Protolytic Catalysis of Anilide Methanolysis. Spectator Catalysis of Leaving-Group Departure[1]

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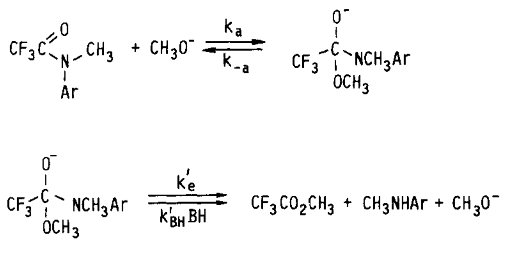
Substituted phenols serve as general-acid catalysts of leaving-group departure from the adduct of methoxide ion with m-$NO_2C_6H_4N(CH_3)COCF_3$ in methanol at 25 °C. Sufficiently high concentrations of general acid convert methoxide addition to the rate-limiting step, allowing determination of rate constants for methoxide addition to substrate carbonyl ($k_a = 300\ M^{-1}\ s^{-1}$), for overall solvent-assisted leaving-group departure ($k_e = k_a k_e'/k_{-a} = 5.9\ M^{-1}\ s^{-1}$) and for overall general-acid-catalyzed leaving-group departure ($k_{BH} = k_a k_{BH}'/k_{-a} = 2400 \pm 1200\ M^{-2}\ s^{-1}$ for five substituted phenols with pKa's from 12.7 to 14.6). Thus the Brønsted $\alpha \sim 0$. It is suggested that the general acid is a spectator at spontaneous expulsion of the leaving group, producing catalysis by fast subsequent trapping of CH_3NAr^-. The Jencks clock shows the tetrahedral intermediate to have a minimum characteristic lifetime of 1-10 ns.

Anilides undergo hydrolysis in a complex manner in basic aqueous solution. The kinetic law exhibits terms both first and second order in hydroxide ion, and the rate-determining step changes with base concentration.[3] Some simplification is achieved with methoxide-catalyzed methanolysis, which is simply first order in methoxide.[4] Solvent isotope effects for methanolysis indicate protolytic assistance by solvent in the departure of the leaving group.[4,5] Substituent effects show a strong increase in the amount of negative charge in the transition-state leaving group, as the substituents become more capable of stabilizing it.[4] Thus $\rho \sim 0$ for electron donors like p-OCH_3 in the anilide ring, but $\rho \sim 2.9$ for electron acceptors like m-NO_2 or p-NO_2. At the same time as the negative charge increases, the isotope effect associated with the catalytic proton decreases,[5] from around 7 for p-OCH_3 to around 2.6 with m-NO_2. These features indicate protolytic assistance of leaving-group departure, and in addition, the expected buffer catalysis is observed.[4]

In the present paper, we report an analysis of the buffer dependence of the rate of methanolysis of m-$NO_2C_6H_4N(CH_3)COCF_3$. Some information on the status of the catalyst in the transition state and on the lifetime of the tetrahedral intermediate is obtained.

Scheme I



Let $M = [CH_3O^-]$; $BH = [\text{Buffer acid}]$; $B = [\text{Buffer base}]$;
$k = k'k_a/k_{-a}$; k_o = observed first-order rate constant

$$k_o = \{k_a M\ (k'_e + k'_{BH}BH)\}/\{k_{-a} + k'_e + k'_{BH}BH\}$$

$$k_o = \{k_a M\ (k_e + k_{BH}BH)\}/\{k_a + k_e + k_{BH}BH\} \quad (1)$$

Table I. First-Order Rate Constants for the Methanolysis of m-$NO_2C_6H_4N(CH_3)COCF_3$ in Methanolic Buffers at 25.0 ± 0.1 °C ($\mu = 0.2$ M with $LiClO_4$)

