

Fig. 1.—Ultraviolet spectra of reactants and products in $5 \times 10^{-5} M$ methanolic solution: 1, CTK; 2, *p*-toluic acid; 3, sodium nitrite; 4, ϵ -caprolactam.

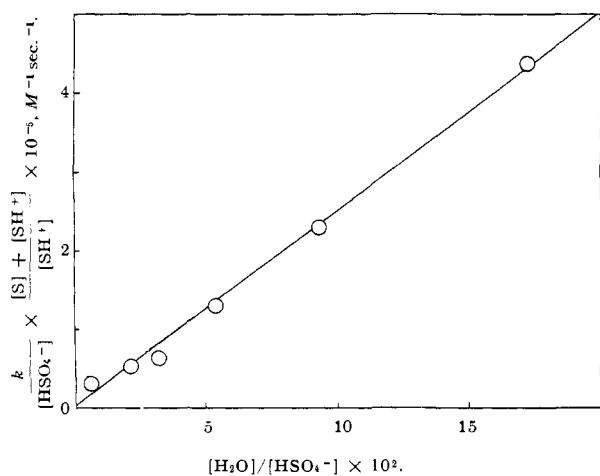


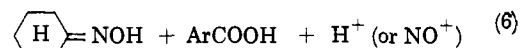
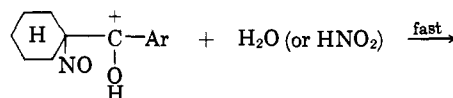
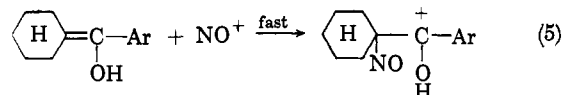
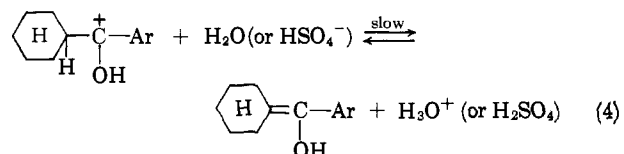
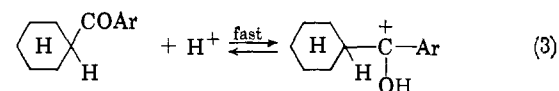
Fig. 2.—Plot on the effect of acidity for the nitrosation of cyclohexyl *p*-tolyl ketone in 84.0–94.9% sulfuric acid at 60° .

which led to an equation similar to eq. 1 for this reaction.

$$k = \frac{[\text{SH}^+]}{[\text{S}] + [\text{SH}^+]} (2.5 \times 10^{-4}[\text{H}_2\text{O}] + 1.0 \times 10^{-6}[\text{HSO}_4^-]) \quad (2)$$

These facts suggest a mechanism having a rate-determining deprotonation⁷ from protonated ketone carbon to yield enol, followed by a rapid nitrosation of

(7) Equation 2 shows that water acts as base 250 times as powerful as bisulfate ion.



the enol and then the Beckmann rearrangement. Here, the nitrosating species may be nitrosonium ion, since nitrous acid is converted almost completely to nitrosonium ion in this concentrated sulfuric acid.^{8,9}

The rate constant for step 7, which increased with the acidity of the solution in contrast to that for step 4, was reported to be $1.02 \times 10^{-4} \text{ sec}^{-1}$ at 60° in 89.4% sulfuric acid.²

This mechanism coincides with the fact that the introduction of an electron-releasing group (CH_3) to CPK retards the reaction as expected from the rate-determining deprotonation; *i.e.*, rate constants ($k \times 10^{-4} \text{ sec}^{-1}$) in 87.6% sulfuric acid at 60° for CPK and CTK were 6.20 and 1.21, respectively. Cyclohexyl *p*-methoxyphenyl ketone did not give the expected products because of the side reaction.

First-order constants ($k \times 10^5 \text{ sec}^{-1}$) for CTK in 89.6% sulfuric acid at 50, 60, 70, and 80° were found to be 2.95, 5.64, 16.8, and 39.2, respectively, which gave a straight line in a plot of $\log k$ vs. $1/T$ and thence a value of 21.0 kcal./mole for the energy of activation.

Acknowledgments.—The authors are grateful to Dr. M. Hojo and Mr. K. Okano for their aid in performing these experiments, and also to Teijin Co. and Toyo Rayon Co. for their gifts of materials.

(8) K. Singer and P. A. Vamplew, *J. Chem. Soc.*, 3971 (1956).

(9) N. S. Bayliss and D. W. Watts, *Chem. Ind. (London)*, 1353 (1955).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ALBERTA, CALGARY, ALBERTA, CANADA]

Specific Solvation in Binary Solvent Mixtures. III. The Solvolysis of *o*-, *m*-, and *p*-Methyl and Nitrobenzyl Chlorides in Ethanol–Water Mixtures

By J. B. HYNE AND R. WILLS

RECEIVED JANUARY 14, 1963

The effect of variation of position of ring substitution of methyl and nitro groups on the kinetic parameters of solvolysis of benzyl chloride in ethanol–water mixtures has been studied as a further test of the role of specific solvation in such kinetic systems. The observations are in accord with the model presented previously and indicate the steric effect of *ortho* substituents in inhibiting solvation of the reaction center.

