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Correlation of the Rates of Solvolysis of 2-Phenyl-2-ketoethyl Bromide and Tosylate

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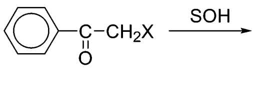

X = Br: $\log(k/k_0) = 1.15N_T + 0.46Y_{Br} + 0.08$
X = OTs: $\log(k/k_0) = 1.03N_T + 0.56Y_{OTs} - 0.04$

k_{OTs}/k_{Br}: 0.8-3.6

The extended Grunwald−Winstein equation has been applied to the specific rates of solvolysis of 2-phenyl-2-ketoethyl bromide and tosylate and the correlation parameters are consistent with an S_N2 mechanism over the full range of solvents. The k_{OTs}/k_{Br} ratios are close to unity, consistent with this assignment. Comparisons with the specific rates of solvolysis of 2-phenylethyl bromide and methyl tosylate show only a modest influence upon introduction of the carbonyl group.

The mechanism of nucleophilic substitution at a site with a carbonyl group directly attached has long been of interest. Almost a century ago, it was shown that reactions, much later designated as S_N2, can have an enhanced rate in the presence of the substituent.[1,2] Later, it was shown that this was not a general phenomenon and weak nucleophiles do not have their rates of attack significantly enhanced.[3,4] This represents an apparent breakdown of the reactivity−selectivity principle.[5] A molecular-orbital analysis[6] has shown that the increases in *both* selectivity and reactivity result from a stabilizing frontier orbital interaction between the carbonyl π system and a high-energy π-type three-center orbital situated along the reaction coordinate axis.

The long-held belief that the adjacent carbonyl group would severely hinder S_N1 (plus E1) reaction because of a positive dipole adjacent to the developing carbocation has been shown to be only partially correct and silver-ion assisted[7] or solvolytic[8−10] generation of tertiary carbocations with a directly attached carbonyl group is possible. It has been suggested[8−10] that the incipient cation at the transition state is stabilized by a conjugative interaction involving movement of the carbonyl π electrons, with the positive charge developing partially on the oxygen. Takeuchi[11] has confirmed that this can indeed occur but, in the absence of special effects blocking the rearside of the carbon atom undergoing attack, nucleophilic solvent participation was observed even for the solvolyses of a quite crowded tertiary structure. Evidence came largely from a dichotomy of solvolytic behavior, with the rearside-blocked 1,1,3,3-tetramethyl-2-oxobutyl methanesulfonate showing[8] a good correlation with the simple Grunwald−Winstein equation[12] (eq 1, without the lN term) and the structurally similar, but ring-closed, 1,3,3-trimethyl-2-oxycyclopentyl methanesulfonate requiring[11] correlation using the extended (two-term) Grunwald−Winstein equation[13−15] (eq 1). In eq 1, k and k_0 represent the specific rates of solvolysis of a substrate RX in a given solvent and in the standard solvent (80% ethanol), respectively; l is the sensitivity of the solvolysis to changes in the solvent nucleophilicity (N_T);[15] m is the sensitivity of the solvolysis to changes in solvent ionizing power (Y_X, for a leaving group X);[16] and c is a constant (residual) term.

$$\log(k/k_0)_{RX} = lN_T + mY_X + c \qquad (1)$$

In the present paper, we apply the extended Grunwald−Winstein equation to the solvolyses of 2-phenyl-2-ketoethyl (phenacyl) bromide (**1**) and *p*-toluenesulfonate (tosylate; **2**). For comparison purposes, a study is also made in a few of the solvents of the solvolyses of 2-phenylethyl bromide. The use of both the bromide and the tosylate allows a consideration of tosylate/bromide

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TABLE 1. Specific Rates of Solvolysis (k) of α-Bromoacetophenone (1) and 2-Phenyl-2-ketoethyl Tosylate (2) at 62.5 °C, Together with k_{OTs}/k_{Br} Ratios and N_T, Y_{Br}, and Y_{OTs} Values for the Solvents

