Mechanism of the Basic Methanolysis of Benzanilides

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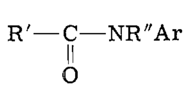
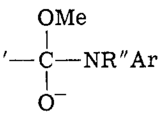
The rate constants for the basic methanolysis of a series of benzanilides (PhCONMeAr), unlike those for the corresponding acetanilides, give a linear Hammett plot. One mechanism operates throughout and is not affected by a change in the acyl aryl substituent. The results are consistent with rate-determining breakdown of the tetrahedral intermediate *via* a transition state involving solvent-assisted C–N bond cleavage.

There is considerable current interest[1] in the details of the basic hydrolysis and alcoholysis of amides. One characteristic feature that has emerged is that, for simple acyclic anilides (1, R′ = H,[1] CH_3,[2,3] CF_3[4]), the Hammett plot for aryl-substituted compounds is curved (the apparent ρ value increases with an increase in the electron-withdrawing power of the substituent). This has been interpreted[4] as being due to a change in the mechanism for the rate-determining breakdown of the intermediate (**2**, for methanolysis) with change in the aryl substituent. Examples of the two extreme transition states are illustrated in **3** and **4**.



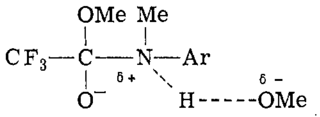
$R'{-}C({=}O){-}NR''Ar$

1



$R'{-}C(OMe)(O^-){-}NR''Ar$

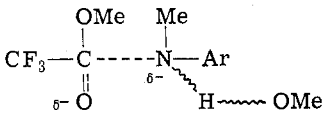
2



3

poor leaving group

$\rho = 0$ (ref 4)

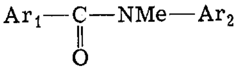


4

good leaving group

$\rho = 2.9$ (ref 4)

We decided to investigate the analogous reaction of *N*-methylbenzanilides (**5**),[5] since it was reasoned that the substituent dependence of Ar_1 on rate would vary according to the mechanism of the reaction, determined by the nature of Ar_2. This would then provide another diagnostic probe for investigating such mechanistic changes. The existing data[6,7] on benzanilide reactivity were insufficient to provide the required information and, as they were derived from reaction of the NH compounds, were presumably also complicated by conjugate base formation. We report here a detailed study of substituent effects on the basic methanolysis of *N*-methylbenzanilides where we have found in fact that the complexities evident in the acetanilide system do not occur.



$Ar_1{-}C({=}O){-}NMe{-}Ar_2$

5a, Ar_1 = Ph; Ar_2 variable
b, Ar_1 variable; Ar_2 = p-$NO_2C_6H_4$
c, Ar_1 variable; Ar_2 = Ph

Results and Discussion

Three series (**5a–c**) of substituted *N*-methylbenzanilides were prepared and their rates of basic methanolysis were measured by a standard spectrophotometric method under pseudo-first-order conditions. The complete kinetic results are given in Table I.

The original aim of the product was voided when the results of series **5a** were obtained. Surprisingly, these data give a linear Hammett plot (using σ^- values for p-NO_2 and p-CO_2Me substituents) with a ρ_2 value of 2.5 (373°K). Thus, unlike for the acetanilides, this reaction proceeds *via* the same rate-determining transition state irrespective of the substituent. The change of acyl substituent from alkyl to phenyl is sufficient to overcome any effect of substituent in Ar_2 on the mechanism.

The question then arose as to whether changes in Ar_1 could cause a change in mechanism in a series in which the substituent in Ar_2 was kept constant. Results from series **5b** and **5c** showed that this is not the case. Again the Hammett plots for the data from each series are linear (σ value for NO_2 substituents), indicating the occurrence of one common mechanism. The agreement of the ρ_1 values [1.73 (339°K) and 1.76 (373°K), respectively] is probably fortuitous because of the different temperatures involved. However, from the linear plots and similar ρ values, one can conclude that the reaction proceeds by the same mechanism through essentially the same transition state for the complete reactivity range from **5b** (Ar_1 = m-$NO_2C_6H_4$; Ar_2 = p-$NO_2C_6H_4$) to **5c** (Ar_1 = p-$MeOC_6H_4$; Ar_2 = Ph). The change of acyl substituent from alkyl (acetanilides) to aryl produces a far greater effect on the mechanism than does any variation in the aryl group.

