

Figure 13. New synthesis of bulnesol found by the program.

program allows the simple addition of tests during the retrosynthesis and the immediate perception of their effects. This interactive procedure avoids time consuming shuttles: quite the retrosynthesis, enter in the input reaction module, come back to the retrosynthesis.

In order to visualize the retrosynthesis tree and/or select a new target among the precursors, the tree option is available. Figure 11 shows the screen when this option is activated. Precursors are stored on the internal drive of the Macintosh. The size of this file is 200 Kb. The number of saved precursors is a function of the number of atoms: approximately 300 precursors of 64 atoms or 600 of 32 atoms.

**E. Results.** MARSEIL/SOS has been used to solve several problems and is used by students.<sup>14</sup> Figures 12

and 13 show two new examples of synthesis found by the program for yohimbine<sup>15</sup> and bulnesol.<sup>16</sup> These schemes show the main weakness of the program: presently, there is no treatment of stereochemistry and this evaluation is left to the chemist. Nevertheless, the program is able to propose interesting ideas such as an internal Diels-Alder reaction to build the D and E rings of the yohimbine skeleton or an intramolecular De Mayo reaction to build the seven-membered ring of bulnesol. For step 5 in this synthesis, the program indicates that the other ketone must be protected. For the synthesis of bulnesol from precursor 3, the program proposes another sequence:  $\text{CO} \rightarrow \text{CHOH} \rightarrow \text{CHBr} \rightarrow \text{CHMgBR} + \text{CH}_3\text{COCH}_3 \rightarrow \text{bulnesol}$ .

### Conclusion

The program MARSEIL/SOS offers new features in the field of computerized organic synthesis design, such as personalized analysis of the target, which allows the user to easily add his own chemistry; graphical description of reactions, which allows their easy input; graphical description of bibliography; and the possibility of graphic evaluation. The program is also able to show the different groups that may influence the reaction. Then, because the program is interactive, it is also possible to add new tests during the retrosynthesis.

The next stage of this project will be the development of stereochemistry.

MARSEIL/SOS is written with MacFORTH and runs on a Macintosh+ microcomputer with one external drive.

**Acknowledgment.** We thank Prof. J. B. Hendrickson for useful suggestions during the writing of this paper.

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## Separation of Mass Law and Solvent Effects in Kinetics of Solvolyses of *p*-Nitrobenzoyl Chloride in Aqueous Binary Mixtures

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Received October 3, 1987

Rates and products for solvolyses of *p*-nitrobenzoyl chloride in aqueous binary mixtures with acetone, ethanol, and methanol are reported. Product selectivities,  $S = [\text{ester}][\text{water}]/[\text{acid}][\text{alcohol}]$ , increase in more aqueous media, in contrast to published data for solvolyses of benzoyl chloride. Logarithms of first-order rate constants are relatively insensitive to solvent ionizing power ( $Y$ ), showing marked dispersions for the three aqueous binary mixtures and unusual rate maxima for aqueous alcohol mixtures. Logarithms of calculated third-order rate constants for solvolyses in aqueous acetone (assuming these solvolyses are second order in water) show a linear Grunwald-Winstein plot ( $m = -0.18$ ), interpreted as the medium effect. Similarly, third-order rate constants for ethanol and methanol are calculated from solvolyses in the pure alcohols. Rate data in aqueous alcohols are explained quantitatively by an additional third-order pathway (first order in alcohol and in water), and product data are well explained if this process leads to ester. Thus mass law and medium effects of solvent molecules are separated, and it is shown that rate-product correlations of acceptable precision explain the unusual features of these solvolyses.

Classifications of reaction mechanisms in solution are usually based on the concept of molecularity: the number

of molecules necessarily undergoing covalency change during the rate-determining stage of the reaction.<sup>1a</sup> This

