]	1.4460[c]	0.704	0.738[h]
Butane-2,3-diol	21.65[b]	1.4310[c]	0.651	0.602[h]
Pentane-1,5-diol	27.17[b]	1.4494[c]	0.654[d]	0.603[h]
Diethylene glycol	31.69	1.4475	0.713	0.615[e]
Triethylene glycol	23.69	1.4558	0.704	0.480[e]

[a] Values are from ref. 26 unless otherwise indicated. [b] Value from ref. 27. [c] Value from ref. 28. [d] Value from ref. 29. [e] Value from ref. 30. [f] Value from ref. 31. [g] Value from $\Delta_v H$, at 25 °C, in ref. 32. [h] Value from $\Delta_v H$, at temperatures far below the boiling point, in ref. 33. [i] Estimated value from the structural comparison between butane-1,3- and -1,4-diol and propane-1,2- and -1,3-diol.

of a solvent to gas of zero pressure and V is the molar volume of the solvent.[14]

The values of these solvent properties are listed in Table 2 and the results of the application of eqn. (1), using all possible combinations of the four solvent parameters, to the solvolysis of Bu^{t}Cl are given in Table 3. The decision about the best-fit equation was made by applying Ehrenson's criterion.[10,15] We reach the same conclusion as before, when Bu^{t}Br and Bu^{t}I solvolysis were under investigation, although in a somewhat different set of solvents. For that reason, the multiparameter approach was repeated for bromide and iodide using the values summarized in Table 1; however, no significant change was observed. The statistically preferred correlations for the three halides are given in eqn. (2)–(4).

$$\log k_{\mathrm{Bu^tCl}} = -17.881 + 18.143\,\mathrm{g}(\eta) + 8.7309\,E_T^N + 1.6681 \times 10^{-3}\,C \quad (2)$$

$$(N = 19;\ r = 0.992;\ \sigma = 0.204)$$

$$\log k_{\mathrm{Bu^tBr}} = -13.987 + 16.772\,\mathrm{g}(\eta) + 5.7570\,E_T^N + 1.9809 \times 10^{-3}\,C \quad (3)$$

$$(N = 19;\ r = 0.988;\ \sigma = 0.225)$$

$$\log k_{\mathrm{Bu^tI}} = -13.393 + 13.988\,\mathrm{g}(\eta) + 7.5177\,E_T^N + 1.1834 \times 10^{-3}\,C \quad (4)$$

$$(N = 19;\ r = 0.981;\ \sigma = 0.264)$$

From these results it is apparent that the polarizability of the solvent [g(η) term], the dipolarity and the HBD acidity of the solvent (E_T^N term) and the disruption of solvent molecules on account of the cavity effect (C term) constitute the fundamental influences on the total solvent effect on the rate constant values of *tert*-butyl halide solvolysis in hydroxylic media.

A meaningful regression analysis performed on the rate constants should give a_0 values [eqn. (1)] similar to those obtained in the gas phase and, in fact, the independent coefficients in eqns. (2)–(4) are quite reasonable when compared with the values reported by Macoll.[16]

Simultaneous Treatment of Solvent and Substrate Effects.—According to Palm,[7] if the reactivity can be formulated in terms of solvent and substrate effects, making use of one single constant scale for each variable factor, the relationship in eqn. (5) is obtained, where P_1 and P_2 are, respectively, the chosen

$$\log k = a_0 + a_1 P_1 + a_2 P_2 + a_{1,2} P_1 P_2 \quad (5)$$

solvent and substrate properties. The interdependence of these effects is formally reflected by the cross-term $a_{1,2} P_1 P_2$.

However, the application of this simple approach shows serious limitations since it has been demonstrated that for many reactions no relevant statistical meaning can be found when single empirical solvent parameters are used to describe the solvent effect. This feature is exemplified by the solvolytic reactions of *tert*-butyl halides[1,8–10] and, as expected, no

Table 3 Correlations of rates of Bu^{t}Cl solvolysis at 25 °C. $\log k = a_0 + a_1\,f(\varepsilon) + a_2\,g(\eta) + a_3\,E_T^N + a_4 \times 10^{-3}\,C$.

a_0	a_1	a_2	a_3	a_4	r^a	σ^b
−67.592	130.59	—	—	—	0.862	0.796
−4.9745	—	−5.2112	—	—	—^{c}	1.563
−15.356	—	—	13.441	—	0.973	0.362
−8.6268	—	—	—	3.2413	0.868	0.778
−66.928	130.37	−2.2581	—	—	0.862	0.819
−11.826	−8.5191	—	14.137	—	0.973	0.371
−43.074	75.370	—	—	1.9402	0.938	0.561
−17.214	—	6.8930	13.662	—	0.978	0.341
−17.333	—	32.749	—	4.0540	0.954	0.484
−14.679	—	—	11.926	0.47745	0.975	0.357
−10.348	−17.142	7.7708	15.091	—	0.979	0.342
−36.255	46.275	24.370	—	3.0473	0.973	0.382
−13.884	−1.9604	—	12.125	0.46504	0.975	0.369
−17.881	—	18.143	8.7309	1.6681	0.992	0.204
−15.608	−5.6457	18.229	9.2906	1.6380	0.993	0.210

[a] Simple or multiple linear correlation coefficient. [b] Standard deviation of the fit. [c] Cannot be calculated due to the close parallelism to the x axis of the estimated straight line.[34]

Table 4 Selected properties of the substrates

Substrate	V^a/cm^3 mol^{-1}	μ^b/D
Bu^{t}Cl	109.9	2.14
Bu^{t}Br	112.2	2.21
Bu^{t}I	119.1	2.20

[a] Values from ref. 28. [b] Values from ref. 35.