All the results are consistent with a common mechanism proceeding *via* a transition state analogous to **4**, *i.e.*, solvent-assisted C–N bond cleavage. The ρ_2 value for series **5a** is very similar to that found[4] by Schowen for the trifluoroacetanilide reaction proceeding through this transition state and the lower, but appreciable, ρ_1 values in **5b** and **5c** are consistent with this mechanism.

The alternative extreme mechanism involving breakdown of the tetrahedral intermediate, *viz.*, rate-determining protonation of the nitrogen, **3**, is not compatible with the results. Reaction *via* this transition state has been shown[4] to have a low ρ_2 value and ρ_1 would also be expected to be much smaller for protonation at the distant nitrogen than was experimentally observed. For example, ρ = 1.05 (298°K) for the dissociation of substituted benzylammonium ions.[8] In addition, the large rate enhancement observed at both ends of the reactivity scale on changing the solvent to 80% DMSO–methanol (a factor of 454 at 286.5°K for $PhCONMeC_6H_4NO_2$-p and 330 at 373°K for PhCONMePh) is consistent with reaction by way of **4** but not **3** (in which a negligible solvent effect occurs).[9]

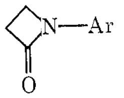
The unlikely possibility that the rate-determining step has changed from breakdown to formation of the tetrahedral intermediate is readily discounted. In such a situation ρ_1 would be expected to be greater than ρ_2. This is found in the $B_{Ac}2$ mechanism of ester hydrolysis. For example, the hydrolysis of Ar_1COOEt and CH_3COOAr_2 in aqueous acetone at 273°K give[10] $\rho_1 = 2.6$ and $\rho_2 = 1.65$. Anilide hydrolysis studies[1,2,11] have established that the ρ_2 value for hydroxide attack on the carbonyl group is

Table I
Kinetic Data for the Basic Methanolysis (MeO^- = 5×10^{-3} to 0.1 *M*) of Some *N*-Methylbenzanilides[a] ($XC_6H_4CONMeC_6H_4Y$) and *N*-Arylazetidinones[a]

Registry no.	Series	X	Y	Analyt. λ, nm	Temp, °K	$10^3 k_2$, M^{-1} sec^{-1}
33675-68-2	**5a**	H	*p*-MeO	232	373	0.16
1934-92-5	**5a,c**	H	H	233	373	0.32
51774-34-6	**5a**	H	*p*-Br	309[b]	373	2.09
51774-35-7	**5a**	H	*m*-Br	302[b]	373	4.09
51774-36-8	**5a**	H	*p*-CO_2Me	304	373	29.6
51774-37-9	**5a**	H	*m*-NO_2	230	373	61.0
33672-82-1	**5a**	H	*p*-NO_2	385	373	525[c]
51774-38-0	**5b**	*p*-MeO	*p*-NO_2	385	339	28.0
51774-39-1	**5b**	*p*-Me	*p*-NO_2	385	339	39.5
	5b	H	*p*-NO_2	385	339	62.1
51774-40-4	**5b**	*p*-Cl	*p*-NO_2	385	339	201
51774-41-5	**5b**	*m*-Cl	*p*-NO_2	385	339	320
51774-42-6	**5b**	*m*-NO_2	*p*-NO_2	385	339	1310
33672-81-0	**5c**	*p*-MeO	H	254	373	0.19
51774-43-7	**5c**	*m*-Cl	H	238	373	2.10
51774-44-8	**5c**	*m*-NO_2	H	248	373	8.6
961-61-5	**5c**	*p*-NO_2	H	250	373	10.8
5099-95-6	**6**	H		250	304	2.65
38560-29-1	**6**	*m*-NO_2		390	304	85.5
19018-01-0	**6**	*p*-NO_2		380	304	427

[a] Substrate ~1×10^{-4} *M*. [b] Substrate ~5×10^{-4} *M*. [c] By extrapolation, 7.00 (310°K), 16.3 (321°K), 62.1 (339°K); E_a = 15.7 kcal mol^{-1}; ΔS_{298}^* = −20 eu.

~1.3. We have briefly examined methanolysis in one model amide system to confirm the expected lower susceptibility to *N*-aryl substituents in this mechanism. Recent work[12] has shown that, because of a rate-enhancing relief of steric strain in the breakdown of the intermediate, the hydrolysis of *N*-arylazetidinones (**6**) proceeds by



6

rate-determining hydroxide attack. We have measured the rates of basic methanolysis of three of these compounds. The results are given in Table I, and the Hammett plot (using σ^- for *p*-NO_2) gives ρ_2 = 1.7 (304°K). This is somewhat greater than that found[12] for hydrolysis (1.25) but is much less than ρ for the benzanilide reaction (especially when the temperature difference is considered).