Table I. Rates and Products for Solvolyses of *p*-Nitrobenzoyl Chloride (1) in Aqueous Alcohols at 25 °C

solvent <sup>a</sup>	products <sup>b</sup>		rates (k/s <sup>-1</sup> )		contributions (%) to k <sub>calcd</sub> (eq 4) <sup>f</sup>			ester (%)	
	[ester]/[acid]	S <sup>c</sup>	obsd <sup>d</sup>	calcd <sup>e</sup>	k <sub>aa</sub>	(k <sub>aw</sub> + k <sub>wa</sub> )	k <sub>ww</sub>	calcd <sup>g</sup>	obsd
98% EtOH	9.85	0.65	0.0173	0.0156 <sup>h</sup>	61.8	36.7	1.5	98.5	90.8
95% EtOH	5.41	0.92	0.0265	0.0218	35.2	59.2	5.6	94.4	84.4
90% EtOH	3.66	1.32	0.0358 <sup>i</sup>	0.0315	17.5	70.1	12.4	87.6	78.5
80% EtOH	2.42	1.96	0.0480 <sup>j</sup>	0.0488	6.5	70.1	23.4	76.6	70.8
70% EtOH	1.78	2.47	0.0580 <sup>i</sup>	0.0622	3.0	64.7	32.3	67.7	64.0
60% EtOH	1.44	3.11	0.0690	0.0715	1.5	58.4	40.1	59.9	59.0
50% EtOH	1.12	3.63	0.0751	0.0760	0.8	51.9	47.3	52.7	52.8
40% EtOH	0.859	4.18	0.0807	0.0760	0.4	45.1	54.5	45.5	46.2
30% EtOH	0.647	4.89	0.0777 <sup>k</sup>	0.0727	0.2	37.4	62.4	37.6	39.4
20% EtOH	0.400	5.18	0.0687	0.0712 <sup>l</sup>	0.1	27.4	72.5	27.5	28.6
98% MeOH	42	1.9	0.0520 <sup>m</sup>	0.0536 <sup>o</sup>	67.6	32.1	0.3	99.7	97.7
95% MeOH	20.4	2.4	0.0665 <sup>p</sup>	0.0720	43.6	55.1	1.3	98.7	95.3
90% MeOH	14.02	3.50	0.0897	0.0949	25.1	71.5	3.4	96.6	93.3
80% MeOH	8.76	4.92	0.125	0.125	11.2	81.0	7.8	92.2	89.8
60% MeOH	5.28	7.91	0.151	0.144	3.4	79.6	17.0	83.0	84.1
40% MeOH	2.94	9.91	0.135	0.131	1.1	69.8	29.1	70.9	74.6
20% MeOH	1.11	9.98	0.0947	0.104 <sup>q</sup>	0.2	49.8	50.0	50.0	52.6