Introduction

The effect of variation of the *p*-substituent in benzyl chlorides on the activation parameters of solvolysis as the composition of the binary solvent system changes

was reported in the previous paper of this series.¹ These effects were shown to be in accord with the spe-

(1) J. B. Hyne, R. Wills, and R. E. Wonkka, *J. Am. Chem. Soc.*, **84**, 2041 (1962).

TABLE I
RATES, ACTIVATION ENERGIES, AND ENTROPIES OF SOLVOLYSIS OF *o*-, *m*-, AND *p*-SUBSTITUTED BENZYL CHLORIDES
IN ETHANOL-WATER MIXTURES

Rates and activation parameters	Mole fraction ethanol				
	0.00	0.04	0.08	0.125	0.203
<i>o</i> -Nitrobenzyl chloride					
$k \times 10^6 \text{ sec.}^{-1}$ (78.30°)	11.39	7.916	4.953	3.015	1.517
$k \times 10^6 \text{ sec.}^{-1}$ (60.44°)	21.05	15.14	9.695	5.617	2.778
ΔE^* , cal./mole (69.40°)	21,976	21,531	21,224	21,695	22,088
ΔS^* , e.u./mole ^a	-16.3	-18.3	-20.1	-19.8	-20.0
<i>m</i> -Nitrobenzyl chloride					
$k \times 10^6 \text{ sec.}^{-1}$ (78.30°)	11.44	7.679	4.990	3.126	1.689
$k \times 10^6 \text{ sec.}^{-1}$ (60.44°)	21.46	15.27	10.32	6.276	3.276
ΔE^* , cal./mole (69.40°)	21,749	21,040	20,509	20,693	21,342
ΔS^* , e.u./mole	-17.0	-19.8	-22.1	-22.5	-21.9
<i>p</i> -Nitrobenzyl chloride					
$k \times 10^6 \text{ sec.}^{-1}$ (78.30°)	8.239	5.711	3.809	2.449	1.384
$k \times 10^6 \text{ sec.}^{-1}$ (60.44°)	15.56	11.46	7.727	4.875	2.623
ΔE^* , cal./mole (69.40°)	21,691	20,902	20,760	21,006	21,646
ΔS^* , e.u./mole	-17.8	-20.7	-21.9	-22.1	-21.4
<i>o</i> -Methylbenzyl chloride					
$k \times 10^6 \text{ sec.}^{-1}$ (41.06°)	75.32	45.73	25.36	11.43	3.466
$k \times 10^6 \text{ sec.}^{-1}$ (22.44°)	88.93	61.69	37.39	16.70	4.543
ΔE^* , cal./mole (31.75°)	21,117	19,856	18,975	19,065	20,141
ΔS^* , e.u./mole	-7.4	-12.6	-16.6	-18.0	-16.9
<i>m</i> -Methylbenzyl chloride					
$k \times 10^6 \text{ sec.}^{-1}$ (41.06°)	13.85	9.399	5.457	2.752	0.9425
$k \times 10^6 \text{ sec.}^{-1}$ (22.44°)	15.54	11.55	7.750	4.012	1.178
ΔE^* , cal./mole (31.75°)	21,682	20,781	19,347	19,087	20,613
ΔS^* , e.u./mole	-9.2	-12.8	-18.5	-20.7	-18.0
<i>p</i> -Methylbenzyl chloride ^b					
ΔE^* , cal./mole (31.75°)	22,659	21,700	20,209	19,440	20,830
ΔS^* , e.u./mole	0.0	-4.2	-10.4	-14.7	-13.1

^a ΔS^* values are mean of values calculated using median temperature activation energy with rate values at each temperature; deviation approximately ± 0.1 e.u. ^b *p*-Methylbenzyl chloride data from ref. 1.

cific solvation hypothesis previously advanced as an explanation for the observed activation parameter behavior in mixed solvents.² The various *p*-substituents were chosen to represent both electron-donating and withdrawing groups. The observed effects on the activation parameter behavior were interpreted largely in terms of assistance or resistance to the development of polarity in the transition state. In turn, the degree of charge development was reflected in the specificity with which the transition state was solvated by the more polar component of the solvent mixture. The effect of variation of *position* of a given ring substituent on the activation parameter behavior remained to be investigated as a logical counterpart study to the *p*-substituent variation.

We report here a comparison of the solvolytic behavior of *o*-, *m*-, and *p*-methyl and nitrobenzyl chlorides in ethanol-water mixtures, so choosing a representative example of both donor and withdrawer groups for substituent position variation. The intent of the study was primarily to investigate the effect of the steric influence on solvation of the substituents in the *o*-position, and, as a secondary purpose, to determine whether the proposed specific solvation behavior responded in the expected manner to the reduced interaction of a *m*-substituent with the reaction center.