	10^6k,[b] s^{-1}					
solvent[a]	**1** (k_{Br})	**2** (k_{OTs})	k_{OTs}/k_{Br}[c]	N_T[d]	Y_{Br}[e]	Y_{OTs}[e]
100% EtOH	1.15 ± 0.11	2.82 ± 0.15	2.45	0.37	−2.4	−1.75
95% EtOH	2.62[f]			–[g]	–[g]	–[g]
80% EtOH	4.12 ± 0.09[h]	11.9 ± 0.2	2.89	0.00	0.00	0.00
60% EtOH	7.84 ± 0.17	16.2 ± 1.0	2.07	−0.39	1.26	0.92
50% EtOH	10.0[f]			−0.58	1.88	1.29
40% EtOH	13.7 ± 0.7	22.9 ± 1.2	1.67	−0.74	2.62	1.97
100% MeOH	2.80 ± 0.17	5.12 ± 0.15	1.83	0.17	−1.12	−0.92
90% MeOH		10.2 ± 0.1		−0.01	−0.14	−0.05
80% MeOH	6.27 ± 0.25	14.3 ± 0.4	2.28	−0.06	0.70	0.47
60% MeOH	11.4 ± 0.7	23.0 ± 0.5	2.02	−0.54	2.04	1.52
40% MeOH	16.8 ± 0.8			−0.87	3.14	2.43
80% acetone	2.03 ± 0.07	1.61 ± 0.6	0.79	−0.37	−0.7	−0.94
60% acetone	5.65 ± 0.28	5.32 ± 0.17	0.94	−0.52	1.03	0.66
80% TFE	0.257 ± 0.012	0.599 ± 0.022	2.33	−2.19	2.67	1.94
60% TFE	1.03 ± 0.08	2.12 ± 0.17	2.07	−1.85	2.91	2.07
80T-20E		0.420 ± 0.029		−1.76	1.62	0.98
60T-40E	0.380 ± 0.014	1.38 ± 0.07	3.63	−0.94	0.31	0.21
90% HFIP		0.038 ± 0.004		−3.84	3.82	2.90
70% HFIP	0.317 ± 0.009	0.508 ± 0.031	1.60	−2.94	–[g]	2.40

[a] On a volume−volume basis at 25.0 °C, except for TFE−H_2O and HFIP−H_2O (on a weight−weight basis). [b] With associated standard deviation. [c] Ratio of specific rates of solvolysis of **2** and **1** ($k_{(2)}/k_{(1)}$). [d] From ref 15. [e] From ref 16. [f] By interpolation within data of ref 4. [g] Not available. [h] Interpolation within data of ref 4 gives a value of 5.43; in the correlation a mean value of 4.78 is used.

TABLE 2. Specific Rates of Solvolysis of 2-Phenylethyl Bromide (3)[a] and a Comparison with Values for the Solvolyses of 2-Phenyl-2-ketoethyl Bromide (1)

solvent	10^7k,[b] s^{-1}	$k_{(1)}/k_{(3)}$
80% EtOH[c]	5.88 ± 0.22	7.0
80% MeOH[c]	8.05 ± 0.37	7.8
60% acetone[c]	5.00 ± 0.23	11.3
60% TFE[d]	4.09 ± 0.14	3.6
70% HFIP[d]	2.86 ± 0.24	1.1

[a] At 62.5 °C. [b] With associated standard deviation. [c] On a volume−volume basis at 25.0 °C. [d] On a weight−weight basis.

rate ratios (k_{OTs}/k_{Br}), a useful probe of the S_N1-S_N2 spectrum.[17]

The specific rates of solvolysis of 2-phenyl-2-ketoethyl bromide (phenacyl bromide; α-bromoacetophenone) and of 2-phenyl-2-ketoethyl tosylate were determined at 62.5 °C in ethanol and methanol and in binary mixtures of water with ethanol, methanol, acetone, 2,2,2-trifluoroethanol (TFE), and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). Determinations were also made in TFE−ethanol mixtures.

The specific rates are reported in Table 1, together with two values for **1** estimated from data in ref 4. Also presented are the k_{OTs}/k_{Br} ratios and the appropriate values for N_T,[15] Y_{Br},[16] and Y_{OTs}.[16] Specific rates of solvolysis of 2-phenylethyl bromide (**3**) and the ratio of the specific rates of solvolysis of α-bromoacetophenone (**1**) relative to those of **3** are presented in Table 2.