<sup>a</sup> Solvents are % v/v alcohol/water; molar concentrations of alcohol and water are calculated by ignoring the small volume of mixing as follows ([ROH], [H<sub>2</sub>O]). For ethanol/water: 98E, 16.79, 1.11; 95E, 16.28, 2.78; 90E, 15.42, 5.55; 80E, 13.71, 11.10; 70E, 11.99, 16.65; 60E, 10.28, 22.20; 50E, 8.57, 27.75; 40E, 6.85, 33.31; 30E, 5.14, 38.86; 20E, 3.43, 44.41. For methanol/water: 98M, 24.21, 1.11; 95M, 23.47, 2.78; 90M, 22.23, 5.55; 80M, 19.76, 11.10; 60M, 14.82, 22.20; 40M, 9.88, 33.31; 20M, 4.94, 44.41. <sup>b</sup> Average deviations in product ratios usually <±2%, except for triplicate measurements in 60% EtOH and 80% MeOH (±3%), 95% MeOH (±6%), and 98% MeOH (±14%). <sup>c</sup> From eq 1, substituting the [ester]/[acid] ratios shown and the concentrations of protic solvents (footnote a). <sup>d</sup> Experimentally observed rate constants determined conductimetrically in duplicate (average deviation <±3%); additional kinetic data summarized in ref 16a. <sup>e</sup> Calculated first-order rate constant given by eq 4; molar concentrations of protic solvents are given in footnote a, and third-order rate constants k<sub>aa</sub>, k<sub>aw</sub>, and (k<sub>aw</sub> + k<sub>wa</sub>) are given in footnote f. <sup>f</sup> Calculated third-order rate constants are as follows: k<sub>aa</sub> = 3.95 × 10<sup>-5</sup> M<sup>-2</sup> s<sup>-1</sup> in pure ethanol (k/s<sup>-1</sup> = 0.0116, average of ref 9b, 17a, and 17b) and 6.69 × 10<sup>-5</sup> M<sup>-2</sup> s<sup>-1</sup> in pure methanol (k/s<sup>-1</sup> = 0.0408, ref 16a); k<sub>aw</sub> = 2.18 × 10<sup>-5</sup> M<sup>-2</sup> s<sup>-1</sup> in pure water; (k<sub>aw</sub> + k<sub>wa</sub>) = 2.25 × 10<sup>-4</sup> M<sup>-2</sup> s<sup>-1</sup> in 80% ethanol/water (Y = 0) and 5.10 × 10<sup>-4</sup> M<sup>-2</sup> s<sup>-1</sup> in methanol/water (Y = 0); all of these third-order rate constants are corrected for the medium effect by an *mY* term (eq 2, 3, and 5), with optimized *m* values for k<sub>aw</sub> (eq 5); the percentage contribution of k<sub>aa</sub> to the overall rate is given by 100 k<sub>aa</sub>[ROH]<sup>2</sup>/k<sub>calcd</sub>, and other contributions are calculated similarly.<sup>g</sup> <sup>h</sup> Contributions from k<sub>aa</sub> and k<sub>aw</sub> (columns 6 and 7 of this table), assuming a rate-product correlation and assuming that k<sub>wa</sub> is 0. <sup>i</sup> If *m* = -0.18 (eq 5), k = 0.0201 s<sup>-1</sup>. <sup>j</sup> Reference 17a. <sup>k</sup> Average of two published values (ref 9b and 17a). <sup>l</sup> Quadruplicate measurement of rate constant. <sup>m</sup> If *m* = -0.18 (eq 5), k = 0.0634 s<sup>-1</sup>. <sup>n</sup> Additional kinetic data at lower temperatures: (k/s<sup>-1</sup>, T/°C) (8.68 ± 0.17) × 10<sup>-3</sup>, 0.0; (1.86 ± 0.01) × 10<sup>-2</sup>, 10.2; Δ*H*<sup>‡</sup> = 11.0 kcal/mole, Δ*S*<sup>‡</sup> = -27.4 eu. <sup>o</sup> If *m* = -0.18 (eq 5), k = 0.0597 s<sup>-1</sup>. <sup>p</sup> Triplicate measurement of rate constant. <sup>q</sup> If *m* = -0.18 (eq 5), k = 0.0899 s<sup>-1</sup>.

definition implies that kinetic terms due to mass law and solvent effects can be separated, which is difficult to achieve for many reactions, particularly in aqueous media. Water can act as base, nucleophile, and electrophile as well as the reaction medium, and such reactions were initially termed polymolecular.<sup>2</sup> High and variable kinetic orders (e.g., 4–6) in water were later obtained for solvolyses in aqueous binary mixtures (e.g., with acetone or dioxane) from the slopes of plots of logarithms of pseudo-first-order rate constants vs logarithms of water concentrations.<sup>3</sup> These plots ignore solvent effects on reactivity,<sup>4</sup> and discussions of solvolysis mechanisms are now based on the concepts of unimolecular (S<sub>N</sub>1) or bimolecular (S<sub>N</sub>2) activity.<sup>6</sup> A wide range of reactions have been similarly classified in this qualitative way.<sup>1</sup>

More quantitative studies have adopted linear free energy relationships and empirical parameters.<sup>7</sup> Solvent effects on reactivity have been investigated by relating

observed rate constants to empirical parameters.<sup>8</sup> In such studies, mass law effects of solvent may be underestimated, e.g., S<sub>N</sub>2 solvolytic rate data are usually interpreted directly, without attempting to incorporate the mass law effects of solvents.<sup>9,10</sup>

A complete description of reaction mechanisms will require either an amalgamation of or a simultaneous consideration of both mass law and solvent effects. The former approach is being achieved theoretically with large numbers of solvent molecules (e.g., 250) in Monte Carlo simulations,<sup>11</sup> and with ab initio calculations,<sup>12</sup> and studies of solvated clusters in the gas phase<sup>13</sup> are also promising. However, the latter approach will continue to be required as a theoretical framework for interpreting kinetic data in solution. This approach may currently be considered to

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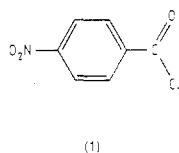
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be either qualitative or very approximate, but we now report that unexpected rates and products for solvolyses of *p*-nitrobenzoyl chloride (1) in aqueous alcohols can be explained quantitatively by separating mass law and solvent effects.<sup>14</sup>