buffer acid,[a] buffer ratio = [acid]/[base]	$10^4 k_o$,[b] s^{-1} ([buffer acid], M)
o-chlorophenol, 1.0	23.5 (0.10), 20.4 (0.08), 16.5 (0.06), 12.0 (0.04), 7.0 (0.02)
o-chlorophenol, 2.0	17.4 (0.20), 16.3 (0.16), 13.1 (0.12), 10.2 (0.08), 5.9 (0.04)
p-carbomethoxyphenol, 1.0	17.4 (0.10), 14.9 (0.08), 11.9 (0.06), 8.5 (0.04), 5.8 (0.02)
p-chlorophenol, 0.5	66.5 (0.05), 61 (0.02), 57 (0.015), 48 (0.01), 40 (0.005)
p-chlorophenol, 1.0	42.5 (0.10), 43.5 (0.08), 36.5 (0.06), 30.0 (0.04), 18.5 (0.02)
p-bromophenol, 1.0	55 (0.10), 49 (0.08), 40 (0.06), 35 (0.04), 25 (0.02), 21 (0.01)
p-methylphenol, 1.0	296 (0.10), 297 (0.08), 267 (0.06), 233 (0.04), 178 (0.02)

[a] Buffer bases added as sodium salts. [b] Mean of 3-5 determinations, reproducible within about 3%.

Results

The expected[3-5] mechanism and kinetic law are shown in Scheme I. Table I lists the observed rate constants, for a number of buffer solutions, of methanolysis of m-$NO_2C_6H_4N(CH_3)COCF_3$. The reaction is catalyzed by these buffers, but as shown in the upper part of Figure 1, the rate increase is less than proportional to the buffer concentration. This is in accord with the kinetic law of eq 1, Scheme I. Scheme II suggests a rearrangement of eq 1, to the form of eq 2, which should give a linear double-reciprocal plot. The lower part of Figure 1 shows that this is true. As Scheme II also demonstrates (see Appendix for details), the fact that the buffer induces a change in rate-determining step allows us to calculate the three characteristic rate constants k_a (addition of methoxide); k_e (overall solvent-catalyzed elimination); and k_{BH} (overall

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[1] This research was supported by the National Institutes of Health and the National Science Foundation.

[2] Currently a member of the Department of Natural Sciences, University of North Florida, Jacksonville, FL 32216.

[3] Kershner, L. D.; Schowen, R. L. J. Am. Chem. Soc. 1971, 93, 2014. Drake, D.; Schowen, R. L.; Jayaraman, H. Ibid. 1973, 95, 454.

[4] Schowen, R. L.; Hopper, C. R.; Bazikian, C. M. J. Am. Chem. Soc. 1971, 94, 3095. See also: Broxton, T. J.; Deady, L. W. Tetrahedron Lett. 1973, 3915. Broxton, T. J.; Deady, L. W.; Williams, P. R. A. Aust. J. Chem. 1974, 27, 1053. Broxton, T. J.; Deady, L. W.; Lim, R. H. K. Ibid. 1981, 34, 1993 and intervening papers.

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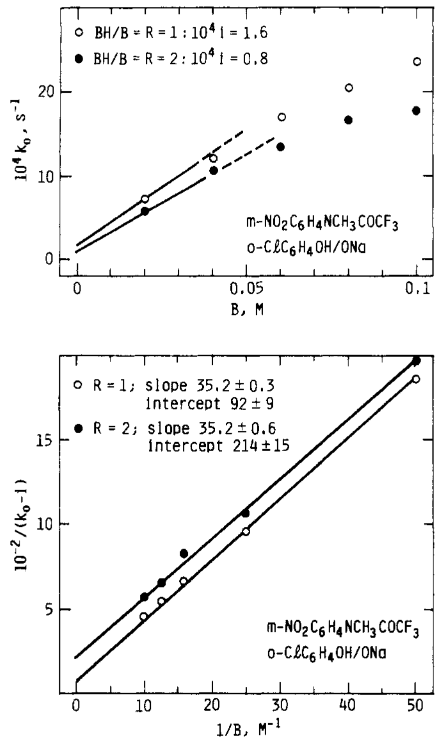


Figure 1. Upper panel: nonlinear dependence of k_0 on *o*-chlorophenol buffer concentration, showing extrapolation to obtain i at $B = 0$. Lower panel: double-reciprocal plot according to eq 2 of Scheme II. Note that, as found, the slopes should be identical for the two buffer ratios. The intercepts should be related by a factor of 2, which is only roughly true.