There seems no doubt then that the mechanism of *N*-methylbenzanilide methanolysis proceeds by rate-determining breakdown of the tetrahedral intermediate *via* a transition state analogous to **4**.

The occurrence of linear (benzanilides) *vs.* nonlinear (acetanilides) Hammett plots clearly illustrates that the transition state is determined by the acyl substituent as well as by the leaving group. The effect of an aryl group on the acyl carbon is to give a pseudo-improvement in the leaving group nature of the amine. This presumably comes about because the aryl substituent can conjugate with the developing carbonyl bond. This favorable interaction provides additional impetus to C–N bond cleavage and prior protonation is now unnecessary for the poorer leaving groups.

Understandably, σ^- values are needed to correlate the data for the resonance-withdrawing substituents (*p*-NO_2 and *p*-CO_2Me) in Ar_2 in the rate-determining CN cleavage mechanism. It is worthy of note that in this and other studies[1,11,12] it has also been found necessary to use σ^- values to correlate data for methoxide and hydroxide attack on the distant carbonyl group. The same does not apply in the analogous ester reaction[10] and indicates the greater resonance interaction between the carbonyl group and nitrogen of an amide than oxygen of an ester.

Experimental Section

***N*-Methylanilines.** *N*-Methylaniline and *p*-*N*-methylaminobenzoic acid were commercial samples. Esterification of the latter (MeOH-sulfuric acid) gave methyl *p*-*N*-methylaminobenzoate, mp 94–95° (lit.[13] mp 95.5°). *p*-Nitro-*N*-methylaniline, mp 149° (lit.[14] mp 152°), was prepared from methylamine and *p*-chloronitrobenzene. *m*-Bromo-, *p*-bromo-, *p*-methoxy-, and *m*-nitro-*N*-methylaniline were prepared[11,15] from the corresponding acetanilides.

3′- and 4′-Substituted *N*-Methylbenzanilides (5a). These were prepared by reaction of benzoyl chloride with the appropriately substituted *N*-methylaniline under Schotten–Baumann conditions. The products were extracted with ether, washed with water, dried, concentrated, and chromatographed (silica–ethyl acetate). They were then recrystallized or distilled and are described in Table II.

4′-Methoxycarbonyl-*N*-methylbenzanilide was prepared by the same method, but in dry tetrahydrofuran solvent. An attempted synthesis under Schotten–Baumann conditions resulted in hydrolysis of the ester group.

3- and 4-Substituted *N*-Methyl-4′-nitrobenzanilides (5b). These were prepared by reaction of a solution of *N*-methyl-*p*-nitroaniline (7 g, 0.05 mol) in dry tetrahydrofuran (40 ml) with a solution of the substituted benzoyl chloride (0.05 mol) in dry tetrahydrofuran (20 ml). After addition was complete, the mixture was refluxed (1 hr), then cooled and evaporated to dryness. Water was added and the benzanilide was filtered off and recrystallized from ethanol. The products are described in Table II.

3- and 4-Substituted *N*-Methylbenzanilides (5c). These were prepared by reaction of a solution of *N*-methylaniline (0.1 mol) in dry tetrahydrofuran (20 ml) with the substituted benzoyl chloride (0.05 mol) in dry tetrahydrofuran. The mixture was refluxed (1 hr), then cooled and evaporated to dryness. The residue was dissolved in chloroform and washed with 1 *M* hydrochloric acid (3 × 100 ml), 2 *M* sodium hydroxide (3 × 50 ml), and water (2 × 100 ml), then dried and concentrated. The products were recrystallized from ethanol–water and are described in Table II.

***N*-Arylazetidinones (6).** These were prepared as described[12] by Blackburn and Plackett.

Rate Measurements. The methanolysis reactions, which were first order under the conditions used, were followed spectrophotometrically using a Varian-Techtron 635 recording spectrophotometer. Details of concentrations and analytical wavelengths are given in Table I. Reactions in series **6** were carried out in ther-