The choice of substrate for this work was based on recent studies of solvolyses of para-substituted benzoyl chlorides in aqueous binary mixtures with acetone, ethanol, and methanol. For 1 there was no evidence for mechanistic changes even over a wide range of solvent ionizing power, so 1 was chosen for this investigation of rate-product correlations. Mechanisms of solvolyses of other para-substituted benzoyl chlorides change from carbonyl addition to S<sub>N</sub>2-S<sub>N</sub>1 as solvent ionizing power increases,<sup>16,17</sup> and rate-product correlations will be more difficult to achieve.

### Results

The experimental pseudo-first-order rate constants for alcohol/water mixtures are summarized in Table I, with observed product ratios and selectivities (*S*) calculated from appropriate molar concentrations (eq 1); for details

$$S = \frac{[\text{ester or ether}][\text{water}]}{[\text{acid or alcohol product}][\text{alcohol solvent}]} \quad (1)$$

see Table I, footnote *a*. The inverse of eq 1<sup>18a</sup> has sometimes been adopted,<sup>18</sup> but is less appropriate.<sup>16c</sup>

### Discussion

**Rates and Products.** The selectivities (Table I) are unusual because they increase in more aqueous alcoholic media to a more marked extent than ethanol/water selectivities in published work.<sup>19</sup> Also, for solvolyses of benzoyl chloride, *S* decreases in more aqueous media.<sup>16b</sup> Greater *S* values for methanol/water than for ethanol/water are well established.<sup>16b,18f,g</sup> Interpretations of rate and product data in mixed solvents may be complicated by solvent sorting,<sup>20</sup> possibly leading to atypical concentrations of solvent at the reaction site and hence to difficulties in quantifying mass law effects. However, product selectivities can be interpreted by using eq 1, in which bulk

(14) In this paper, we calculate mass law effects from molar concentrations, as many other authors have also done.<sup>3,5</sup> This ignores effects due to nonideality, which we include in the medium effect. For a critical discussion, see ref 15.

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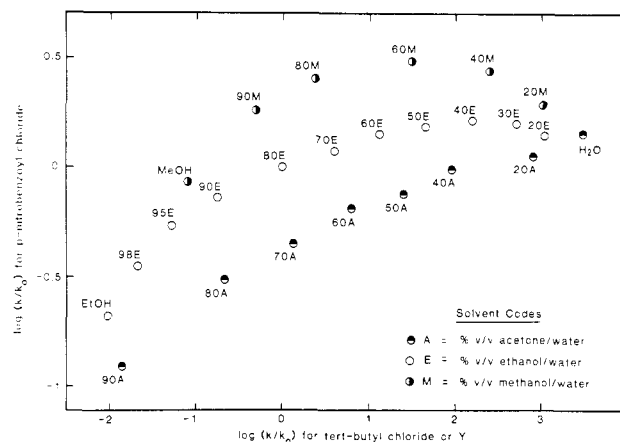
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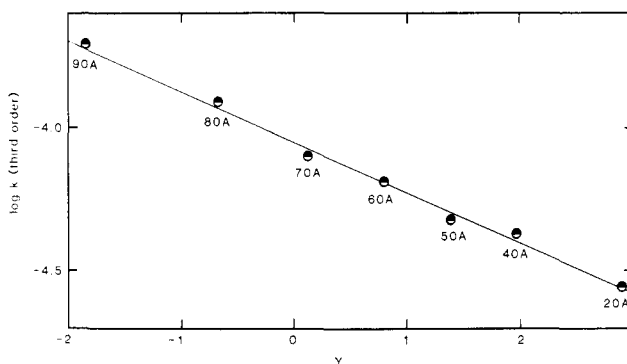
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**Figure 1.** Logarithms of first-order rate constants for solvolyses of *p*-nitrobenzoyl chloride at 25 °C vs Grunwald-Winstein *Y* values (ref 21). Kinetic data for alcohol/water mixtures are from Table I and for acetone/water mixtures are from ref 9b and 16a; the data point for water is calculated by extrapolation of Figure 2.