Scheme II

Let: i = intercept of k_0 vs. B at constant R, where $R = BH/B$

Then: $i = k_M M = k_a k_e M/(k_a + k_e)$

$k_0 = \{k_a M(k_e + k_{BH}RB)\}/\{k_a + k_e + k_{BH}RB\}$

$(k_0 - i) = \{k_a^2 k_{BH} MRB\}/\{(k_a + k_e)(k_a + k_e + k_{BH}RB)\}$

$$1/(k_0 - i) = [(k_a + k_e)/k_a M]\left\{\frac{(k_a + k_e)}{k_a k_{BH} R} \bullet \frac{1}{B} + \frac{1}{k_a}\right\} \quad (2)$$

For $1/(k_0 - i)$ vs. $1/B$ at constant R, M:

slope $= [(k_a + k_e)/k_a]^2/k_{BH}RM$

intercept $= (k_a + k_e)/k_a^2 M$

$i \bullet$ intercept $= k_e/k_a$

$[(k_e/k_a) + 1]\,k_M = k_e$

$[(k_e/k_a) + 1]^2/\text{slope} \bullet RM = k_{BH}$

general-acid-catalyzed elimination).

The data shown in Figure 1 for *o*-chlorophenol buffers give $k_a/k_e \sim 68$ ($R = 1$), 58 ($R = 2$). The most reliable of the remaining buffer data, together with these, suggest that $k_a/k_e \sim 50 \pm 20$. Thus, since we know that $k_M = 5.75\ M^{-1}\ s^{-1}$, $k_a \sim 300\ M^{-1}\ s^{-1}$ and $k_e \sim 5.9\ M^{-1}\ s^{-1}$. As previously supposed,[4,5] elimination determines the rate almost wholly for the methoxide-catalyzed reaction.

Values of k_{BH} were estimated from plots like those of Figure 1 for each of the phenol buffers studied and are presented in Table II. They are not of high reliability, but it is clear that k_{BH} does not vary greatly or systematically with the acidity of the general catalyst. An attempted Brønsted correlation gives $\alpha = 0.07 \pm 0.15$.

Discussion

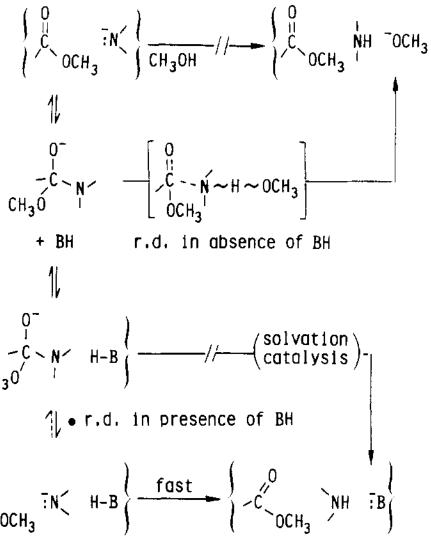
These results, taken together with earlier studies of substituent effects and solvent isotope effects, suggest the mechanistic picture of Scheme III. This should be valid *only for reactive leaving groups* such as the *N*-methyl-*m*-nitroaniline under examination here.

Table II. Estimated General-Acid-Catalytic Constants for XC_6H_4OH in Overall Leaving-Group Expulsion from the Methoxide Adduct of $m\text{-}NO_2C_6H_4N(CH_3)COCF_3$

X	pK_a	k_{BH}, $M^{-2}\ s^{-1}$
o-Cl	(12.7)[a]	1200
p-CO_2CH_3[4]	13.2[b]	2700
p-Cl	13.7[c]	3600
p-Br	13.6[d]	2700
p-CH_3	14.6[c]	1800

[a] Estimated from the methoxide concentration in the buffers, as measured from the "uncatalyzed" component of the methanolysis rate. [b] Mitton, C. G.; Schowen, R. L.; Gresser, M.; Shapley, J. *J. Am. Chem. Soc.* **1969**, *91*, 2036. [c] Schowen, R. L.; Latham, K. S., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 4677. [d] Rochester, C. H.; Rossall, B. *J. Chem. Soc. B* **1967**, 743.