Experimental

The precision conductimetric method employed for first-order rate determinations and the preparation of solvent systems and the *p*-substituted solutes used have been reported previously.¹ Eastman *m*-nitrobenzyl chloride was twice recrystallized from 90–120° ligroin, yielding off-white needles, m.p. 45°, lit. m.p. 44.5°. *o*-Nitrobenzyl chloride was prepared in 62% yield by

treating *o*-nitrobenzyl alcohol with a slight excess of thionyl chloride in ligroin. The crystals recovered from the ligroin after removal of excess thionyl chloride by distillation were recrystallized twice from 90 to 120° ligroin yielding pale yellow crystals, m.p. 49.0° (very sharp), lit. m.p. 49.0°. *o*- and *m*-Methylbenzyl chlorides were prepared by benzoyl peroxide-catalyzed monochlorination of the corresponding xylenes using sulfuryl chloride.³ The products were fractionated in a spinning-band column at 5 mm. pressure and the fractions used characterized by refractive index: *o*-methylbenzyl chloride, n_D^{20} 1.5442, lit. n_D^{20} 1.5425⁴; *m*-methylbenzyl chloride, n_D^{20} 1.5340, lit. n_D^{20} 1.5345.⁴

Results

First-order rate constants for the solvolysis in various solvent mixtures at two temperatures for each of the solutes are recorded in Table I. It should be noted that the *p*-nitrobenzyl chloride system has been repeated and the rates differ slightly from those previously reported.¹ Limits of error and the method of calculation of the activation parameters are the same as reported before.¹ ΔE^* uncertainties are shown in Fig. 2. Nuclear magnetic resonance spectra of solutes used were run in 5% solution in carbon tetrachloride on a Varian A60 spectrometer. Chemical shifts in p.p.m. relative to tetramethylsilane = 10 p.p.m. were read directly from the calibrated chart paper and were reproducible to ± 0.03 p.p.m.

Discussion

Mechanism of Hydrolysis.—Hill and Fry⁵ have recently reported Cl³⁷ kinetic isotope effects on the hydrolysis of *p*-substituted benzyl chlorides and have concluded that the transition states for *p*-CH₃O, *p*-

(3) M. S. Kharasch and H. C. Brown, *ibid.*, **61**, 2142 (1939).

(4) P. Bivort and P. J. C. Fierens, *Bull. soc. chim. Belges*, **67**, 975 (1956).

(5) J. W. Hill and A. Fry, *J. Am. Chem. Soc.*, **84**, 2763 (1962).

(2) J. B. Hyne, *J. Am. Chem. Soc.*, **82**, 5129 (1960).

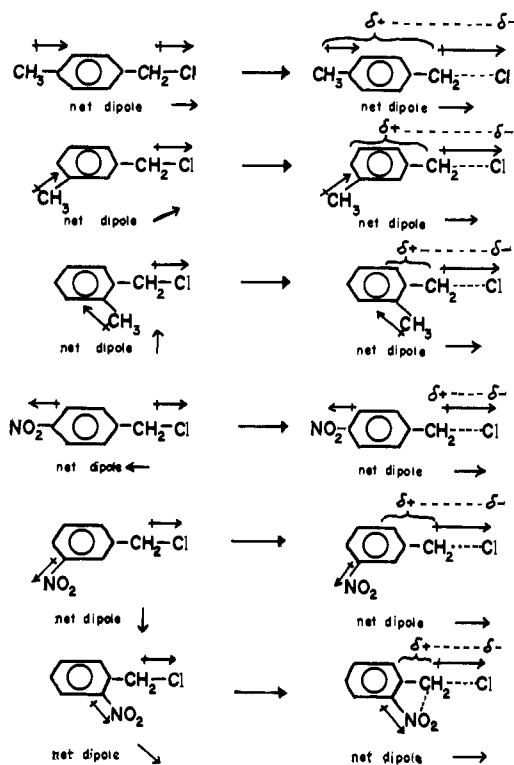
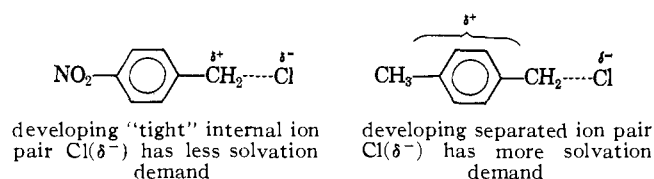


Figure 1.

CH_3 , $p\text{-Cl}$, and $p\text{-NO}_2$ benzyl chlorides are all very similar and that the hydrolysis mechanism is very close to ideal $\text{S}_{\text{N}}1$ in all cases. While an $\text{S}_{\text{N}}1$ -type mechanism has been generally accepted as being appropriate for the $p\text{-CH}_3\text{O}$ and $p\text{-CH}_3$ cases, its applicability to the other substituted benzyl chlorides has not been widely substantiated. In the previous paper of this series¹ we have avoided this contentious point by arguing that even if the $p\text{-NO}_2$ case were not ideal $\text{S}_{\text{N}}1$ there would still be strong dipolar development in the C-Cl bond in a more $\text{S}_{\text{N}}2$ -like transition state. However, if the conclusion of Hill and Fry is correct, the extent of heterolysis of the C-Cl bond and consequently the degree of net charge creation in the transition state of all substituted benzyl chlorides should be the same. This might then lead to the conclusion that demand for solvation stabilization by the ion-like transition states should be the same in all cases. As Hill and Fry pointed out, however, the very considerable rate differences in the hydrolysis of substituted benzyl chlorides can be attributed to the different abilities of the substituents to delocalize the developing positive charge on the methylene carbon, notwithstanding the fact that the degree of charge creation (*i.e.*, size of δ) in all transition states is the same. This argument can also be used to predict that the demand for solvation stabilization by the various transition states will also vary. In the case of the methyl substituents the delocalization of the developing positive charge on the methylene will be much larger than in the case of the nitro substituents. Accordingly, the departing $\text{Cl}(\delta^-)$ will be much less like an ion in a "tight" internal ion pair than will be the chloride entity in the transition state of the nitrobenzyl chlorides. The $\text{Cl}(\delta^-)$ entity in transition state with