**Figure 2.** Logarithms of calculated third-order rate constants for hydrolysis of *p*-nitrobenzoyl chloride in acetone/water at 25 °C vs Grunwald-Winstein *Y* values (ref 21). Kinetic data are from ref 9b and 16a. Slope  $m = -0.176 \pm 0.006$ ; intercept =  $-4.046 \pm 0.010$ ; correlation coefficient = 0.997.

solvent concentrations are assumed to refer to the reaction site. For solvolyses of 1- and 2-adamantyl substrates, *S* values (eq 1) are almost constant over a wide range of compositions of aqueous ethanol for a variety of leaving groups;<sup>18</sup> these results would be a remarkable coincidence if solvent sorting were important.<sup>20</sup>

Logarithms of pseudo-first-order rate constants, plotted on an expanded scale against Grunwald-Winstein *Y* values (Figure 1), show a low response to solvent ionizing power and large dispersion between the curves for the three binary mixtures before they coalesce at the point representing pure water. Unprecedented rate maxima are observed in aqueous alcohol mixtures at  $Y \sim 2$ . The only other maxima in Grunwald-Winstein plots are for perchlorates<sup>22a</sup> and picrates<sup>22b</sup> and may be attributed to differences in solvation between the leaving groups. To try to avoid this effect, we are attempting to minimize leaving-group effects by comparing solvolyses of two chlorides (Figure 1). As solvolyses of  $\alpha$ -phenylethyl chloride show correlation lines with only a small dispersion into plots for various binary mixtures,<sup>23</sup> we assume that the solvation of aryl groups does not cause the major anomalous effects

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in Figure 1.<sup>24</sup> A similar plot for solvolyses of benzoyl chloride versus *Y* is linear and of unit positive slope for the following solvents: 40M, 30A, 30E, 30M, 20A, 20E, 20M, 10A, 10E, 10M, and H<sub>2</sub>O;<sup>25</sup> dispersion is much less than for 1.

Third-order kinetics is well established for alcoholyses of acid chlorides in acetonitrile,<sup>26a,d</sup> acetone,<sup>26b,d</sup> ether,<sup>26c,d</sup> and dioxane.<sup>26d</sup> Chloride ion can act as a general base catalyst replacing one of the alcohol molecules in the transition state.<sup>26a,e</sup> Similarly, hydrolyses of esters activated in the acyl portion may proceed by a third-order (B<sub>Ac</sub>3) mechanism in which water acts as a general base.<sup>27a</sup> Hydration of carbonyl groups<sup>27b</sup> and addition of alcohols to carbocations<sup>27c</sup> also involve general base catalysis. The kinetic data for solvolyses of 1 in acetone/water can also be interpreted as third order. Logarithms of the third-order rate constants  $k_{\text{obsd}}/[\text{H}_2\text{O}]^2 = k_{\text{ww}}$  for hydrolysis in acetone/water plot linearly versus *Y* (Figure 2) with a slope  $m = -0.18$ .<sup>28</sup> This line was extrapolated from *Y* = 2.9 to give the estimated solvolysis rate in pure water (*Y* for H<sub>2</sub>O = 3.49).<sup>30</sup>

**Correlation of Rate Data.** The kinetic data for alcohol/water mixtures will now be incorporated. Values of  $k_{\text{ww}}$  in alcohol/water mixtures (ROH/H<sub>2</sub>O) can be obtained from eq 2, assuming that the same medium effect

$$(\log k_{\text{ww}})_{\text{ROH}/\text{H}_2\text{O}} - (\log k_{\text{ww}})_{\text{H}_2\text{O}} = -0.18(Y_{\text{ROH}/\text{H}_2\text{O}} - Y_{\text{H}_2\text{O}}) \quad (2)$$

(*m*, Figure 2) applies to alcohol/water mixtures as to acetone/water mixtures. Third-order rate constants in the pure alcohols ( $k_{\text{aa}}$ ) can also be calculated: e.g.,  $k_{\text{aa}}$  for MeOH =  $k_{\text{obsd}}/[\text{MeOH}]^2$ , and values of  $k_{\text{aa}}$  in alcohol/water mixtures of various *Y* values can be obtained by assigning the same *m* value (-0.18) to  $k_{\text{aa}}$  (eq 3) and  $k_{\text{ww}}$  (eq 2).