Scheme III



The substituent effects for the solvent-catalyzed reaction[4] indicate $\rho \sim 2.9$, showing that some negative charge is present in the leaving group at the transition state. Solvent isotope effects[4,5] are consistent with a catalytic bridge with an isotope effect contribution of 2–3, such as is observed in "solvation catalysis",[6] as depicted in the upper part of Scheme III. If the reaction had proceeded by rapid C–N bond fission and rate-limiting proton transfer from solvent to CH_3NAr^-, which might also generate a ρ value around 3, a larger isotope effect would have been anticipated. Thus *if* C–N bond fission is occurring unimolecularly, very rapid recombination to return to the tetrahedral intermediate must prevent protolytic trapping of CH_3NAr^- by the weakly acidic methanol solvent.

When a general acid such as a phenol, some 10^2–10^4 times more acidic than methanol, is present in a common solvent cage with the tetrahedral intermediate, however, it may trap the CH_3NAr^- on essentially every event of its formation. This, as shown in the lower part of Scheme III, allows for effective catalysis by BH while not postulating any interaction between BH and the decomposing tetrahedral intermediate in the rate-limiting transition state for C–N bond fission. Thus $\alpha = 0$ for this mechanism. The general acid is a "spectator" during the bond fission, and the catalysis is of the type we have called *spectator catalysis*[3] and Jencks and his school have elucidated very

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(6) Swain, C. G.; Kuhn, D. A.; Schowen, R. L. *J. Am. Chem. Soc.* **1965**, *87*, 1553.

intensively as *preassociation catalysis*.[7]

It is conceivable that the diffusional approach of BH to the tetrahedral adduct is the rate-limiting step. Since this is the fastest catalytic action possible for BH, it enables us to set a minimum lifetime for the tetrahedral intermediate, by use of the Jencks clock.[8] For the various phenols in Table II, k_{BH} averages around 2400 $M^{-2}\ s^{-1}$. We recall that $k_{BH} = k_a k'_{BH}/k_{-a}$ and that $k_a \sim 300\ M^{-1}\ s^{-1}$: thus $(k'_{BH}/k_{-a}) \sim 8\ M^{-1}$. Then if k'_{BH} had its maximum value of, say, $10^{9-10}\ M^{-1}\ s^{-1}$, k_{-a} would have its maximum value of around $10^{8-9}\ s^{-1}$. Of course k'_{BH} may by smaller (if events after diffusion together of BH and adduct limit the rate); then k_{-a} will be proportionally smaller. Therefore the tetrahedral adduct must have a characteristic lifetime of at least 1–10 ns.

Experimental Section

Materials. The substrate m-$NO_2C_6H_4N(CH_3)COCF_3$ was available from previous work.[3,5] p-Bromophenol and p-chlorophenol, both from Eastman Kodak, were recrystallized from petroleum ether (30–60 °C), o-chlorophenol and p-cresol were distilled at reduced pressure, and methyl p-hydroxybenzoate (Matheson, Coleman and Bell) was used as supplied. Methanol was purified by the method of Lund and Bjerrum[9] but gave identical results when used as supplied (Mallinckrodt reagent grade). Sodium methoxide solutions were prepared by dissolution of cleaned metallic sodium, stored in polyethylene, and standardized against potassium hydrogen phthalate with phenolphthalein. Buffers were prepared by dilution of weighed samples of phenol with appropriate volumes of methanol and sodium methoxide solutions.

Kinetics. Buffer solutions (2.5 mL) were thermostated in a 10-mm cuvet in the constant-temperature cell holder of a Cary 16 or Beckman DB spectrophotometer, at 25.0 ± 0.1 °C. To initiate reaction, 10 μL of a stock solution of substrate were injected with an Eppendorf pipet. Absorbances at 390 nm were collected to 80% reaction, the final absorbance was read after 10 half-life times, and first-order rate constants were calculated by a nonlinear least-squares method.

