Notes

Effect of Added Dimethyl Sulfoxide on the Alkaline Hydrolysis of *p*-Nitroacetanilide

R. M. Pollack

Department of Chemistry, University of Maryland Baltimore County, Baltimore, Maryland 21228

Received November 13, 1973

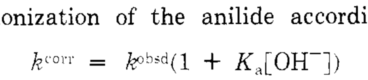
The effect of added dimethyl sulfoxide on the alkaline hydrolysis of anilides has recently been examined by Gani and Viout.[1] They observed that at 1 *M* NaOH, addition of DMSO caused a rate increase for *N*-methyl-*p*-nitroacetanilide and a rate decrease for *N*-methyl-*p*-methoxyacetanilide and *N*-methylacetanilide. These effects were explained as indicating rate-determining addition of hydroxide ion for *N*-methyl-*p*-nitroacetanilide hydrolysis, but rate-determining breakdown of the intermediate for the anilides without electron-withdrawing substituents. This interpretation of the *p*-nitroanilide data has been challenged by Broxton and Deady[2] on the basis of effects of DMSO on the methanolysis of substituted 2,2,2-trifluoro-*N*-methylacetanilides. They argue that an increase in hydrolysis rate on addition of DMSO does not necessarily imply that the addition step is rate determining.

In order to resolve this controversy, we have determined the effect of added DMSO on the alkaline hydrolysis of *p*-nitroacetanilide under conditions where addition of hydroxide is known to be rate determining and under conditions where breakdown of the intermediate is known to be rate determining. Our data show that the effect of DMSO cannot be used as a probe for the rate-determining step in anilide hydrolysis. In addition, these results provide confirmatory evidence for different types of transition states in the breakdown of the tetrahedral intermediate in anilide hydrolysis depending on substituent.[3]

Results

Pseudo-first-order rate constants were measured at 25.0 ± 0.2° in 50 vol % DMSO at an ionic strength 0.5 (NaCl) and hydroxide ion concentrations of 0.001–0.3 *M*. Reactions at higher hydroxide ion concentrations were followed to completion, but those at lower base concentrations were analyzed by measuring initial rates.

Although *p*-nitroacetanilide hydrolysis is complicated by ionization to give an unreactive anion (eq 1),[4] this side reaction can be easily corrected for. The equilibrium constant for eq 1 was measured and found to be 59 M^{-1} in 50% DMSO. The observed rate constants were then corrected for ionization of the anilide according to eq 2.



$$\mathrm{CH_3C(=O)NHAr + OH^- \rightleftharpoons CH_3C(=O)\bar{N}Ar} \qquad (1)$$

$$k^{\mathrm{corr}} = k^{\mathrm{obsd}}(1 + K_a[\mathrm{OH^-}]) \qquad (2)$$

These rate constants are given in Table I and plotted in Figure 1, along with the rate constants for the entirely aqueous system.[4,5]

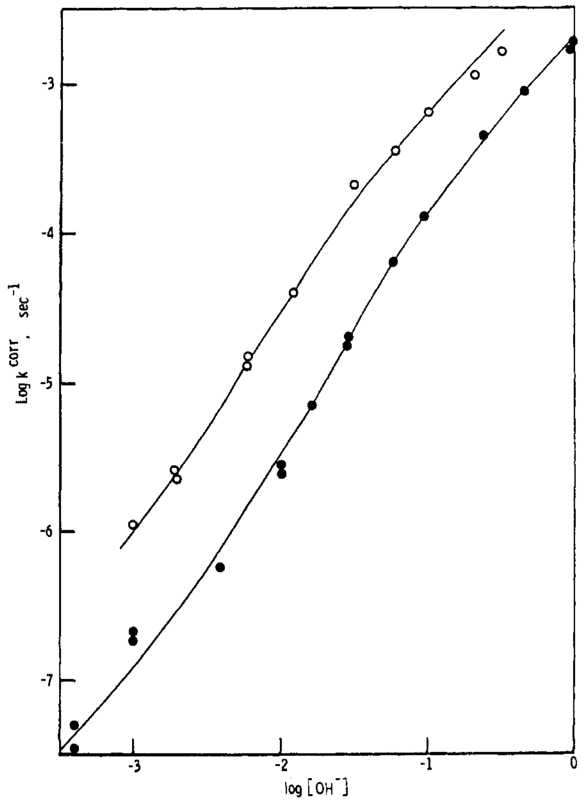
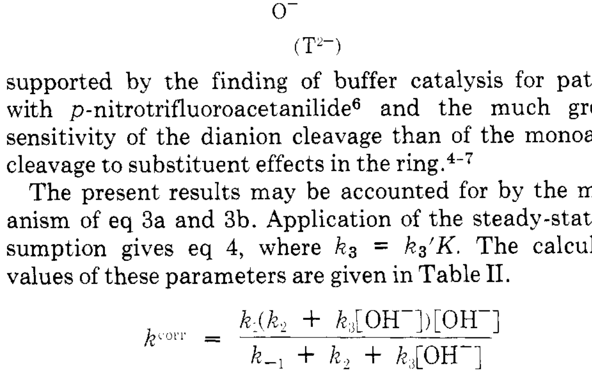