$$(\log k_{\text{aa}})_{\text{ROH}/\text{H}_2\text{O}} - (\log k_{\text{aa}})_{\text{ROH}} = -0.18(Y_{\text{ROH}/\text{H}_2\text{O}} - Y_{\text{ROH}}) \quad (3)$$

All of the third-order rate constants discussed so far are based strongly on experimental data, so they are not freely adjustable. The rate constants  $k_{\text{ww}}$  and  $k_{\text{aa}}$  are well-defined in pure water and alcohol, respectively. The contributions from these two pathways decline as cosolvent is added, and

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(27) (a) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* 1961, 83, 1743. Euranto, E. K.; Cleve, N. *J. Acta Chem. Scand.* 1963, 17, 1584. (b) Funderburk, L. H.; Aldwin, L.; Jencks, W. P. *J. Am. Chem. Soc.* 1978, 100, 5444. (c) Ta-Shma, R.; Jencks, W. P. *J. Am. Chem. Soc.* 1986, 108, 8040. Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* 1984, 106, 1396.

(28) The *m* value depends on the assumed kinetic order in water. First-order solvolyses of *tert*-butyldimethylsulfonium ions give  $m = -0.09$ ,<sup>10b</sup> because there is only a small difference in charge between the initial state and the transition state. Reactions strongly susceptible to solvent nucleophilicity (*N*) also give low *m* values, e.g., solvolyses of triethyloxonium hexafluorophosphate in aqueous ethanol give  $m = -0.28$ ,<sup>10b</sup> the correlation with *Y* arises from the relationship between *N* and *Y* in aqueous binary mixtures.<sup>29</sup> Both of these factors could contribute to the negative *m* value (Figure 2). Third-order rate constants for chloride ion catalyzed methanolysis of acetyl chloride in acetonitrile decrease as the chloride concentration increases.<sup>28e</sup>

(29) Kaspi, J.; Rappoport, Z. *Tetrahedron Lett.* 1977, 2035.

(30) A referee has questioned whether the plot vs *Y* (Figure 2) is appropriate because the acid chloride solvolyses may be very different from solvolyses of *tert*-butyl chloride. In addition to the empirical result that the plot is satisfactory and other comments,<sup>28</sup> a plot vs *Y* is justified because the transition state for methanolysis of 1 must have considerable cleavage of the carbon-halogen bond; Br/Cl rate ratios as high as several hundred have been observed.<sup>31-33</sup>

the assumed medium effect on  $k_{\text{ww}}$  and  $k_{\text{aa}}$  ( $m = -0.18$ , eq 2 and 3) is an approximation that does not seriously affect our correlations.

A satisfactory quantitative fit to all of the rate data for the seven methanol/water mixtures (Table I) can be obtained with one extra and freely adjustable parameter based on the further assumption that there is an additional third-order rate constant, first order in alcohol and first order in water. We will refer to this *one* kinetic parameter as ( $k_{\text{aw}} + k_{\text{wa}}$ ) because there are two possible pathways distinguishable when products are considered (see later). An analogous parameter is required to fit the rate data for the 10 ethanol/water mixtures. The calculated first-order rate constant is then given by eq 4.

$$k_{\text{calcd}} = k_{\text{aa}}[\text{ROH}]^2 + (k_{\text{aw}} + k_{\text{wa}})([\text{ROH}][\text{H}_2\text{O}]) + k_{\text{ww}}[\text{H}_2\text{O}]^2 \quad (4)$$

Medium effects on  $k_{\text{aw}}$  and  $k_{\text{wa}}$  were initially assumed to be the same as those for  $k_{\text{ww}}$  and  $k_{\text{aa}}$  (i.e.,  $m = -0.18$ , analogous to eq 2 and 3). Predictions based on this incomplete model (Table I, footnotes *h*, *l*, *o*, and *q*) show systematic deviations: e.g., predicted rates are too high in highly alcoholic media and too low in highly aqueous media. A second adjustable parameter was then introduced to model more accurately the solvent effect (*m*) on ( $k_{\text{aw}} + k_{\text{wa}}$ ); see eq 5. Variation of *m* to give the optimum

$$[\log (k_{\text{aw}} + k_{\text{wa}})]_{\text{ROH}/\text{H}_2\text{O}} - [\log (k_{\text{aw}} + k_{\text{wa}})]_{Y=0} = mY_{\text{ROH}/\text{H}_2\text{O}} \quad (5)$$

agreement between observed and predicted rates gave  $m = -0.11$  for methanol/water mixtures and  $m = -0.08$  for ethanol/water mixtures. These two values are reassuringly similar and differ only slightly from our original choice of -0.18 (Figure 2). The calculated and observed rates agree well (Table I).

