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Solvation effects in the heterolyses of 3-X-3-methylpentanes (X = Cl, Br, I)[†]

Filomena Martins,[1]* Ruben Elvas Leitão[2] and Luís Moreira[1]

[1]Department of Chemistry and Biochemistry, Faculty of Sciences, University of Lisbon, CQB, Ed. C8, Campo Grande 1749-016 Lisbon, Portugal
[2]Department of Chemical Engineering, Engineering Institute (ISEL), Polytechnic Institute of Lisbon, CQB, R. Conselheiro Emídio Navarro, 1900 Lisbon, Portugal

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ABSTRACT: A comparative study of the heterolysis reactions of 3-X-3-methylpentanes (X = Cl, Br, I) in a set of protic and aprotic solvents was performed at 25.00 °C. Rate constant values were correlated with solvent descriptors using the TAKA multiparametric equation. Our results point towards a decrease in both hydrogen bond donor acidity (electrophilicity) and hydrogen bond acceptor basicity (nucleophilicity) contributions, and towards an increase in the dipolarity/polarizability term on going from the chloride substrate to iodide. These features suggest the formation of an increasingly early transition state, in contrast to the classical Hughes–Ingold rationale, but in agreement with the Hammond postulate. Furthermore, there seems to be no evidence for a shift in solvation from an electrophilic (or anionic) mode in the chloride substrate to a nucleophilic (or cationic) mode in the iodide, as claimed by some authors. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: reaction kinetics; 3-halo-3-methylpentane; solute–solvent interactions; linear solvation energy relationships

INTRODUCTION

The continuing interest in studies on the effect of solvent on reaction rates derives these days not so much from the possibility of making predictions of rate constants for other solvents but, in particular, from the need to reach a better understanding of the factors that influence these processes. Specifically, researchers are seeking a comprehensive perception of the nature of solute–solvent interactions at the molecular level.

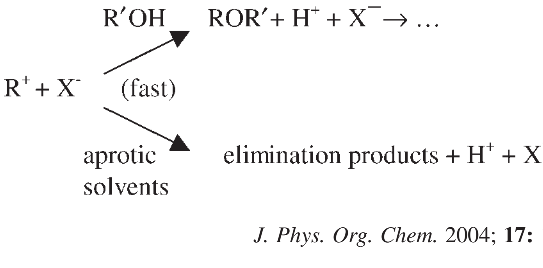
Solvolyses of *t*-butyl halides are amongst the reactions most used to probe solvent and solvation effects. Traditionally, medium effects on these reactions, rightly considered as keystones of physical organic chemistry,[1–3] have been interpreted by means of the Grunwald–Winstein relations,[4] specifically designed to address solvolyses in aqueous organic media.

In pure organic solvents, the most common approach to the study of the solvent influence on the reactions of *t*-butyl halides, and, in general, *t*-alkyl halides, has been through the application of multiple linear regression analysis (MLRA). The multiparametric equations devised correlate the logarithm of the rate constant, $\log k$, or the Gibbs energy of activation, $\Delta G^{\ddagger}$, with several microscopic and/or macroscopic solvent parameters.[5–11] The application of these equations allowed the identification of relevant interaction mechanisms for the set of substrates and solvents used in the analyses.[8,11] Some authors have, however, called attention to the need to use an adequate number of solvents in MLRA, both in number and/or diversity, in order to attain a higher statistical significance in the correlations and, more importantly, to provide a better insight into the importance of each solvent parameter or descriptor.[1,3,8]

Throughout this work we will be using the TAKA equation,[12] which offers a significant advantage over equations based on scales built upon reference substrates and solvents, since it does not imply any *a priori* hypothesis as regards solvent effects. Moreover, it is based on a sound physicochemical model, the cavity theory of solution.

Another point we would like to mention from the outset is that despite the fact that the mechanism of these heterolysis reactions is essentially S_N1 in hydroxylic solvents, while in aprotic solvents (in the absence of hydroxylic reagents) it is basically elimination ($E1$),

$$RX \rightarrow R^+ + X^- (\text{slow}) \qquad (1)$$



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*Correspondence to: F. Martins, 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

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in this paper our attention will be focussed solely on the rate-determining ionization, irrespective of the fate of ions, ion pairs or other species subsequently formed. Indeed, it is widely accepted[13–15] that reactions of tertiary alkyl halides in solution proceed through a common unimolecular ionization step (1), with the formation of a contact ion pair for both S_N1 and E1 processes.