Figure 1. Plot of log k^{corr} *vs.* log [OH⁻] for the hydrolysis of *p*-nitroacetanilide in water (closed circles) and in 50% DMSO–water (open circles). Data for water is from ref 4 and 5. The lines are calculated from eq 4 using the parameters given in Table II.

Discussion

The alkaline hydrolysis of *p*-nitroanilides has been shown to proceed through two parallel paths:[4-7] (1) decomposition of the monoanion of the tetrahedral intermediate (T^-) with general acid catalysis to give the carboxylic acid and free amine (eq 3a); and (2) decomposition of the dianion (T^{2-}) without general catalysis to give carboxylate ion and anilide ion (eq 3b). This mechanism is supported by the finding of buffer catalysis for path 3a with *p*-nitrotrifluoroacetanilide[6] and the much greater sensitivity of the dianion cleavage than of the monoanion cleavage to substituent effects in the ring.[4-7]



$$\mathrm{OH^- + RCONHAr \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RC(O^-)(OH)NHAr\ (T^-) \xrightarrow{k_2} RCOOH + NH_2Ar} \qquad (3a)$$

$$\mathrm{T^- \overset{K[OH^-]}{\rightleftharpoons} RC(O^-)(O^-)NHAr\ (T^{2-}) \xrightarrow{k_3'} RCOO^- + {}^-NHAr} \qquad (3b)$$

The present results may be accounted for by the mechanism of eq 3a and 3b. Application of the steady-state assumption gives eq 4, where $k_3 = k_3'K$. The calculated values of these parameters are given in Table II.

$$k^{\mathrm{corr}} = \frac{k_1(k_2 + k_3[\mathrm{OH^-}])[\mathrm{OH^-}]}{k_{-1} + k_2 + k_3[\mathrm{OH^-}]} \qquad (4)$$

Table I
Rates of Alkaline Hydrolysis of *p*-Nitroacetanilide in 50% DMSO–Water at 25.0°

[OH⁻], *M*	k^{obsd}, sec⁻¹	k^{corr}, sec⁻¹ [a]	Method[b]
3.00×10^{-1}	8.37×10^{-5}	1.58×10^{-3}	C
2.00×10^{-1}	8.75×10^{-5}	1.12×10^{-3}	C
1.00×10^{-1}	9.04×10^{-5}	6.28×10^{-4}	C
6.00×10^{-2}	7.59×10^{-5}	3.47×10^{-4}	C
3.00×10^{-2}	7.37×10^{-5}	2.05×10^{-4}	C
1.20×10^{-2}	2.37×10^{-5}	4.07×10^{-5}	C
6.00×10^{-3}	9.67×10^{-6}	1.31×10^{-5}	I
6.00×10^{-3}	1.06×10^{-5}	1.44×10^{-5}	C
2.00×10^{-3}	1.96×10^{-6}	2.19×10^{-6}	I
2.00×10^{-3}	2.45×10^{-6}	2.74×10^{-6}	C
1.00×10^{-3}	1.07×10^{-6}	1.13×10^{-6}	I

[a] Corrected by eq 2. [b] C = followed to completion; I = initial rate.