Tertiary substrates with a carbonyl group directly adjacent to the site of attack and which have an appreciable steric hindrance to attack from the rear have been observed to solvolyze by an ionization lacking any appreciable nucleophilic assistance.[8,11] However, for molecules where the steric hindrance was reduced, substantial nucleophilic assistance from the solvent has been observed.[11] Ionization has not been observed for secondary substrates of this type, and a substantial dependence on solvent nucleophilicity, increase in rate on adding the conjugate base to the solvent, and inversion of configuration have all suggested an S_N2 mechanism.[8] Pasto[4] studied the solvolyses of **1** in five solvents and, for two of the solvents, the influence of ring substitution was studied. No rearranged products were observed. He concluded that the solvolyses proceed “via a highly nucleophilic displacement of halide by the solvent molecules”.

Accordingly, one would anticipate an S_N2 solvolysis for the primary substrates (**1** and **2**) of this study. The study of the effect of varying the solvent upon the specific rates (Table 1) is analyzed for each of the substrates in terms of eq 1. For **1** (14 solvents), the derived values are 1.15 ± 0.08 for l, 0.46 ± 0.04 for m, and 0.08 ± 0.05 for c; the multiple correlation coefficient (R) is 0.974 and the F-test value is 102 (see Figure 1). For **2** (16 solvents), the values are 1.03 ± 0.04 for l, 0.56 ± 0.04 for m, and −0.04 ± 0.12 for c; the R value is 0.990 and the F-test value is 315 (see Figure 2).

In a simple Grunwald−Winstein treatment (eq 1 without the lN_T term) of the data in aqueous ethanol, Pasto[4] obtained an m value of 0.20 ± 0.01 in correlation against the original Y scale[16] (based on solvolyses of *tert*-butyl chloride). An identical slope is obtained if Y_{Br} values are substituted. For 100−50% ethanol, there is good correlation between N_T and Y_{Br} values, with a slope of −0.22 (correlation coefficient of −0.983). Therefore, the observed m_{expt} value of 0.20 can be estimated from the two-term l and m values as $m - 0.22l$, leading to a value of 0.21, essentially identical with the observed value. In general, the m value observed in aqueous ethanol from correlation against only solvent ionizing power can be related in this way to the l and m values of the two-term (eq 1) treatment, with low values being favored by a high sensitivity to changes in solvent nucleophilicity (l value).

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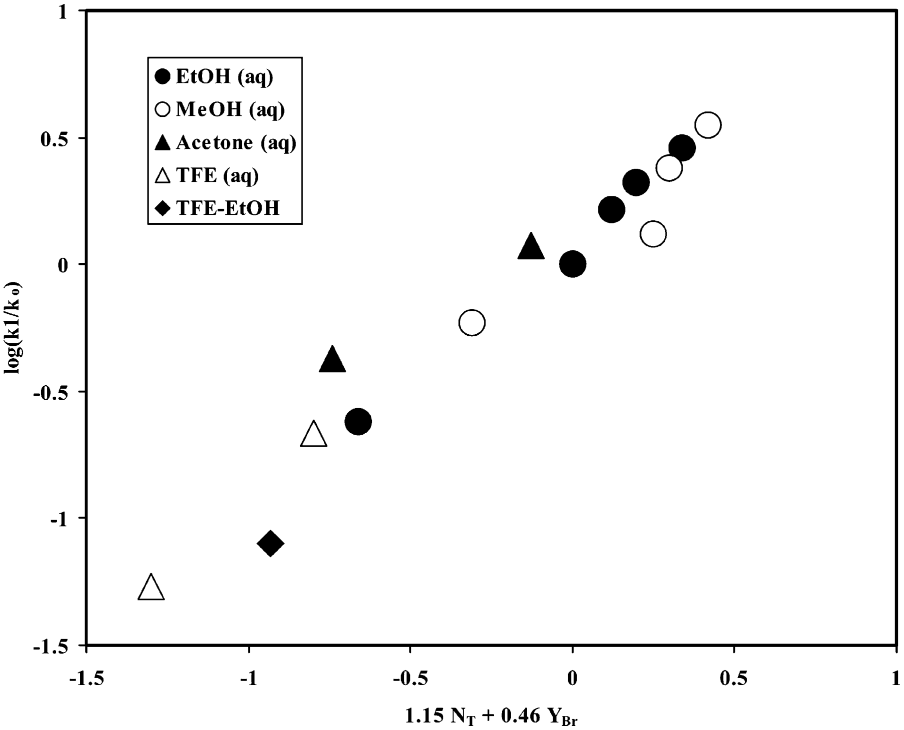