more "tight ion pair" character will have less solvation stabilization demand than will the transition state where the developing chloride ion is "less neutralized" by a more dispersed δ^+ charge. By this argument the kinetic isotope effect evidence of Hill and Fry can be accommodated, but the greater solvation demand of the methyl-substituted transition state remains. The need for this solvation stabilization is reflected in the fact that while the rate of hydrolysis of $p\text{-NO}_2$ benzyl chloride decreases by only a factor of six in passing from water to 0.203 mole fraction of ethanol (Table I) the rate for $p\text{-CH}_3$ decreases by a factor of 40 over the same range of reduction of solvent polarity.¹

Activation Parameters of Hydrolysis.—In the previous paper of this series¹ the differences in the ΔE^* and ΔS^* values for $p\text{-CH}_3$ and $p\text{-NO}_2$ benzyl chloride hydrolysis were explained on the basis of the assumption that the C-Cl bond in the transition state of both compounds developed equal ionic character; *i.e.*, in keeping with the isotope effect evidence. The very large differences in ΔS^* were rationalized by considering the relative changes in net dipole vector direction in the activation process for the two hydrolyses. This argument, together with the charge dispersal effects discussed in the previous paragraph, may be extended to account for the observed changes in ΔE^* and ΔS^* of hydrolysis as the position of both the methyl and the nitro ring substituents is varied. As an aid to the discussion an attempt has been made to depict the activation processes in Fig. 1.

The decrease in ΔE^* on passing from $p\text{-CH}_3$ through $m\text{-CH}_3$ to $o\text{-CH}_3$ benzyl chloride can be accounted for in terms of decreasing separation of the dispersed δ^+ charge from the departing $\text{Cl}(\delta^-)$. While the magnitude of the δ -charge in all three cases may be approximately the same, the extent of separation of the δ -charges will not be the same. Greatest charge separation will characterize the $p\text{-CH}_3$ case leading to the highest work requirement and the highest ΔE^* . A similar argument has been used to explain the generally higher ΔE^* values for $\text{S}_{\text{N}}1$ -type reactions compared with analogous $\text{S}_{\text{N}}2$ reactions where less charge separation is involved in attaining the transition state configuration. The $p\text{-CH}_3$ transition state will also have the least "tight ion pair" character resulting in a relatively high demand for solvation stabilization by the departing $\text{Cl}(\delta^-)$. This is reflected in the much greater sensitivity to solvent polarity exhibited by the $p\text{-CH}_3$ compared with the $o\text{-CH}_3$ and $m\text{-CH}_3$ benzyl chlorides.

In Fig. 1 an attempt has been made to depict the change in vector direction of the net dipole of the reacting solute in the activation process. In the transition state the dominant dipole must be that of the partially ionic C-Cl bond and, to a good approximation, the C-Cl bond axis will represent the net dipole vector direction of the transition state. In the $p\text{-CH}_3$ case the vector direction of the net dipole undergoes no change on activation so that the solvent molecules require little reorientation from their initial state configuration to achieve the most favorable solvation shell for the transition state. Electrostriction of the solvent molecules, of course, will be increased. As a result $-\Delta S^*$ for the $p\text{-CH}_3$ case is small (zero on the relative scale). In the $m\text{-CH}_3$ activation process the net dipole vector does undergo some change in direction requiring reorientation of the solvent molecules leading to a sizable $-\Delta S^*$ value. On the basis of this argument the largest $-\Delta S^*$ value would be expected for the $o\text{-CH}_3$ case while in fact the observed value is less than that for the $m\text{-CH}_3$ substituent. This must be a reflection of the steric inhibition to solvation exerted by the $o\text{-CH}_3$ substituent. While the solvent reorganization predicted

from the large change in dipole vector direction in the *o*-CH₃ case is greatest, it is physically impossible for the solvent molecules to approach the screened side of the methylene, and the actual degree of reorganization is consequently reduced.