Table II
Properties of *N*-Methylbenzanilides

Substituents	Mp or bp, °C (mm)	Lit. mp, °C	Formula[g]
4′-NO_2	109	111–112[a]	
4′-NO_2	147.5–148.5		$C_{14}H_{11}ClN_2O_3$
4′-NO_2-4-MeO	74–75		$C_{15}H_{14}N_2O_4$
3,4′-di-NO_2	140–141		$C_{14}H_{11}N_3O_5$
4′-NO_2-4-Cl	90–92		$C_{14}H_{11}ClN_2O_3$
4′-NO_2-4-Me	89–91		$C_{15}H_{14}N_2O_3$
3′-NO_2	102–103		$C_{14}H_{12}N_2O_3$
3′-Br	214–218 (15)		$C_{14}H_{12}BrNO$
4′-Br	72–73	77[b]	
H	55–57	63[a]	
4′-MeO	76–78	79–80[c]	
4′-CO_2Me	63		$C_{16}H_{15}NO_3$
4-NO_2	109–110	110–111[d]	
3-NO_2	107–109	109[e]	
3-Cl	33–35	40[f]	
4-MeO	Oil, tlc pure		$C_{15}H_{15}NO_2$

[a] See ref 14. [b] F. B. Dains and F. Eberly, *J. Amer. Chem. Soc.*, **55**, 3859 (1933). [c] F. W. Bentley and R. A. W. Johnstone, *J. Chem. Soc. B*, 1804 (1971). [d] R. N. Ring, J. G. Sharefkin, and D. Davidson, *J. Org. Chem.*, **27**, 2428 (1962). [e] D. H. Hey and R. A. J. Long, *J. Chem. Soc.*, 4110 (1959). [f] P. Grammaticakis, *Bull. Soc. Chim. Fr.*, 862 (1963). [g] Satisfactory analytical data were obtained for all new compounds listed.

mostatted cuvettes in the spectrophotometer, while sealed ampoules were required for the higher temperature reactions in series 5. First-order rate constants were calculated graphically from plots of log ($D_\infty - D_t$) *vs.* time. All rate constants listed in Table I are averages of two or more runs, with agreement between runs being within 4%.

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Synthetic Reactions by Complex Catalysts. XXXII. Reaction of *o*-Xylylene Halides with Copper–Isonitrile Complex. *o*-Xylylene Intermediates

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The system of *o*-xylylene halide with Cu(0)–*tert*-butyl isocyanide was subjected to the reaction with an electron-deficient olefin such as acrylate, fumarate, and maleate. In the case of *o*-xylylene dibromide, tetrahydronaphthalene derivative **3** was produced in a moderate yield. As one of possible mechanisms, an unstable intermediate of *o*-xylylene (**6**) was proposed. The system of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene with Cu(0)–*tert*-butyl isocyanide reacted with an electron-deficient olefin to produce naphthalene derivatives (**4**). Similarly, the intermediacy of α,α'-dibromo-*o*-xylylene (**7**) was proposed for the production of 1,4-dibromotetrahydronaphthalene followed by dehydrobromination to the final naphthalene derivative. In the case of *o*-xylylene dichloride, tetrahydronaphthalene derivative (**3**) as well as the dihydronaphthalene derivative (**5**) were produced, for which two *o*-xylylene intermediates (**6** and **8**) were presented, respectively. Concerning the formation of **6** and **8**, the effect of substituents in the aromatic ring on the product ratio of **5** to **3** was examined. The ratio of **5** to **3** increases with the increase of σ^+ of the substituent.

Intramolecular dehalogenation of *o*-xylylene dihalide by means of a transition metal has provided a convenient route[1] leading to the transient formation of a reactive intermediate of *o*-xylylene. Metallic iron has often been used for this purpose.[2] Roth and Meier[3] succeeded in the isolation of unstable *o*-xylylene in the form of a stable π complex with iron tricarbonyl in the reaction of *o*-xylylene dibromide with diiron nonacarbonyl.

The present paper deals with systems in which *o*-xylylene halides are treated with Cu(0)–*tert*-butyl isocyanide in the presence of an electron-deficient olefin. In the course of our investigations of copper–isonitrile complexes,[4] we found that metallic copper was dissolved in liquid isonitrile under nitrogen to form a soluble complex. The complex exhibited a broad, unresolved esr signal (g value = 2.0041), which was taken to suggest a Cu(0)–isonitrile species. Interestingly, the Cu(0)–isonitrile complex[4] was found to react with the carbon–halogen bond and sometimes the carbon–hydrogen bond to form the organocopper–isonitrile complexes. In these reactions, the oxidative additions of the carbon–halogen bond and of the carbon–hydrogen bond, respectively, onto the Cu(0)–isonitrile complex may probably be assumed. For example, the Cu(0)–isonitrile complex reacts with benzyl halide to give a benzylcopper–