Given the numerous questions still open to discussion regarding the reactivity of tertiary butyl halides, in particular, the issues of the importance of nucleophilic and electrophilic solvation, and the query about the ionic character of the transition states, it seemed of interest to reinvestigate these problems. We report in this paper a comparative study of the reactivity of similar, yet more crowded, substrates, 3-X-3-methylpentanes ($X = Cl$, Br, I), hereafter referred to as 3Cl, 3Br and 3I, in a balanced set of 22 solvents, both protic and aprotic. The choice of these systems is also aimed at an enlargement of the substrate and solvent matrix available within our chemical kinetics group, and further studies with both bromide and iodide substrates are in progress. We believe that the information gathered here will contribute to a better understanding of some of the aspects mentioned above.

RESULTS AND DISCUSSION

Reactions were performed at 25.00 °C, using conductance (G) as a kinetic probe. The experimental rate constants, k, are listed in Table 1.

The k values were derived using a new approach involving an EXCEL spreadsheet designed by us for this purpose. Using this application's 'solver' add-in to obtain a non-linear curve fitting for $G = f(t)$, the worksheet searches for the k value leading to the maximum correlation coefficient (r) between experimental and calculated data points. Conductance values are assumed to be linearly related to the concentration of acid ($[H^+]$) formed during the reaction and thus linearly related to the extent of reaction (ξ). In the cases where lack of linearity between G and $[H^+]$ was observed, calibration curves were obtained.

Table 1. $-\log k$ values and solvent descriptors for the reactions of 3-X-3-MePe ($X = Cl$, Br, I) in 22 solvents, at 25.00 °C

		Descriptors[a]				$-\log(k/s^{-1})$		
	Solvent	π^*	α	β	C[b]	3-Cl-3-MePe[a]	3-Br-3-MePe[h]	3-I-3-MePe[i]
Training set								
1	MeOH	0.60	1.09	0.73	0.858	5.34	3.67	3.12
2	EtOH	0.55	0.88	0.80	0.679	6.04	4.58	3.97
3	1-PrOH	0.53	0.79	0.85	0.597	6.39	4.87	4.31
4	1-BuOH	0.54	0.74	0.84	0.542	5.78	5.03	4.46
5	2-Me-1-PrOH	0.50	0.71	0.92	0.520	5.99	5.04	4.48
6	2-Me-1-BuOH	0.51	0.64	0.93	0.480	6.54[i]	5.17	4.63
7	DiEtglycol	0.92	0.72	0.67	0.838[c]	5.44	3.42	2.70
8	TriEtglycol	0.88	0.66	0.69	0.737[c]	5.52	3.61	2.89
9	$1,2\text{-}Pr(OH)_2$	0.76	0.83	0.78	0.840	5.31	3.49	3.11
10	$1,3\text{-}Pr(OH)_2$	0.84	0.80	0.77	0.970	4.83	3.01	2.57
11	$1,2\text{-}Bu(OH)_2$	0.71	0.80	0.71	0.739[c]	5.69	4.19	3.70
12	TFE	1.13[d]	1.51[e]	0.00[e]	0.573[c]	2.95[i]	1.70[i]	1.63
13	DMSO	1.00[f]	0.00[f]	0.88[g]	0.707	6.76[i]	3.90	2.11
14	DMF	0.88[f]	0.00[f]	0.69[f]	0.582	7.37[i]	4.89	3.03
15	Nitromethane	0.85[e]	0.22[e]	0.25[e]	0.663	7.27[i]	4.63[i]	2.95
16	Propylene carbonate	0.83[e]	0.00[e]	0.40[e]	0.737[c]	7.47[i]	4.75[i]	3.00
Test set								
17	2-PrOH	0.48	0.68	0.93	0.560	6.11	5.13	4.47
18	2-BuOH	0.54	0.54	0.91	0.511	5.52	5.16	4.68
19	$2,3\text{-}Bu(OH)_2$	0.75	0.68	0.88	0.621[c]	5.87	3.72	—
20	$1,4\text{-}Bu(OH)_2$	0.84[d]	0.63	0.68	0.833	5.42	3.71	3.06
21	$1,3\text{-}Bu(OH)_2$	0.75	0.76	0.74	0.725	5.60	3.66	—
22	$1,2\text{-}Et(OH)_2$	0.89	0.88	0.72	1.168	4.14	2.65	2.10