Differences between ΔE^* 's and ΔS^* 's for the various nitrobenzyl chlorides are much less pronounced than in the methyl cases. The similarities in ΔE^* reflect the much reduced effect of the nitro group on the dispersal of the developing δ^+ charge irrespective of the position of substitution. Hence the transition states in all the nitrobenzyl cases might be viewed as rather "tight ion pairs." The somewhat higher ΔE^* for the *ortho* case may reflect the particular ability of the *o*-NO₂ group to influence charge delocalization at the reaction center by virtue of its close proximity. The very large $-\Delta S^*$ values for all three nitrobenzyl chlorides reflects the great extent of solvation molecule reorganization necessary on activation due to large changes in vector direction of the over-all dipole. Small though the $-\Delta S^*$ differences in the nitro cases are, the order is that which would be predicted from a consideration of change in net dipole vector direction on activation. In the *p*-NO₂ case the group dipole is directly opposed to the developing dipole at the reaction center, and the vector direction and magnitude change will be greatest in this case leading to considerable solvent reorganization. In the *o*-NO₂ case the group dipole is only 60° out of alignment with the developing reaction center dipole and net vector direction change will be considerably less than in the *para* case with correspondingly reduced solvent molecule reorganization. The *meta* case, as expected on the basis of this argument, is intermediate.

Activation Parameters in EtOH-H₂O Mixtures.—In Fig. 2 the usual minima in the plots of ΔE^* vs. mole fraction of ethanol are observed, as is characteristic of solvolytic reactions where the activation process involves charge or polarity creation in the transition state. It has been shown previously¹ that increasing depth of the $\Delta\Delta E^*$ minimum ($\Delta E^*(\text{H}_2\text{O}) - \Delta E^*(\text{min.})$) can be accounted for by an increase in specific demand by the reacting solute transition state for selective solvation by the more polar component of the binary solvent mixture, *viz.*, water.⁶ The plots in Fig. 2 therefore suggest that specific solvation demand by all three of the methylbenzyl chlorides is greater than that of the nitrobenzyl chlorides. Our main interest in this work, however, is in the variation of $\Delta\Delta E^*$ for a given substituent as the position of the substituent on the ring is varied.

In Table II the pertinent activation parameter data for the methylbenzyl chlorides are shown in comparison to the unsubstituted benzyl chloride. The n.m.r. chemical shifts of the benzyl methylene protons, shown in Table II, are all very similar. This may be taken as an indication that the substituent has relatively little effect on the polarity of the C-Cl bond in the initial state since any variation would presumably change the shielding of the methylene protons. It may therefore be assumed that the initial states of the four benzyl chlorides in Table II are essentially the same as far as the polarity of the C-Cl bond is concerned. Consequently, solvation stabilization demand by the initial

(6) In a recent communication (*J. Am. Chem. Soc.*, **85**, 1350 (1963)) Arnett and co-workers state that data on the heats of solution of *t*-butyl chloride in ethanol-water mixtures show that virtually all of the activation energy minimum in the solvolysis of this halide can be associated with changes in solvation of the ground state, leaving transition state changes in solvation negligible. While initial state solvation behavior of the type suggested by these authors would alter the form of the energy vs. solvent composition curve for the initial state as used throughout this series—extremum behavior would now show in the initial state curve—specific solvation of the transition state is explicitly required.

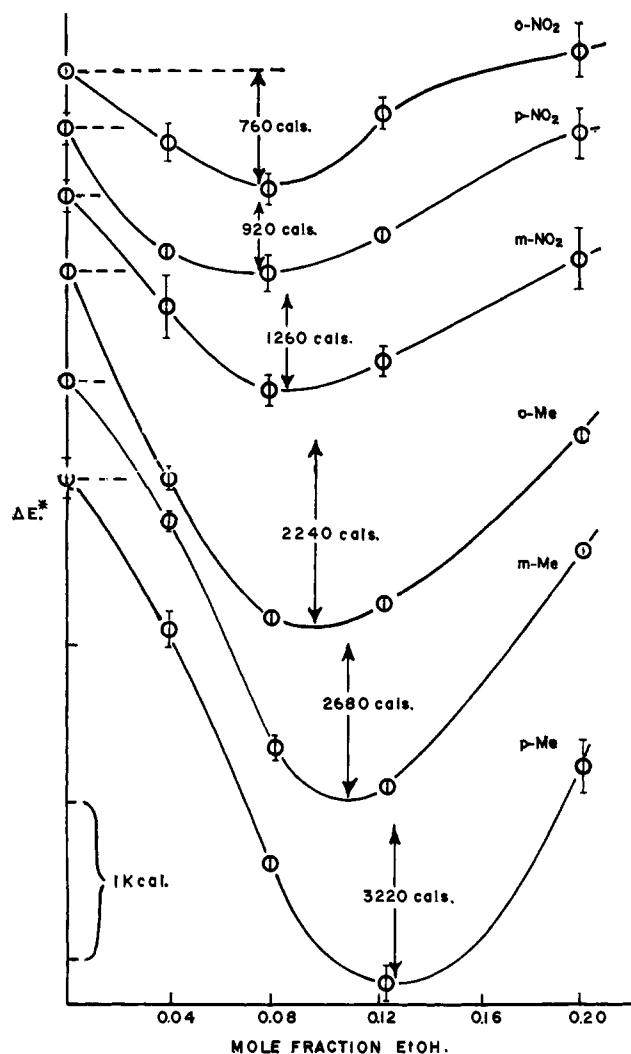


Fig. 2.—Activation energy vs. mole fraction of ethanol for methyl and nitrobenzyl chloride solvolysis. ΔE^* scale has variable zero point but same unit interval.

