THE EFFECT OF DMSO ON THE BASIC METHANOLYSIS OF ANILIDES
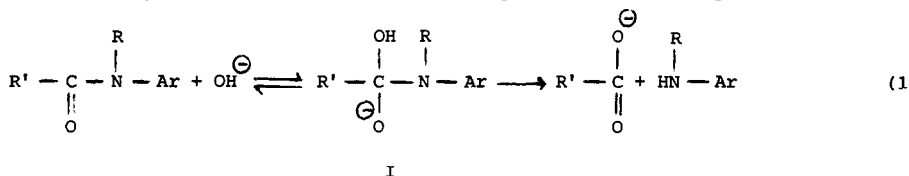
T.J. Broxton and L.W. Deady,

Department of Organic Chemistry, La Trobe University,
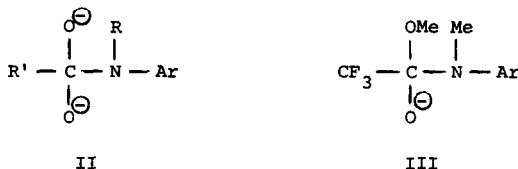
Bundoora, Vic. 3083, Australia

Recent detailed kinetic studies[1] of basic amide hydrolysis have shown that a complex mechanism is involved. Overall, the reaction is summarised in equation (1) where either the formation of I or its decomposition can be rate-determining. The intermediacy of a bianionic

$$R' - \overset{\overset{\displaystyle R}{|}}{\underset{\underset{\displaystyle O}{||}}{C}} - \overset{\overset{\displaystyle R}{|}}{N} - Ar + OH^{\ominus} \rightleftharpoons R' - \overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle O}{\underset{\ominus|}{|}}}{C}} - \overset{\overset{\displaystyle R}{|}}{N} - Ar \longrightarrow R' - \overset{\overset{\displaystyle \overset{\ominus}{O}}{|}}{\underset{\underset{\displaystyle O}{||}}{C}} + H\overset{\overset{\displaystyle R}{|}}{N} - Ar \qquad (1$$

$$I$$

intermediate, II, under certain conditions further complicates the mechanism.

$$R' - \overset{\overset{\displaystyle \overset{\ominus}{O}}{|}}{\underset{\underset{\displaystyle O\ominus}{|}}{C}} - \overset{\overset{\displaystyle R}{|}}{N} - Ar \qquad\qquad CF_3 - \overset{\overset{\displaystyle OMe}{|}}{\underset{\underset{\displaystyle O\ominus}{|}}{C}} - \overset{\overset{\displaystyle Me}{|}}{N} - Ar$$

$$II \qquad\qquad\qquad III$$

The effect of a solvent change on anilide hydrolysis has only recently been reported.[2] A study of the basic hydrolysis of some aryl substituted N-methylacetanilides in DMSO-water gave results which were interpreted as indicating a change in rate-determining step from breakdown of I for electron donor aryl substituents to formation of I for strong withdrawing substituents. From similar solvent effect studies on a related reaction we wish to show that this explanation is not the only one compatible with the results and will not, in fact, fit other experimental evidence.

We have carried out a study of basic methanolysis of some aryl substituted N-methyl-2,2,2-trifluoroacetanilides in DMSO-methanol since, in a recent study[3] of this reaction, Schowen and co-workers presented considerable evidence in favour of rate-determining breakdown of III to products, irrespective of the aryl substituent. Basic methanolysis can

be represented essentially by a similar scheme to equation (1) but is mechanistically simpler

than is hydrolysis, since intermediate II is not possible.

The experimental procedure followed was essentially that detailed by Schowen.[3]

Good pseudo first order kinetics were obtained and the reaction was shown to be first order

in methoxide. The second order rate constants for the three compounds studied, in the

various solvents, are listed in the Table and represent average values for duplicate runs,

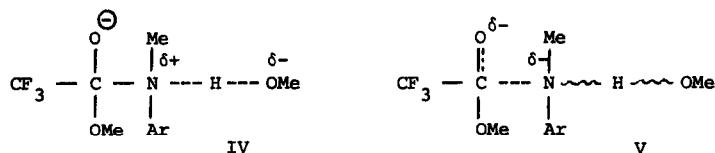reproducible to ±2%. It is clear that there is a marked dependence of the solvent effect

TABLE

Kinetic data ($10^2 k_2 M^{-1} s^{-1}$) for the basic methanolysis

$(MeO^{\ominus} = 10^{-2} - 10^{-4} M)$ of $X-C_6H_4-NMe-COCF_3$

X	MeOH	50% DMSO	80% DMSO	$\dfrac{k_{50\% \text{ DMSO}}}{k_{MeOH}}$
p-MeO[a]	5.89	7.43	25.8	1.4
H[b]	9.77	17.7	249	1.8
m-NO$_2$[c]	162	12800	d	79

[a] T = 298K   [b] T = 296K   [c] T = 284K   [d] Too fast to be measured

on the nature of the substituent. These results are rather similar to those observed in the

recent hydrolysis study,[2] though we have studied a higher DMSO content solvent.