[a] Descriptors and k values for 3-Cl-3-MePe for solvents 1–11 and 17–22 are taken from Ref. 10.
[b] Ref. 16.
[c] Ref. 17.
[d] unpublished work by Abraham and Elvas-Leitão.
[e] Ref. 18.
[f] Ref. 8.
[g] Ref. 19.
[h] unpublished work by Martins, Elvas-Leitão, Moreira and Moita.
[i] This work.

The mathematical expressions in Eqn (3) were involved in the calculation of k.

$$[\mathrm{H}^+] \propto \xi = 1 - e^{-kt}$$

and

$$G = a_0 + b_0[\mathrm{H}^+] \quad \therefore \; G = a_0 + b_0(1 - e^{-kt}) \qquad (3)$$

Taking $Y = G$ and $X = (1 - e^{-kt})$, 'solver' can determine k by maximizing r. The (G, t) points chosen were in the range of 20–90% in ξ and all r values obtained were better than 0.999 90.

The use of this method offers clear advantages over traditional time-lag methods such as the Guggenheim and the Kezdy–Swinbourne methods,[20] given its greater sensitivity to the influence of subsequent reactions and because it does not require an equally spaced data collection.

Once the set of k values was obtained, the TAKA equation [Eqn (4)][12]

$$\log k = a_0 + a_1\pi^* + a_2\alpha + a_3\beta + a_4C \qquad (4)$$

was used to quantify the dominant solute–solvent interactions affecting the reactivity of the three substrates. According to this equation, solvents are characterized by: their dipolarity/polarizability (π^*), taken as a measure of non-specific solvent–solute interactions related to the capacity of the solvent to generate a spread of charges in the cybotactic region of the substrate; their hydrogen bond donor (HBD) acidity (α) and hydrogen bond acceptor (HBA) basicity (β) abilities, regarded as measures of specific solvent–solute 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 and/or with a solvent reorganization/electrostrictive effect. The a_i coefficients are the complementary solute-dependent coefficients of the solvent parameters.

Table 2. Determination matrix (r^2) for the training set descriptors

	π^*	α	β	C
π^*	1.00	0.02	0.43	0.09
α		1.00	0.02	0.01
β		—	1.00	0.00
C		—	—	1.00

In order to guarantee that the application of Eqn (4) as a quantitative structure–reactivity relationship is reliable and to some extent predictive, one has to assure that the results from its application are statistically significant and robust (internal validation), and valid for an independent data set (external validation). In fact, no quantitative structure–property relationship should be used for interpretation and/or prediction purposes unless it is correctly validated first.[21] Otherwise, we may end up with a meaningless correlation and therefore a misunderstanding as to the origin of the observed response. External validation was thus performed through the introduction of a test set of solvents. Although, ideally, the dimensions of the training and test sets should be similar, given the number of solvents analysed, it seemed reasonable to choose a training set of 16 solvents and a test set of 6 solvents. Orthogonality among descriptors was also checked and, as can be seen from Table 2, there is almost no correlation among pairs of descriptors.

The effect of each descriptor was analysed in all cases using a stepwise procedure. The selection/elimination of variables and the choice of the best equations were performed according to a significance level (SL) for each regression coefficient better than 95%, also taking into consideration the standard deviation of the fit, σ_{fit}, the multiple linear correlation coefficient, R, and the F statistics. The statistically significant results are summarized in Table 3.