states should not be significantly different in the four cases. As discussed in the previous section, however, the solvation stabilization demand of the departing $\text{Cl}(\delta^-)$ in the transition state varies considerably depending upon the extent to which the developing δ^+ charge can be delocalized away from the $\text{Cl}(\delta^-)$. As illustrated in Fig. 1, the solvation demand of $\text{Cl}(\delta^-)$ decreases in the order *p*-CH₃ > *m*-CH₃ > *o*-CH₃. Since this solvation stabilization can be best achieved by the polar water, selective solvation of the transition states by water will persist longest, as ethanol composition is increased, in the case of *p*-CH₃ and will break down at lowest ethanolic composition in the case of *o*-CH₃. Fig. 3a is a schematic presentation of the effects of such specific solvation of the transition states on the activation energy, incorporating the arguments used in the previous papers of this series.^{1,2} The dependence on solvent composition of the energy of interaction of the initial states with the solvation shell is assumed to be the same in all cases in view of the n.m.r. evidence discussed above. While specific hydration of the transition states persists, the energy of interaction with the solvation shell will remain relatively constant. Figure 3a shows that the activation energy would thus be expected to pass through the deepest minimum ($\Delta\Delta E^*$) in the case of *p*-CH₃ and the shallowest minimum in the *o*-CH₃ case, as found experimentally (Fig. 2). While the experimental location of the minima on the solvent com-

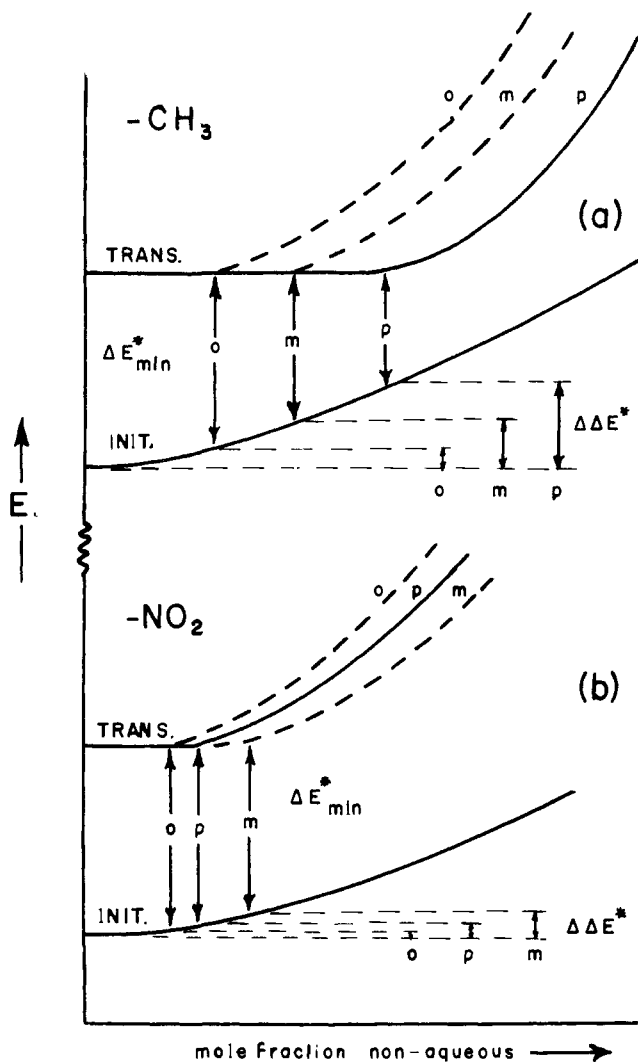


Fig. 3.—Schematic diagrams illustrating origin of activation energy behavior for (a) methylbenzyl chlorides and (b) nitrobenzyl chlorides.

position axis is somewhat dubious, it should be noted that the prediction of Fig. 3a in this regard is borne out by the experimentally observed trend in Fig. 2.

TABLE II
ACTIVATION PARAMETER AND N.M.R. DATA FOR METHYLBENZYL CHLORIDES

	$\Delta\Delta E^*$ (31.75°), $\Delta\Delta S^*$ (31.75°)		γ_{CH_2} , p.p.m.
	cal.	e.u.	
<i>p</i> -CH ₃ ^a	3220	15.0	5.53
<i>o</i> -CH ₃	2240	10.5	5.47
<i>m</i> -CH ₃	2680	11.5	5.55
H ^b	2240	9.3	5.50

^a $\Delta\Delta E^*$ erroneously shown as 2820 cal. in ref. 1. ^b Data obtained from ref. 1 by extrapolation to 31.75°.