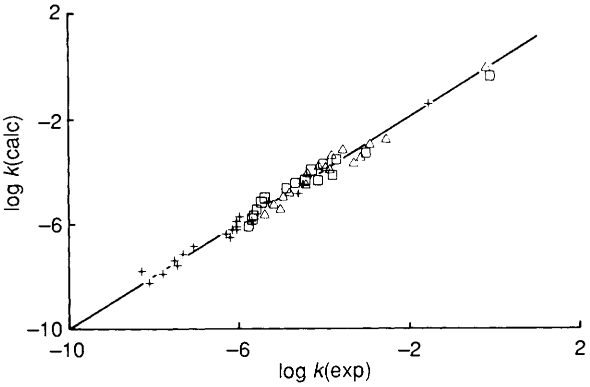

Fig. 1 Plot of log k calculated according to eqn. (7) against the experimental log k values for Bu^{t}Cl(+), Bu^{t}Br(□) and Bu^{t}I(△)

relevant correlation was found between log k (Table 1), E_T^N [the solvent property which gives the best uniparameter relationship (Table 3 of this paper and Table 4 of ref. 10)] and a property of the substrate chosen from a collection of data.

Although the general procedure proposed by Palm[1] does not impose any restrictions on the number of factors influencing each interaction type, when that number increases the formal interactions can no longer be identified with physical interaction models.

The dependence of the experimentally determined rate constants on the properties of the solvents and of the substrates simultaneously was then evaluated using a method based on the Glikberg and Marcus approach.[5]

First, the log k values were described in terms of the most statistically relevant solvent properties, P_i, [eqns. (2)–(4)].

$$\log k = a_0 + \sum_{i=1}^{n} a_i P_i \qquad (6)$$

Second, 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 interdependences. The selected substrate properties were the dipole moment, μ, and the molar volume, V (Table 4). Finally, a common model relating all solvents and substrates was obtained. The result of applying this procedure is given by an excellent correlation of log k values for the solvolytic reactions with the combined set of solvent and solute parameters according to eqn. (7).

$$\begin{aligned}\log k = {}& -102.37 - 38.460\,g(\eta) + 65.669\,E_T^N + \\ & 3.9877 \times 10^{-3}\,C + 39.962\,\mu + 48.211\,g(\eta)\,V - \\ & 26.706\,E_T^N\mu - 2.0924 \times 10^{-3}\,C\,V \qquad (7)\end{aligned}$$

$$(N = 57;\ \sigma = 0.237)$$

The fit achieved with this final equation is represented in Fig. 1, where the calculated log k values from eqn. (7) are plotted against the experimental values (Table 1). The continuous straight line corresponds to the perfect correlation.

Conclusions

The research field of chemometrics demands a great number of chemical data to provide maximum chemical information. In this paper 12 new rate constant values for the solvolysis of Bu^{t}Cl in alcohols, at 25 °C, are presented, which allow us to extend and confirm our knowledge of the reactions of *tert*-butyl halides. It is shown that there is a general relationship between k values for each *tert*-butyl halide, involving the refractive index, E_T^N and the cohesive energy density of the solvent. This leads us to conclude that solvent effects in hydroxylic media are dominated by the non-specific interaction due to the polarizability, the solvent HBD acidity and the work necessary to separate the solvent molecules sufficiently to create a cavity large enough to accommodate the solute molecule.

A common multiple regression equation for the solvolytic reactions with the combined set of three solvent parameters [g(η), E_T^N and C] and two solute parameters (μ and V) was found to be most adequate to describe the 57 rate constant values, no significant differences between experimental and calculated values being observed (Fig. 1). Moreover, the presence of all solvent and substrate parameters in eqn. (7) is warranted at a confidence level >99.99%, according to the criterion of Ehrenson.[15] Although eqn. (7) has been obtained through a statistical model and, consequently, its validity is founded only on statistical grounds, the results may be examined from a physico-chemical point of view.

Since each regression coefficient a_i in eqn. (6) describes the sensitivity of log k to a particular solvent parameter, we may expect that the selected substrate properties statistically related to that solvent parameter also show a relevant physico-chemical relationship. In this sense it is quite interesting to note that the coefficients of the dipolarity term depend on the polarity of the solute, represented by μ, and the polarizability and the cavity terms depend on the molar volume of the substrate V.

It is clear that the results from the approach presented above are in good agreement with the general mechanistic features previously revealed for the solvolytic reactions of *tert*-butyl halides in hydroxylic media, as far as the electrostatic and non-electrostatic or cavity contributions are concerned.[17]

We also conclude that it is possible to devise a general equation that can be used to reproduce and predict rate constants of those reactions from solvent and substrate properties.

Acknowledgements

This work was supported by the Instituto Nacional de Investigação Científica.

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Paper 0/05359G
Received 28*th November* 1990
Accepted 1*st February* 1991