From Table 3 and Fig. 1 we can see that very good linear correlations are obtained from the plot of calculated vs experimental values for all three sets of results. The occurrence of two outliers in the chloride test set and

Table 3. Rate constant correlations ($\log k$) for the reactions under study

Substrate	$a_0 \pm \sigma(a_0)$ (% SL)[e]	$a_1 \pm \sigma\,(a_1)$ (% SL)	$a_2 \pm \sigma\,(a_2)$ (% SL)	$a_3 \pm \sigma\,(a_3)$ (% SL)	$a_4 \pm \sigma\,(a_4)$ (% SL)	σ_{fit}[a]	N[b]	R[c]	F[d]
3-Cl-3-MePe	−10.55 ± 0.57 (>99.99)	3.06 ± 0.44 (>99.99)	2.68 ± 0.16 (>99.99)	0.86 ± 0.34 (97.40)	—	0.242	16	0.981	102.92
3-Br-3-MePe	−9.25 ± 0.34 (>99.99)	3.85 ± 0.30 (>99.99)	1.52 ± 0.10 (>99.99)	0.38 ± 0.21 (89.82)	1.42 ± 0.30 (99.98)	0.145	16	0.991	154.88
3-I-3-MePe	−7.18 ± 0.23 (>99.99)	4.30 ± 0.23 (>99.99)	— —	— —	0.87 ± 0.34 (97.45)	0.158	15	0.987	229.29

[a] Standard deviation of the fit.
[b] Number of points.
[c] Multiple linear correlation coefficient.
[d] Fischer statistics value.
[e] Significance level.

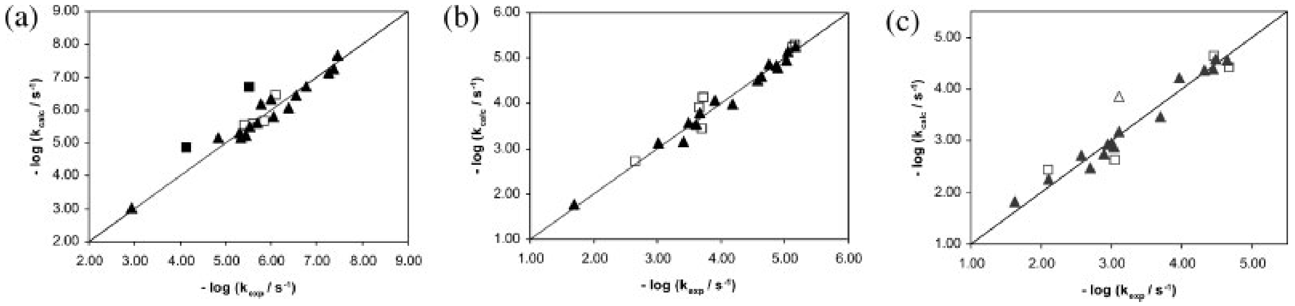

Figure 1. Calculated vs experimental $-\log k$ values for (a) 3-Cl-3-MePe, (b) 3-Br-3-MePe and (c) 3-I-3-MePe: ▲, training set; □, test set; ■, test set outlier; △, training set outlier

one outlier in the iodide training set is noticed. These will be investigated further in order to eliminate the possibility of having used either k values obtained for different solvent batches (literature reported values for 3Cl are taken from different sources) or, possibly, an incomplete description of the interaction mechanisms involved.

The quality of the statistical parameters from internal validation, and the success of the external validation substantiate a physicochemical discussion of the results in terms of the factors that influence the reactivity of these substrates.

From the analysis of Table 3 and Fig. 2, the first noteworthy result is the linear variation of all the a_i coefficients (scaled), other than C, (Fig. 2) with a property of the substrate, which accounts for its size and nature, in this case, the molar volume. We added the average (absolute) value of the a_0 coefficients ($\log k_0$) to each individual a_0 value so that this coefficient could fit on the same scale as all the other a_i coefficients. The coefficients of the non-significant parameters in the correlations shown in Table 3 were taken as zero in Fig. 1. Once we have a larger number of substrates in a convenient set of solvents, this relationship can be further examined by studying, simultaneously, the effect of solvent and substrate, as done by Gonçalves *et al.* for the reactions of *t*-BuX,[11,22] in order to identify the most relevant substrate properties and any significant interdependences.