**Correlation of Rates and Products.** Given only the dissected rate data (eq 4), the products can now be calculated assuming that  $k_{\text{wa}}$  (leading to acid product) is negligible;  $k_{\text{aw}}$  leads to ester product. Agreement between calculated and observed products (% ester, Table I) is particularly good for methanol/water mixtures. The derivation of eq 4 was based solely on kinetic data and required a separation of mass law effects from solvent effects. The subsequent, satisfactory calculation of product compositions from eq 4 strongly supports the validity of the approach. While enough parameters were incorporated to ensure that eq 4 fitted the rate data well, no further "fitting" of results was needed to calculate the product data (Table I).<sup>34</sup>

**Quantitative Implications.** According to the above mechanistic model, there are four competing third-order

(31) Miller, J.; Ying, O.-L.; *J. Chem. Soc., Perkin Trans.* 2 1985, 323.

(32) Kevill, D. N.; Wang, W. F. K. *J. Chem. Soc., Chem. Commun.* 1967, 1178. Professor Kevill has informed us that the rate constants for benzoyl chloride in acetonitrile/methanol are 10-fold lower than those he reported, so the Br/Cl rate ratio (third order process) is 140.

(33) Our own data for solvolyses of benzoyl bromide in pure methanol are as follows: ( $k/s^{-1}$ ,  $T/^\circ\text{C}$ ) ( $1.91 \pm 0.01$ )  $\times 10^{-2}$ , -10.0, single measurement; ( $4.33 \pm 0.10$ )  $\times 10^{-2}$ , -0.1, quadruplicate measurement; ( $3.4 \pm 0.3$ )  $\times 10^{-1}$ , 25.0, quadruplicate measurement;  $\Delta H^\ddagger = 12.4$  kcal mol<sup>-1</sup>,  $\Delta S^\ddagger = -19$  cal mol<sup>-1</sup> K<sup>-1</sup>. At 25 °C the Br/Cl rate ratio is 80.

(34) Minor deviations are again systematic, so a minor contribution from  $k_{\text{wa}}$ , leading to acid product was included. Estimates of  $k_{\text{wa}}$  were subtracted from optimized values of ( $k_{\text{aw}} + k_{\text{wa}}$ ) to give estimates of  $k_{\text{aw}}$ . Values of  $k_{\text{aw}}$  and  $k_{\text{wa}}$  were then optimized to give the best fit to the observed products, so only at this stage has there been any consideration of the product compositions. The revised predictions are that only about 2% of the (methanol + water) process gives acid product (i.e.,  $k_{\text{aw}} \sim 50k_{\text{wa}}$ ), whereas about 10% of the (ethanol + water) process leads to acid. Calculated values of ester (%) are 0.1-0.4 lower for methanol/water and 2-5 lower for ethanol/water than shown in Table I.

rate constants; two ( $k_{aa}$  and  $k_{aw}$ ) involve *alcohol* as the nucleophile giving rise to ester product, and two ( $k_{ww}$  and  $k_{wa}$ ) involve *water* as the nucleophile giving rise to acid product. The calculated percentage rate contributions from the three kinetically different pathways (eq 4) are shown in Table I. In methanol/water mixtures, the ( $k_{aw} + k_{wa}$ ) term dominates from 95% to almost 20% compositions and accounts for the relatively rapid increase in rate from pure methanol to 80% methanol/water. The initial decrease in the observed first-order rate constant from 60% methanol/water to pure water is due mainly to the rate-retarding solvent effect on  $k_{aw}$  (eq 5, where  $m$  is negative), and the rate decrease from 40% to 20% methanol/water is also due to a reduction in the mass law term  $[\text{MeOH}][\text{H}_2\text{O}]$ . The trend in  $S$  values (Table I) indicates that a limiting maximum value ( $S_{\text{max}}$ ) may be approached in highly aqueous alcohols. Under these conditions, product ratios are determined mainly by two mechanisms because  $k_{aw}[\text{H}_2\text{O}][\text{ROH}] \gg k_{aa}[\text{ROH}]^2$  and  $k_{ww}[\text{H}_2\text{O}]^2 \gg k_{wa}[\text{H}_2\text{O}][\text{ROH}]$ . Substitution into eq 1 leads to  $S_{\text{max}}$  (eq 6).