Table II
Kinetic Parameters for the Alkaline Hydrolysis of *p*-Nitroacetanilide in Water and 50% DMSO–Water

	Water	50% DMSO
k_1	$2.2 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$	$7.6 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$
k_2/k_{-1}	0.045[a]	0.09
k_3/k_{-1}	$14\ M^{-1}$ [b]	$53\ M^{-1}$

[a] Recalculated from ref 4 and 5. Value in ref 5 is 0.063. [b] Recalculated from ref 4 and 5. Value in ref 4 is 17 M^{-1}.

Evaluation of the kinetic parameters for water and 50% DMSO reveals that the rate constant for hydroxide addition (k_1) is increased by about 3.5-fold on changing the solvent from water to 50% DMSO. Under conditions where breakdown of the intermediate is rate determining ($k_3[\text{OH}^-] \ll k_{-1}$), the overall rate constant for reaction by pathway 3a [$k_1k_2/k_{-1} + k_2$)] is increased sevenfold and by pathway 3b [$k_1k_3/(k_{-1} + k_2)$] 12-fold.

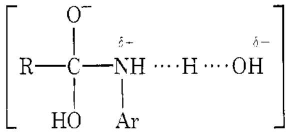
It is immediately obvious that addition of DMSO causes a rate enhancement for *p*-nitroacetanilide hydrolysis whether the rate-determining step is addition of hydroxide ion, breakdown of T⁻, or breakdown of T²⁻. These results support Deady's contention[2] that the effect of DMSO cannot be used to determine the identity of the rate-determining step in the alkaline hydrolysis of anilides.

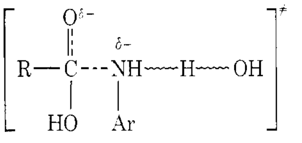
It is of interest to analyze the effect of added DMSO on the different rate processes for this reaction. The addition of dipolar aprotic solvents such as DMSO to aqueous solutions of base is known to have a large effect on the basicity of the solution.[8] For example, the H_- value of 0.011 *M* tetramethylammonium hydroxide changes from 12 in water to 26 in 99.5 mol % DMSO.[9] This large increase in basicity has been attributed to the increased activity of hydroxide ion brought about by reduced solvation by DMSO.[9] Larger anions are less affected by a change in solvent since their solvation requirements are less than for hydroxide ion.

The rate variations observed in our work may be analyzed in the following way. An increase of the value for k_1 on going from water to DMSO is expected since the transition state is a larger anion than hydroxide ion, and large anions are destabilized less than small anions on transfer from water to water–DMSO solutions.[9] Consequently, solvation is less important in the transition state than the ground state and the reaction is accelerated by a less solvating medium.

For path 3b the rate enhancement due to added DMSO can be explained in an analogous manner. This process involves destruction of two hydroxide ions, with generation of water and a more diffuse anion in the transition state. Again, DMSO is expected to increase the rate due to lower solvation requirements of the transition state than the ground state.

The effect of DMSO on the first-order process for hydrolysis (eq 3a), however, cannot be explained so easily. In fact, a slight *decrease* in rate was found for the analogous process for *N*-methyl-*p*-methoxyacetanilide and *N*-methylacetanilide on going from water to 50% DMSO.[1] These results were explained by postulating a dual effect of DMSO. In addition to augmenting the activity of hydroxide ions, added DMSO decreases the activity of water. Since the rate-determining step for the hydrolysis of anilides with poor leaving groups involves slow proton transfer from water prior to C–N bond cleavage (I),[3] the diminished activity of water offsets the increased activity of hydroxide ions. Furthermore, a new hydroxide ion is being generated in the transition state and solvation of this incipient anion becomes important. The net result is a small effect on the overall reaction rate.