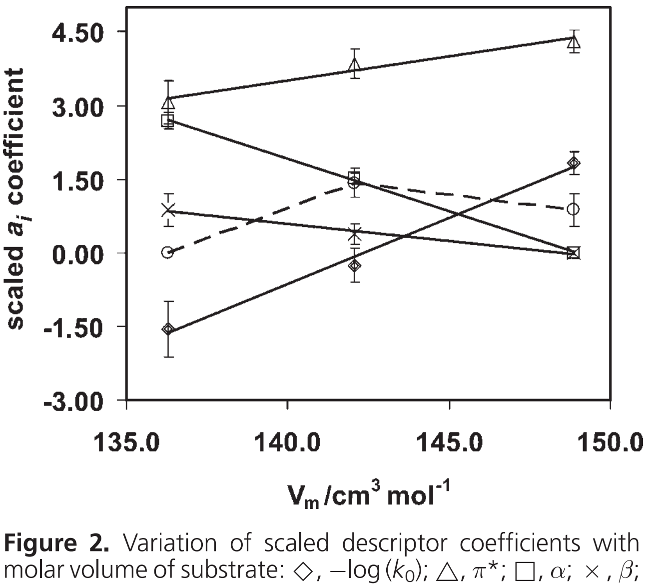

Figure 2. Variation of scaled descriptor coefficients with molar volume of substrate: ◇, $-\log(k_0)$; △, π^*; □, α; ×, β; ○, C

The C coefficient behaves differently from the other coefficients, not being significant for the chloride substrate and approximately constant, within statistical uncertainty, for 3Br and 3I. For a term depending purely on cavity volume, we would expect the same order as that of anion size, i.e. $\mathrm{Cl}^- < \mathrm{Br}^- < \mathrm{I}^-$, which is not the case, nor can the observed variation be rationalized in terms of a solvent reorganization/electrostrictive effect. Thus, we can only say that the intrinsic volume for the ground state and the transition state will be rather close for both 3Br and 3I.

When considering both the α and β coefficients, measures of solvent electrophilicity and nucleophilicity, respectively, we observe a clear decrease from 3Cl to 3I, these coefficients not being statistically relevant for the latter substrate. The total absence of an electrophilic solvation of the leaving group anion in the transition state of 3I is surprising *vis-à-vis* the results of Abraham *et al.*[1,8] for *t*-butyl halides in a set of 21 hydroxylic and aprotic solvents and Gonçalves *et al.*[10,11] for *t*-butyl halides in a set of 18 hydroxylic solvents. Both of these groups observed a systematic decrease (not a fading out) in the α coefficient on going from *t*-butyl chloride (1Cl) to *t*-butyl iodide (1I), which is consistent with the variation in the basicity of the halogen moieties of the activated complex in the same direction. We believe the trend now revealed (i.e. the disappearance of the α coefficient for 3I) may be due mainly to an increase in the alkyl chain. Bentley *et al.* also studied the variation of electrophilicity with the alkyl chain.[23] They concluded, on the basis of the small differences on the I/Br and Br/Cl rate ratios for the solvolyses of *t*-butyl halides and 1-adamantyl substrates in 80% aqueous ethanol, 97% aqueous TFE and 97% aqueous HFIP, that there was no significant sensitivity of α to the alkyl group. Abraham *et al.*[7] obtained the opposite result in a study involving the same substrates in methanol, ethanol, TFE and HFIP. In the context of our work, we need further studies with iodide substrates, in equivalent training sets of solvents, to confirm the observed tendency.

As regards the β coefficient, our results show that we cannot overlook the contribution of the nucleophilicity term for 3Cl, which is small but statistically significant. Our findings are consistent with the inferences of several authors[1,24–27] concerning the role of nucleophilic solvation at both the α-carbon and the β-hydrogen in the heterolysis of *t*-butyl chloride. The steric shielding increases significantly on going from Cl to I. This may reduce the importance of the hydrogen bonding interactions at the transition state between the C—H bonds of the incipient carbocation and the solvent, and thus may account for the observed fall in the β contribution. The possibility of this type of nucleophilic solvation, C—H$\cdots$O—RH, has already been pointed out by Jorgensen *et al.*[28] In fact, although in Table 3 the significance level of the regression β coefficient is less than the chosen 95% value, it is nevertheless sufficiently high and, together with the linear trend shown in Fig. 2, favours the non-exclusion of this descriptor for substrate 3Br. The controversy of the importance (and meaning) of nucleophilic solvation is, however, far from being entirely resolved. Richard *et al.*[29] suggested that one should make a distinction between nucleophilic solvent participation (NSP) taken as 'a stabilization of the transition state for concerted solvolysis by formation of a partial covalent bond to the solvent nucleophile' (i.e. without carbocation intermediate) and nucleophilic solvation (NS), regarded as 'a stabilization of the transition state for stepwise solvolysis through carbocation or ion pair intermediates by charge-dipole interactions with nucleophilic solvents'. Authors such as Fárcaşiu *et al.*[30] and, more recently, Gajewski[3] have questioned the existence of any nucleophilic solvent participation in the transition state of *t*-alkyl chloride solvolysis. This is therefore a field of continuing research.