$$S_{\text{max}} = k_{aw}[\text{H}_2\text{O}][\text{ROH}][\text{H}_2\text{O}] / k_{ww}[\text{H}_2\text{O}]^2[\text{ROH}] = k_{aw} / k_{ww} \quad (6)$$

Interestingly, for methanol/water mixtures  $S$  can increase when reactivity decreases (60%–20% MeOH), is constant (80% and 40% MeOH), or increases (98%–80% MeOH). The increase in  $S$  as water is added to alcohol does not require the trapping of various ion-pair intermediates,<sup>19,20</sup> because several concerted pathways are possible in these mixed solvents.

An alternative explanation of the results (Table I) based on first-order kinetics with respect to solvent is unsatisfactory, although the kinetic data for the range of acetone/water mixtures (Figure 2) give a constant value for  $k_{\text{obsd}}/[\text{H}_2\text{O}]$  of  $(1.3 \pm 0.1) \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ , apparently consistent with a kinetic order of 1 in solvent and with no solvent effect on the overall second-order rate constants (i.e.,  $m = 0$ ). However, the corresponding second-order rate constant for methanolysis would be  $1.65 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$  and the results predicted for 60% methanol/water are  $k_{\text{calcd}} = 5.34 \times 10^{-2} \text{ s}^{-1}$  ( $k_{\text{obsd}} = 1.51 \times 10^{-1}$ ); % ester 45.8 (obsd 84.1). These erroneous predictions emphasize the need to consider solvent effects on rate constants, even when  $m$  values are low; in previous work<sup>5</sup> this has not been done. More complex mechanisms involving higher than third

order kinetics cannot be excluded, but would require more negative  $m$  values.

### Conclusion

Unexpected rates and products in the solvolyses of *p*-nitrobenzoyl chloride in aqueous alcohol mixtures can be related to experimental data in pure alcohols and in acetone/water mixtures. The reactions appear to be at least third order, and an important extra pathway in alcohol/water mixtures is one in which alcohol acts as nucleophile and water acts as general base and/or electrophile ( $k_{aw}$ , Table I). Quantitative rate-product correlations can be obtained by separating, for the first time to our knowledge, the mass law effects of specific solvation from the medium effects of more general solvation.<sup>14,35</sup> Similar new insights into other reaction mechanisms are now anticipated,<sup>19</sup> and extension of theoretical studies of hydration of carbonyl groups<sup>12</sup> to include one molecule of methanol would be worthwhile.

### Experimental Section

Rates (conductimetric) and products (reversed-phase HPLC) were determined at least in duplicate as described previously,<sup>16</sup> with concentrations of substrate ca.  $10^{-4} \text{ M}$  and  $10^{-3} \text{ M}$ , respectively. Selected product studies at higher concentrations (ca.  $10^{-2} \text{ M}$ ) gave very similar results to those at  $10^{-3} \text{ M}$ . Lower concentrations ( $<10^{-4} \text{ M}$ ) were necessary for studies in highly aqueous media. A linear relationship between change in conductance and molar concentration of HCl was established in pure ethanol up to  $1 \times 10^{-4} \text{ M}$ .

**Acknowledgment.** This work was supported by the Science and Engineering Research Council (Grant GR/D19339). We are grateful to W. P. Jencks and D. N. Kevill for helpful comments.

**Registry No.** 1, 122-04-3; PhCOBr, 618-32-6.

(35) The Olsen-Halford equation<sup>36a</sup> gives a relationship between rates and a thermodynamic solvent property (vapor pressure) in alcohol/water mixtures, assuming a bimolecular mechanism. The products are correctly predicted for a limited range of solvolyses of *n*-butyl bromide,<sup>36b</sup> but as would be expected are incorrect for *tert*-butyl chloride.<sup>36c</sup> Equations similar to eq 4 have been applied to kinetic data for solvolyses of *tert*-butyl chloride,<sup>36d,e</sup> but the results were considered to be of little significance.<sup>6a</sup>

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