FIGURE 1. Plot of log(k/k_0) for solvolyses of 2-phenyl-2-ketoethyl bromide against $1.15N_T + 0.46Y_{Br}$.

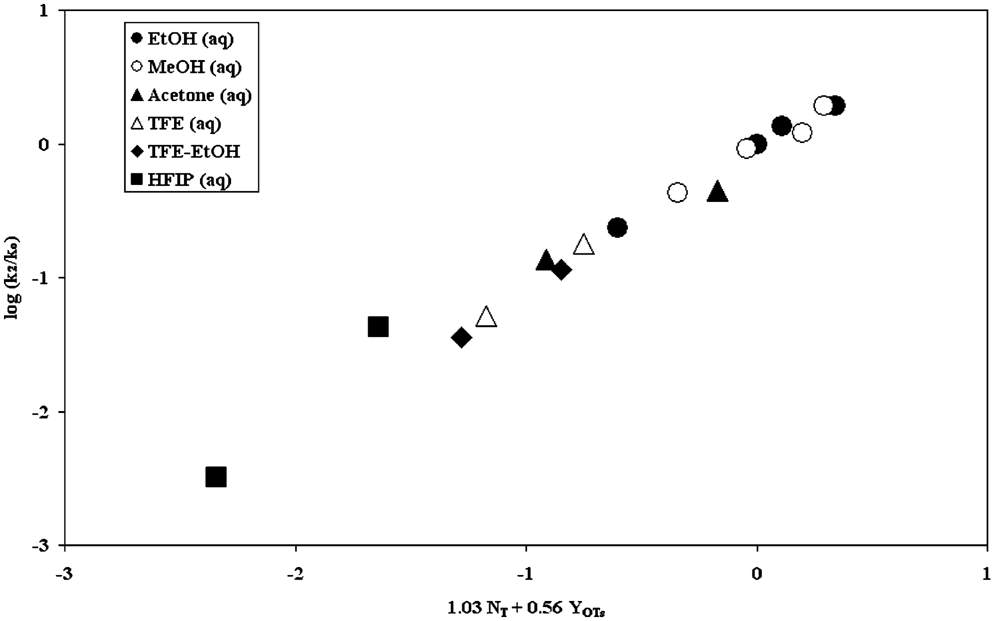

FIGURE 2. Plot of log(k/k_0) for solvolyses of 2-phenyl-2-ketoethyl tosylate against $1.03N_T + 0.56Y_{OTs}$.

For solvolyses in 80% ethanol, Pasto[4] observed a Hammett ρ value of +0.35, indicative of a small amount of negative charge developing at the reaction center in the transition state.

For solvolyses of methyl tosylate, the original standard for the development of an extensive scale of N values (N_{OTs}),[14] the values obtained on application of N_T and Y_{OTs} values within eq 1 are (at 50.0 °C) 0.96 ± 0.04 for l and 0.53 ± 0.04 for m,[18] essentially identical with the values obtained in this study for the solvolyses of **1** and **2**, and consistent with a conventional S_N2 mechanism for all three solvolyses. As regards comparisons of specific rates, to take two solvent compositions as examples, in 80% ethanol, methyl tosylate solvolysis[14] has a value of 2.22×10^{-5} s^{-1} at 50 °C and **2** a lower value of 1.19×10^{-5} s^{-1} at 62.5 °C. Corresponding values in 80% TFE−20% ethanol are 8.3×10^{-7} s^{-1} and 4.2×10^{-7} s^{-1}. The solvolyses of **2** are only about half as fast, even at a temperature that is 12.5 °C higher. From specific rates reported for ethanolysis of methyl tosylate at several

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temperatures,[19] we can calculate a value of 2.28×10^{-5} s^{-1} at 62.5 °C, a value 8.1 times higher than that for the ethanolyses of **2** at this temperature. Accordingly, we can conclude that, as regards solvolysis, the introduction of a benzoyl group into methyl tosylate actually *reduces* the rate of reaction, by a little less than 1 order of magnitude.