Accepting the parallelism established by Swain *et al.*[31] between specific solvent properties such as anionic solvation and electrophilicity, on the one hand, and cationic solvation and nucleophilicity, on the other hand, our results do not seem to indicate the existence of a shift in solvation from an anionic to a cationic assisted mode on going from 3Cl to 3I, as one would expect from the work of Mitsuhashi *et al.* on solvent effects on heterolysis reactions.[32,33] These authors have derived scales for cation, $\chi+$, and anion, $\chi-$, solvation from kinetic data, based on two reference reactions in five solvents, three used to set up the cation solvation scale (DMSO, DMF and acetone), and the other two to set up the anion solvation scale (methanol and ethanol). When we correlate $\chi+$ and $\chi-$ with the TAKA parameters for the five solvents used by Mitsuhashi, we find that while $\chi-$ shows a good correlation with α ($R = 0.99$), $\chi+$ is very well correlated not with one but with two parameters, π^* and C ($R = 0.9999$). We therefore suggest that $\chi+$ values are a blend of C and π^* and not a measure of β, as inferred from Swain's parallelism cited above. Hence our results point not towards a shift from mainly anionic solvation in 3Cl to mainly cationic solvation in 3I but, instead, towards a shift from mostly electrophilic and nucleophilic solvation, by specific interactions, in 3Cl, to a non-specific interaction, largely measured by π^*, in 3I.

Another interesting feature is the increase of the weight of the π^* coefficient on going from 3Cl to 3I (Table 3 and Fig. 2), which was already anticipated by Abraham *et al.* for the *t*-BuX series.[1] This trend is accompanied by a fall in both electrophilic and nucleophilic contributions, as already mentioned. To account for these two, seemingly contradictory, tendencies, we suggest the involvement of an increasingly early transition state, and thus less ionic character development on going from the chloride to the iodide substrate. These findings do not agree with the Hughes–Ingold transition state solvation stabilization rationale but are in line with the Hammond postulate.[15]

Some theoretical investigations performed a few years ago by Hynes *et al.* on the S_N1 ionizations of *t*-alkyl halides in several solvents pointed towards the same apparent ambiguity.[15,34] These authors claimed that, for these reactions, a more polar solvent decreased not only the activation energy, in terms of $\Delta G^\ddagger$, but it also induced a lesser charge development and thus an earlier formation of the activated complex.

The above discussion points out some of the continuing challenges in the study of solvent effects and we believe that our findings constitute an additional contribution to a better understanding of the solute–solvent interactions involved in the reactions of *t*-alkyl halides. Further studies, involving a more complete set of solvents in both the training and test sets, and more congested bromide and iodide substrates are in progress.

EXPERIMENTAL

The substrates were synthesized and purified by column chromatography (Silica gel 60). Their purity was assessed by NMR (^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$). The substrate concentration for kinetic experiments was 0.01 mol dm^{-3}. Solvents were obtained commercially from Merck, BDH and Aldrich (98%+ purity) and their water content was always less than 0.2%. Kinetic measurements were made using an automated conductance bridge. Temperature control was better than ± 0.01 °C. Reactions were followed to 90% of the apparent plateau. Mean k values from substrates 3Br and 3I result from at least 6 different runs and show a standard deviation better than 3%. For 3Cl a smaller number of runs were used given the slowness of the processes.

Acknowledgements

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