While we have not as yet analyzed in detail the entropy of activation as it is related to the specific solvation hypothesis in this series of papers, an elementary consideration of the physical significance of activation entropy reveals that changes in its value ($\Delta\Delta S^*$) can be related to changes in specificity of solvation. The largest $\Delta\Delta S^*$ (*i.e.*, greatest decrease in entropy or increase in organization) is found in the *p*-CH₃ case. This is in keeping with the fact that it is in this case that the greatest "unmixing" of the solvent must take place in order to achieve persistence of specific hydra-

tion of the transition state as ethanol is added to the solvent. $\Delta\Delta S^*$ for the *m*-CH₃ is somewhat less owing to less persistent specificity of solvation and is least for the *o*-CH₃ case where the specific hydration breaks down at lowest ethanolic composition and the extent of solvent "unmixing" required is consequently less.

Differences between the $\Delta\Delta E^*$'s and $\Delta\Delta S^*$'s for the nitrobenzyl systems are much smaller than in the methylbenzyl systems and it could be argued that they are barely significant in view of the experimental error (Table III). The small variation, however, is in keeping with the previous argument that the nitro substituent does little to delocalize the developing δ^+ charge on the methylene and the polarity of the reaction center in the transition state of all three cases is very similar (Fig. 1). This will lead to very similar specific solvation of the transition states and consequently only minor changes in $\Delta\Delta E^*$. The trend in $\Delta\Delta E^*$ variation, however, can be accounted for on the basis of the same arguments as used for the methylbenzyl chlorides.

TABLE III
ACTIVATION PARAMETER AND N.M.R. DATA FOR NITROBENZYL CHLORIDES

	$\Delta\Delta E^*$ (69.4°),	$\Delta\Delta S^*$ (69.4°),	γ_{CH_2} , p.p.m.
	cal.	e.u.	
<i>p</i> -NO ₂	920	4.0	5.37
<i>o</i> -NO ₂	760	4.5	5.03
<i>m</i> -NO ₂	1260	6.0	5.35
H ^a	1642	7.8	5.50

^a Data obtained from ref. 1.

The n.m.r. data for the nitro series (Table III) indicate that the methylene protons are significantly deshielded compared with the unsubstituted benzyl chloride. This suggests that the C-Cl bond in the initial states of the nitrobenzyl chlorides may be more polar than that in the unsubstituted case. In comparing the nitrobenzyl chlorides this would not be of great importance if all three were effected to the same extent. Unfortunately, however, the *o*-NO₂ case has a significantly lower methylene resonance suggesting much greater deshielding of the CH₂ protons. Whether this reflects greater polarity of the C-Cl bond in this case or not is complicated by the known magnetic anisotropy effect of the *o*-NO₂ group.⁷ We have assumed that the anisotropy effect is the dominant one in lowering the *o*-NO₂ methylene resonance and that the polarity of the C-Cl bond in the initial states of all three nitro compounds, while greater than in the unsubstituted case, is the same.

While the nitro substituents, being electron withdrawers, will not aid in delocalizing the developing δ^+ charge in the transition state, the suppressing effect of these substituents on charge delocalization into the ring would be expected to be greatest in the *p*-NO₂ and *o*-NO₂ cases where both the inductive and conjugative interactions with the reaction center are operative. Accordingly, delocalization of the δ^+ charge will be slightly favored in the *m*-NO₂ case leaving the departing Cl (δ^-) with greatest solvation stabilization demand. This is reflected in the greater persistence of specific hydration of the transition state in this case as shown in Fig. 3b with consequent enhancement of $\Delta\Delta E^*$. Whether the $\Delta\Delta E^*$ difference between *p*-NO₂ and *o*-NO₂ is real is questionable, but the close proximity of the nitro group to the reaction center in the *o*-NO₂ case may reduce solvation stabilization demand, and consequently specific solvation, below that of the *p*-NO₂ case. The *o*-NO₂ group may be said to participate

(7) R. E. Klinck and J. B. Stothers, *Can. J. Chem.*, **40**, 1071 (1962).

in intramolecular solvation of the reaction center.^{8,9} The largest $\Delta\Delta S^*$ value for the *m*-NO₂ substituent again supports the argument that it is in this case that the

(8) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

(9) R. E. Lovins, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **84**, 3959 (1962), and references therein.

“unmixing” of the solvent in forming the solvation shell of the transition state is greatest since the specificity of hydration persists to the highest ethanolic composition.

Acknowledgment.—The authors acknowledge financial support for this work from the National Research Council of Canada.

[CONTRIBUTION FROM THE SCHOOL OF PHARMACY, UNIVERSITY OF WISCONSIN, MADISON 6, WIS.]

Facilitated Reversible Formation of Amides from Carboxylic Acids in Aqueous Solutions. Intermediate Production of Acid Anhydride

BY TAKERU HIGUCHI, TOMONORI MIKI, ASHOK C. SHAH, AND ALLEN K. HERD

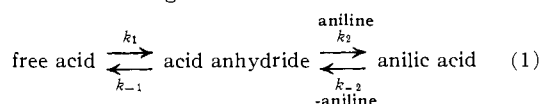
RECEIVED MARCH 21, 1963

The facilitative role of carboxylic grouping on formation and hydrolysis of certain amido acids is shown to be mediated by formation of acid anhydrides, which appears to be the rate-determining step. The mechanism is supported by (1) the pH-rate profile of conversion of succinic acid to succinic anhydride, (2) the pH profile of the reverse reaction, and (3) the independently determined pH profile of the equilibrium constant. The equilibrium concentration of the anhydride in water at 25° is estimated on this basis to be 2 parts per 10⁷ at 25° and 3 parts per 10⁶ at 95°. Citric acid, tartaric acid, and related di- and polycarboxylic acids are believed to react in similar fashion.