I


II

In contrast to the results for *N*-methylacetanilide and *p*-methoxy-*N*-methylacetanilide, we find that DMSO increases the reactivity of *p*-nitroacetanilide by the process of eq 3a. The observed rate increase for *p*-nitroacetanilide hydrolysis may be explained in a manner similar to that used by Deady for the effect of DMSO on the methanolysis rates of *N*-methyl-*m*-nitro-2,2,2-trifluoroacetanilide.[2]

For good leaving groups (*p*-Cl, *m*-NO_2, etc.) the rate-determining step for breakdown of the intermediate is no longer proton transfer to the nitrogen as with poor leaving groups. Rather, it is C–N bond cleavage, with water acting simply to solvate the leaving group (II).[3] Here the transition state is a relatively large anion, with the negative charge spread out between the oxygen and the nitrogen. Although water is needed to solvate the nitrogen in II, it is clear that transition state II is a larger anion than hydroxide ion. Since the charge is more diffuse in II than in hydroxide ion, a rate increase on addition of DMSO for good leaving groups can be explained. For poor leaving groups (transition state I), on the other hand, charge localization is actually greater than for hydroxide ion and a rate decrease is expected. Consequently, the overall rate by the process of eq 3a is increased by addition of DMSO for good leaving groups and decreased for poor leaving groups.

Experimental Section

p-Nitroacetanilide was synthesized by acylation of *p*-nitroaniline with acetic anhydride, mp 214° (lit.[4] mp 214–215°). Dimethyl sulfoxide was purified by distillation from calcium hydride at reduced pressure. Kinetic solutions were made up by pipetting 25 ml of a known concentration of aqueous sodium hydroxide into a 50-ml volumetric flask and diluting to the mark with DMSO.

The kinetics were followed spectrally at 390 nm and analyzed by a nonlinear least-squares regression program for those reactions followed to completion or by measuring initial rates (~2% reaction).[4] All reactions which were followed to completion gave stable infinity points and excellent first-order kinetics.

The equilibrium constant for the ionization of *p*-nitroacetanilide in 50% DMSO–water was determined spectrophotometrically at 390 nm by using hydroxide ion concentrations of 0.006–0.300 *M* and a *p*-nitroacetanilide concentration of 3×10^{-4} *M*. A plot of $1/A^{\text{obsd}}$ *vs.* $1/[\text{OH}^-]$ gave a slope of $1/(K)(A^-)$ where A^{obsd} is the absorbance, A^- is the absorbance of the anion, and *K* is the equilibrium constant. A weighted least-squares analysis of this data gave $K = 59 \pm 6\ M^{-1}$.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We are also grateful to Dr. L. W. Deady for a preprint of ref 2 and Dr. H. B. Silber for helpful discussions.

Registry No.—*p*-Nitroacetanilide, 104-04-1.

References and Notes

(1) V. Gani and P. Viout, *Tetrahedron Lett.*, 5241 (1972).

(2) T. J. Broxton and L. W. Deady, *Tetrahedron Lett.*, 3915 (1973).

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

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

(5) R. M. Pollack and T. C. Dumsha, *FEBS Lett.*, **38**, 292 (1974).

(6) R. M. Pollack and T. C. Dumsha, *J. Amer. Chem. Soc.*, **95**, 4463 (1973).

(7) R. H. DeWolfe and R. C. Newcomb, *J. Org. Chem.*, **36**, 3870 (1971).

(8) C. H. Rochester, "Acidity Functions," Academic Press, New York, N. Y., 1970, Chapter 7.

(9) D. Dolman and R. Stewart, *Can. J. Chem.*, **45**, 911 (1967).

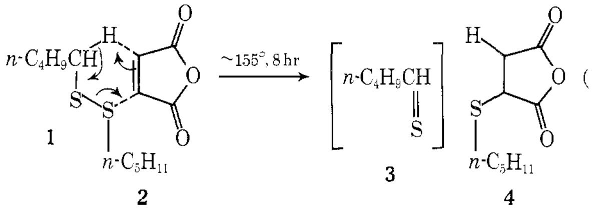
Organic Disulfides and Related Substances. 37. A Possible Counterpart of the Ene Reaction with Di-*n*-pentyl Disulfide and Maleic Anhydride[1]

Lamar Field

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235

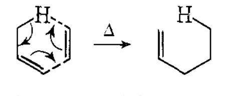
Received January 16, 1974

Interest in uncatalyzed reactions of disulfides with unsaturated systems prompted study of di-*n*-pentyl disulfide (**1**) with maleic anhydride (**2**) because the double-bond system of **2** seemed more likely than an isolated double bond to interact with unshared electrons of the sulfur atoms. The reaction that occurred is shown by eq 1 (with isolation of actual product, **5**, after hydrolysis by eq 2).