Appendix

Derivation of eq 2. See Scheme II for definitions of k_0 and i; then

$$k_0 - i = \frac{k_a M(k_e + k_{BH}RB)}{k_a + k_e + k_{BH}RB} - \frac{k_a k_e M}{k_a + k_e}$$

$$k_0 - i = \frac{{k_a}^2 k_{BH} MRB}{(k_a + k_e + k_{BH}RB)(k_a + k_e)}$$

$$k_0 - i = \left(\frac{k_a M}{k_a + k_e}\right)\left(\frac{k_a k_{BH} RB}{k_a + k_e + k_{BH}RB}\right)$$

$$\frac{1}{k_0 - i} = \left(\frac{k_a + k_e}{k_a M}\right)\left(\frac{k_a + k_e + k_{BH}RB}{k_a k_{BH} RB}\right)$$

$$\frac{1}{k_0 - i} = \left\{\frac{k_a + k_e}{k_a M}\right\}\left\{\left(\frac{k_a + k_e}{k_a k_{BH} R}\right)\left(\frac{1}{B}\right) + \frac{1}{k_a}\right\} \qquad (2)$$

Registry No. m-$NO_2C_6H_4N(Me)COCF_3$, 32368-22-2.

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[7] Jencks, W. P.; Salvesen, K. *J. Am. Chem. Soc.* **1971**, *93*, 1419. Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425.

[8] Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161.

[9] Lund, H.; Bjerrum, I. *Ber.* **1931**, *64*, 210.

Aluminum Chloride Catalyzed Reaction of Acetanilide with Pivalyl Chloride

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Product development was studied in the aluminum chloride catalyzed reaction of acetanilide with pivalyl chloride. 3-*tert*-Butylacetanilide is the major product because of its relative resistance to dealkylation by reaction-produced HCl. At long reaction times all alkylation products are converted back to acetanilide with the only survivor being 2,2-dimethyl-5-*tert*-butyl-7-acetamidoindanone. The crystal structure of this compound was determined. It crystallized in the space group P_{nma} with cell constants a = 12.571 (3) Å, b = 7.302 (1) Å, c = 16.910 (3) Å, V = 1552.24 Å^3, z = 4. Refinement of the 1224 data with $F^2 \geq 3\sigma(F^2)$ resulted in discrepancy indices R_1 = 0.056 and R_2 = 0.074. A novel mechanism for formation of this indanone is proposed, involving nucleophilic attack by alkene on a protonated arene ring.

In the course of our research we found it necessary to prepare ring-substituted pivalophenones. The literature indicates that Friedel–Crafts acylation with pivalyl chloride (PC) is successful when promoted by electron-donating substituents but gives *tert*-butyl substitution with unactivated aromatic compounds. Benzene, for example, gives 4-*tert*-butylpivalophenone and *tert*-butylbenzene but no unsubstituted pivalophenone.[1] Anisole gives 4-methoxypivalophenone, but acetanilide is reported to react with PC in chloroform to give 4-*tert*-butylacetanilide (4-BA) in 55% yield along with recovered acetanilide and no ketonic products.[2] Hoping to redirect this latter reaction by changing the conditions, we studied the reaction of acetanilide with PC and $AlCl_3$ in both CH_2Cl_2 and CS_2. No pivalylation product was formed and, the ortho–para-directing reputation of the acetamido group not withstanding, the major product turned out to be 3-*tert*-butylacetanilide (3-BA). We also isolated a ketone, but this was not 4-pivalylacetanilide. We became sufficiently interested to follow product development and to identify the ketonic compound.

Results

The product distribution for the $AlCl_3$-promoted reaction of PC with acetanilide was followed as a function of added PC and time. The results are displayed in Table I. It may be seen that although the acetanilide recovery

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[1] Pearson, D. E. *J. Am. Chem. Soc.* **1950**, *72*, 4169.

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