Introduction

In a recent preliminary communication¹ we have shown that certain dicarboxylic and polycarboxylic acids such as citric, tartaric, maleic, and succinic acids react relatively rapidly with aromatic amines in aqueous solution to form the corresponding amides. Detailed results of this and further studies elucidating the underlying mechanism responsible for the observed reaction are presented at this time.

Earlier rate measurements at 95° had suggested that the rate of amide formation in a solution of, for example, succinic acid and aniline was apparently second order, being proportional to the free acid and free amine concentrations. Measurements at higher free aniline concentrations and lower temperatures now indicate that under certain conditions the dependence on the amine may become substantially zero order. On this basis, the over-all reaction for a di- or polybasic acid with aniline, for example, is believed to proceed through the following series of reactions.



Data supporting this postulate and rate constants for the individual steps, both limited largely to the succinic acid-aniline interaction, are offered at this time.

Theoretical Considerations

Rate equations implicit in eq. 1 can be readily derived for certain fixed conditions. For the specific case consisting, for example, of a relatively low concentration of aniline in a large excess of succinate buffer we can formulate the relation as follows: Let A_0 represent the total initial concentration of aniline including both the protonated and the unprotonated species; A , the total aniline concentration at time t ; f_2 , the fraction of aniline in its free base form and equal to

$$\frac{K_a'/H^+}{1 + K_a'/H^+}$$

SH, the total concentration of the succinate buffer including the several ionized species; f_1 , the fraction of SH in the free acid form and equal to

$$\frac{1}{1 + K_{a1}/H^+ + K_{a1}K_{a2}/(H^+)^2}$$

$A_0 - A$, the total concentration of succinanic acid formed including both species; and f_{-2} , that fraction of the anilic acid in its free acid form and equal to $1/(1 + K_a/H^+)$. Since the concentration of the anhydride species would be expected to be always very small compared to those of other reactants and intermediates, it would be related to the concentrations of the primary reactants by

$$d[\text{anhyd.}]/dt = f_1 k_1 [\text{SH}] + f_{-2} k_{-2} (A_0 - A) - k_2 f_2 A [\text{anhyd.}] - k_{-1} [\text{anhyd.}] = 0$$

or

$$[\text{anhyd.}] = \frac{f_1 k_1 [\text{SH}] + f_{-2} k_{-2} (A_0 - A)}{k_{-1} + k_2 f_2 A}$$

If we assume that aniline is consumed only by the route indicated in (1), we have

$$dA/dt = f_{-2} k_{-2} (A_0 - A) - f_2 k_2 A [\text{anhyd.}]$$

Substituting this into the above, we have

$$\frac{dA}{dt} = \frac{k_{-1} f_{-2} k_{-2} (A_0 - A) - f_2 k_2 f_1 k_1 [\text{SH}] A}{k_{-1} + k_2 f_2 A} \quad (2)$$

$$= \frac{k_{-1} f_{-2} k_{-2}}{k_{-1} + k_2 f_2 A} \left[A_0 - A \left(1 + \frac{f_2 k_2 f_1 k_1 [\text{SH}]}{k_{-1} f_{-2} k_{-2}} \right) \right] \quad (3)$$

Equation 3 can be simplified by inserting equilibrium values of the components

$$\frac{f_{-2} (A_0 - A_\infty)}{f_1 [\text{SH}] f_2 A_\infty} = \frac{k_1 k_2}{k_{-1} k_{-2}}$$

where the subscript ∞ refers to equilibrium conditions or

$$\frac{A_0}{A_\infty} - 1 = \frac{k_1 k_2}{k_{-1} k_{-2}} \frac{f_2 f_1 [\text{SH}]}{f_{-2}} \quad (4)$$

Substituting eq. 4 into 3, we find

$$\frac{dA}{dt} = \frac{k_{-1} f_{-2} k_{-2}}{k_{-1} + k_2 f_2 A} \left[A_0 - \frac{A_0}{A_\infty} A \right] = \frac{k_{-1} f_{-2} k_{-2} A_0}{k_{-1} + k_2 f_2 A} \left[1 - \frac{A}{A_\infty} \right]$$

On integration we have

$$\frac{(f_2 k_2 / k_{-1})(A_0 / A_\infty)(A_0 - A)}{(A_0 / A_\infty) + A_0 f_2 k_2 / k_{-1}} + \ln \frac{A_0 - A}{A_0 - A_\infty} = \frac{f_{-2} k_{-2} (A_0 / A_\infty)^2 t}{(A_0 / A_\infty) + A_0 f_2 k_2 / k_{-1}} \quad (5)$$

Results and Discussion

The loss of aniline in a reacting system typical of those considered here is shown as a function of time in Fig. 1. The plot shows the residual concentration of

(1) T. Higuchi and T. Miki, *J. Am. Chem. Soc.*, **83**, 3899 (1961).