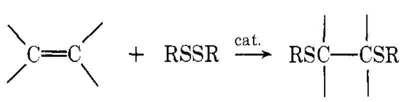
$$4 + H_2O \xrightarrow{KOH; H^+} n\text{-}C_5H_{11}SCH(CO_2H)CH_2CO_2H \quad (2)$$

5



Although the reaction is neither particularly clean nor perhaps synthetically attractive in its present form, it is noteworthy in that the structural outcome suggests a relationship to the broadly important ene reaction (eq 3).[2] According to both eq 1 and 3, a hydrogen atom and the third atom from it add to the anhydride, a widely used enophile.[2] However, development of the new double bond requires cleavage of the S-S bond for **1** in contrast merely to the shift of bond for an alkene. So far as we know, a sulfur counterpart of the ene reaction has not been specifically recognized as such before, although a formulation resembling that of eq 1 was suggested for the reaction of di-*n*-butyl disulfide and acetylene,[3] which also is an enophile.[2] The arrows in eq 1 and 3 are intended merely to point up the similarity of the reactions, not to make a point about the direction of electron shift.

Disulfides have long been known to react with a double bond as shown by eq 4, with suitable catalysis (iodine,[4]



hydrogen fluoride,[5] cobalt sulfide,[6] or ethanesulfonic acid[7]). Free-radical addition also has been observed but leads only to poor yields of 1:1 adducts.[8]

The only reaction apparently reported for a disulfide with **2** is that of eq 5,[9] which also seems to be the only reaction where a disulfide has led to a mono- rather than a bisthio ether. The sequence probably is that of the dotted arrows (eq 5), involving merely reduction of the disulfide to the thiolate ion, which then adds conventionally to **2**.[10]

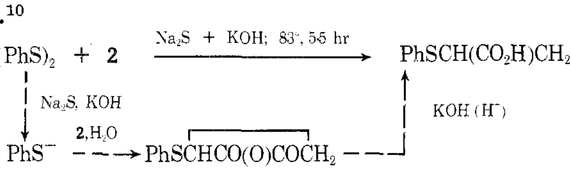


Table I, expt 1, shows conditions for the initial reaction when **1** was heated neat with **2** (eq 1). The fate of the presumed thio aldehyde **3** never became clear, not surprisingly, because **3** would be expected to be highly reactive. That the main product, after hydrolysis (eq 2), was 2-(*n*-pentylthio)succinic acid (**5**) was confirmed by independent synthesis.

Experiment 2 was done at lower temperature and with excess **1** (rather than the usual excess of **2**) to improve the conversion to **5**. The conversion was zero, but the result showed that the reactions of eq 1 and 5 must differ significantly (compare the conditions cited above the arrows). Indeed, when expt 1 was essentially repeated with diphenyl disulfide (15% excess) substituted for **1**, 99% of this disulfide was recovered; cleavage alone of this S-S bond thus did not suffice for a reaction like that of eq 1, so that the α-CH$_2$ moiety of **1** clearly is essential. In expt 3, longer reaction at the lower temperature did lead to **5**, indeed with better results than in expt 1 (*cf.* Table I, footnote *h*).

There was a possibility that the hydrolysis and treatment with alkali used in isolating **5** (eq 2) actually might have led to conversion of **1**, only at this late point, to give *n*-pentanethiolate ion, which then could have added to **2** to produce **4**. Experiment 4 duplicated the isolation alone and, by giving no **5**, ruled out the possibility that **5** merely was an artifact of isolation. That **5** also did not originate during the reaction itself simply through thermally induced cleavage of **1** to 1-pentanethiol was shown by demonstrating high thermal stability of **1** at *ca.* 155° (*cf.* Experimental Section).

Experiments 5–7 were done to improve the conversion further. A plot of conversion against time for expt 1 and 4–7 indicated that the product **4** undergoes further reactions that destroy it when heating is prolonged and that the optimum time of reaction would be *ca.* 7 hr. Experiment 8, based on this inference, gave the best conversion encountered, 44%.

In expt 5, **1** and **2** were carefully purified to obviate possible misinterpretations. An effort then was made to isolate all products. No pure sulfur compound other than **5** could be isolated, despite reworking of mother liquors, capitalization upon differing solubilities, distillation, and chromatography. The material balance was 98%, but the