In the hydrolysis work it was reasoned that, for a strong electron withdrawing

substituent, the rate enhancement observed on addition of DMSO (of the order of that

commonly found in anion-neutral molecule reactions)[4] indicated that formation of I, i.e.,

hydroxide addition, was rate-determining. We believe that our results are compatible with

rate-determining breakdown of the tetrahedral intermediate III irrespective of the aryl

substituent; a spectrum of transition states occurs depending on the relative extent of

proton transfer from the solvent, and C-N bond cleavage, in the rate-determining transition

state. The two ends of the range are depicted in structures IV and V.

$$\begin{array}{ccc}
\overset{\ominus}{O} & Me & \\
\| & | \delta{+} & \delta{-} \\
CF_3 - C - N & --- H --- OMe \\
| & | & \\
OMe & Ar & \\
& IV &
\end{array}
\qquad
\begin{array}{ccc}
\overset{\delta{-}}{O} & Me & \\
\| & \delta{-}| & \\
CF_3 - C --- N \sim\sim\sim H \sim\sim\sim OMe \\
| & | & \\
OMe & Ar & \\
& & V
\end{array}$$

For a poor leaving group (Ar = p-MeOC$_6$H$_4$), proton transfer from the solvent to the nitrogen of the departing amine is rate-determining (IV). This transition state is rather "alkoxide like" in that a new methoxide ion is generated during proton transfer. Thus the rate enhancing desolvation of the methoxide reactant in DMSO-methanol is opposed by rate-diminishing desolvation of the developing methoxide ion generated in the decomposition step. The small solvent effect observed for the methoxy substituted compound indicates that the two effects almost cancel.

For a good leaving group (Ar = m-NO$_2$C$_6$H$_4$), C-N bond cleavage is rate-determining in a solvent assisted breakdown of the intermediate (V). Therefore, there is net charge dispersal in this transition state with respect to reactants. A large rate enhancement occurs in DMSO-methanol, in accord with aprotic solvent effects on anion-neutral molecule reactions.

Hammett[5] correlations of the rates of basic hydrolysis and methanolysis of aryl substituted anilides show a characteristic curvature;[1,3] the apparent rho value increases with the electron withdrawing nature of the substituent. This behaviour is incompatible with a change in rate-determining step. From various studies on anilide hydrolysis, it has been established that the rho value for the addition step is around 1.2,[1,6,7] while that for the decomposition step with good leaving groups is much greater (3-11).[3,8] Therefore, if a change in rate-determining step occurred from breakdown of III (poor leaving group) to formation of III (good leaving group), a point would be reached at which the apparent rho value decreased with a further increase in substituent electron withdrawing effect. This is not observed.

A detailed Hammett study has not been carried out in this study in DMSO-methanol. However, the large difference in response to solvent change at each end of the substituent activation scale shows that the curvature in such a plot would be even greater than it is

in methanol. Thus the argument is valid in either solvent system and the rate-determining step does not change with a change in substituent. It is on this basis that we have interpreted the solvent effects in the methanolysis reaction in terms of rate-determining breakdown of III for all the compounds studied, a mechanism which has been well documented.[3] The similarity in behaviour of the hydrolysis and methanolysis reactions leads us to conclude that this interpretation will also explain the solvent effects observed in the hydrolysis reaction.

REFERENCES

1.   R.H. De Wolfe and R.C. Newcomb, J. Org. Chem., 36, 3870 (1971), provides a compact review of recent work.

2.   V. Gani and P. Viout, Tetrahedron Letters, 5241 (1972).

3.   R.L. Schowen, C.R. Hopper and C.M. Bazikian, J. Amer. Chem. Soc., 94, 3095 (1972).

4.   A.J. Parker, Adv. Phys. Org. Chem., 5, 173 (1967).

5.   L.P. Hammett, 'Physical Organic Chemistry', McGraw-Hill, New York, 1940.

6.   L.D. Kershner and R.L. Schowen, J. Amer. Chem. Soc., 93, 2014 (1971).

7.   M.L. Bender and R.J. Thomas, J. Amer. Chem. Soc., 83, 4183 (1961).

8.   R.M. Pollack and M.L. Bender, J. Amer. Chem. Soc., 92, 7190 (1970).