The study of both the tosylate and bromide derivatives provides a route to mechanistic deductions in terms of the k_{OTs}/k_{Br} rate ratios.[17] The values obtained for the ratio are reported in Table 1. The variation is over a rather narrow range from 0.8 in 80% acetone to 2.9 in 80% ethanol. Values not far removed from unity are considered to be consistent with an S_N2 mechanism, with considerably higher values being observed for substitutions proceeding by the S_N1 mechanism. For example, methyl and ethyl derivatives undergoing ethanolysis at 50 °C show values for the ratio of 16 and 15, respectively, and values below unity can be observed for reactions with powerful nucleophiles, such as with chloride in acetone, or *p*-methylthiophenoxide in ethanol.[17c] It was proposed[17a] that the ratio reflects the amount of charge carried on the leaving group, which can be dispersed effectively for a tosylate leaving group, and as such it reflects the degree of tightness at the transition state. Applying this argument, the lower value for the ratio obtained for ethanolysis of **1** and **2** relative to methyl or ethyl derivatives suggests that the introduction of the benzoyl substituent leads to a tighter transition state.

A comparison of the l and m values (eq 1) for the solvolyses of **1** and **2** shows that **1** has a slightly higher l value and slightly lower m value. This would be consistent with a slightly tighter transition state for **1**.

A study has also been made in five selected solvents of the solvolyses of 2-phenylethyl bromide (**3**) at 62.5 °C. The specific rates are reported in Table 2, together with values for the $k_{(1)}/k_{(3)}$ rate ratio. The differences in specific rate are modest, with slightly higher values for the solvolysis of **1**; values for the ratio vary from 1.1 in 70% HFIP to 11.3 in 60% acetone. The lower value for the ratio in solvents of low nucleophilicity can be rationalized in terms of the rather high sensitivity of the specific rates of solvolysis of **1** to changes in solvent nucleophilicity (l value of 1.15).

In conclusion, it can be seen that, with a primary substrate, the introduction of a carbonyl group adjacent to the site of attack has only a modest effect on the specific rate of solvolysis. Whether the effects are considered to be accelerative or decelerative depends on the standard solvolysis system chosen. If we consider introduction of the benzoyl group into methyl tosylate, then the specific rates are modestly reduced. If we consider the replacement of the 2-position methylene group by a carbonyl group in the solvolyses of 2-phenylethyl bromide (**3**), then the specific rates are modestly increased. The l and m parameters obtained from the extended Grunwald−Winstein treatment of the specific rates of solvolysis of either **1** or **2** are very similar to those previously obtained for methyl tosylate. The Hoffmann k_{OTs}/k_{Br} ratio values are close to unity. All of the evidence obtained here, together with the small positive Hammett ρ value and lack of rearrangement observed by Pasto, is consistent with an S_N2 mechanism for the solvolyses over the full range of solvents and substituents studied.

Experimental Section

The 2-phenyl-2-ketoethyl bromide (**1**, 98%) and 2-phenyl-2-ketoethyl *p*-toluenesulfonate (**2**, 98%) were used as received. All runs were performed with 5×10^{-3} M substrate in sealed tubes at 62.5 °C, usually with 5-mL portions, but with 2-mL portions for runs in HFIP−H_2O mixtures.

For runs in the absence of water, loss of the produced acid by reaction with the solvent was prevented by the addition to the solvolysis of 5.5×10^{-3} M 2,6-dimethylpyridine (lutidine).[20] The determinations of the specific rates of solvolysis were as described previously.[21] All runs were performed, at least, in duplicate. The multiple regression analyses were carried out with the ABSTAT statistical package (Anderson-Bell, Arvada, Colorado).

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