sides should have a similar effect by reducing the nucleophilicity at the N-1 position.

Experimental Section

Materials. Ado, Cyd, Guo, and metal acetylacetonates [M(AA)$_n$] were commercially available. Authentic samples (1-MeAdo, N^6-MeAdo, 2',3'-Me$_2$Ado, 3-MeCyd, O^6-MeGuo, etc.) were prepared according to the literature[12,13] in order to identify minor products described in Tables I and IV. Synthesis of Me$_3$SOH was described previously.[7]

Chromatographic Systems. Thin-layer chromatography (TLC) was performed on silica gel (GF_{254}, type 60, Merck) and cellulose (Eastman chromagram sheet 13254). Dry-packed column chromatography was carried out with silica gel (Merck, art. 7734, 70–230 mesh). The following solvents were used for analysis of products. Silica gel: solvent A (chloroform–methanol, 17:3 v/v) for reaction products of Ado and dAdo; solvent B (chloroform–methanol, 15:1 v/v) for reaction products of 2'-MeAdo, N^6-MeAdo, and 3-MeUrd; solvent C (chloroform–methanol, 5:1 v/v) for reaction products of Cyd, dCyd, 2'-MeCyd, and 3'-MeCyd; solvent D (*n*-propanol–concentrated ammonium hydroxide, 3:1 v/v) for reaction products of Guo, dGuo, and 1-MeGuo. Ion-exchange chromatography was conducted with Dowex 1 × 2, 100–200 mesh, OH^- form.

Methylation Procedure. A mixture of the nucleoside and a methanol solution of Me$_3$SOH in a round-bottomed flask was concentrated in the presence or absence of M(AA)$_n$, using a rotary evaporator. The residue was heated in DMF at 70 °C for 0.5–1 h with magnetic stirring in an atmosphere of nitrogen.

Most products were isolated by silica gel column chromatography. The first fraction gave M(AA)$_n$. The recovery of Cu(AA)$_2$ was particularly good (71–90%). Since 2'-*O*-methyl- and 3'-*O*-methylnucleosides were always eluted in the same fraction in the silica gel chromatography of the reaction mixture, their yield ratio was determined conveniently from the area ratio of the corresponding methoxy groups in the NMR spectrum of the mixture. The O'-methylated nucleosides were then resolved by ion-exchange chromatography according to the methods reported.[1,13]

A product distribution of the reaction mixture was determined easily as follows. A small portion of the reaction mixture in water was mixed with aqueous ammonium sulfide. The resulting metal sulfide was filtered and the solution was processed by the TLC–UV spectroscopic method reported previously.[14]

UV spectra at pH 1, 7, and 13 as well as melting points (mp) of all known isolated compounds agreed with literature values. Their NMR spectra were also coincided with the assigned structures. Compounds that were not isolated were identified by comparison of their mobilities in TLC using several solvents and by comparison of UV spectra (pH 1, 7, and 13) of aqueous extracts of the spots with those of authentic samples. Table V gives the chromatographic data, the melting points, and spectral data for principal products.

Registry No. Ado, 58-61-7; 2'-MeAdo, 2140-79-6; 3'-MeAdo, 10300-22-8; 1-MeAdo, 15763-06-1; N^6-MeAdo, 1867-73-8; N^6,2'-Me$_2$Ado, 57817-83-1; N^6,3'-Me$_2$Ado, 60037-52-7; 2',3'-Me$_2$Ado, 20649-46-1; Cyd, 65-46-3; 2'-MeCyd, 2140-72-9; 3'-MeCyd, 20594-00-7; 3-MeCyd, 2140-64-9; 3-MeUrd, 2140-69-4; 3,2'-Me$_2$Urd, 7103-27-7; 3,3'-Me$_2$Urd, 7103-28-8; 3,2',3'-Me$_3$Urd, 53657-36-6; N^6,N^6,2'-(3')-Me$_3$Ado, 74466-63-0; 1-MeGuo, 2140-65-0; 1,2'-Me$_2$Guo, 73667-71-7; 1,3'-Me$_2$Guo, 74466-66-3; Guo, 118-00-3; 2'-MeGuo, 2140-71-8; 3'-MeGuo, 10300-27-3; O^6-MeGuo, 7803-88-5; N^6,2'-Me$_2$Ado·HCl, 59867-23-1; Me$_3$SoH, 17287-03-5; [Mn(AA)$_2$], 14024-58-9; [Co(AA)$_2$], 14024-48-7; [Zn(AA)$_2$], 14024-63-6; [Ni(AA)$_2$], 3264-82-2; [Cu(AA)$_2$], 13395-16-9; [Fe(AA)$_3$], 14024-18-1.

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Acylanthranils. 10. Influence of Hydrogen Bonding on Hydrolysis of Acetylanthranil in Organic Solvents

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The hydrolysis of acetylanthranil (**1**) to give *o*-acetamidobenzoic acid (**2**) in organic solvents at room temperature was monitored by proton NMR and/or gravimetrically. The results show that the second-order rate constant in benzene is about equal to that in water at pH 6.8. The corresponding rate constant for hydrolysis by a stoichiometric amount of water in proton-acceptor solvents decreases in the order benzene > dimethyl-d_6 sulfoxide > acetone-d_6 > dimethylformamide-d_7 > pyridine, and for hydrolysis in proton donor solvents, it decreases in the order benzene > chloroform-*d* > acetonitrile-d_3. The observed second-order rate "constant" in organic solvents, however, is not a true constant, since it increases linearly with water concentration. It was observed also that the plots of log [H_2O]/[**1**] as a function of time, *t*, show an inflection at some time, t_i, that appears to correspond to a critical equilibrium concentration of available proton from the acid product **2**. The magnitude of t_i is decreased considerably by addition of **2** at time zero, and it is eliminated completely by addition of HCl. On the other hand, it is increased considerably by addition of solutes that are strong proton acceptors, such as 1,8-bis(dimethylamino)naphthalene or 1,4-diazabicyclo[2.2.2]octane. These results are consistent with the hypothesis that hydrolysis of **1** in organic solvents involves interaction with molecular clusters of water such as $(H_2O)_n$ in benzene, S·HOH·S or $(HOH·S)_n$ in proton-acceptor solvents, S, and H_2O·HS in proton donor solvents, SH.

Introduction

In our preceding paper,[1] we reported that the results observed when acetylanthranil (**1**) is made to react with ammonia in organic solvents are consistent with the premise that the nucleophile reacts with **1** as a molecular cluster rather than as an individual molecule and that the mechanism involves association of the cluster by hydrogen bonding with the heterocyclic nitrogen of **1** to form a mixed complex followed by nucleophilic attack at C-2 or C-4, depending on the reaction conditions. We noted that the addition of a small amount of water to these systems caused a sharp change in selectivity and an enormous

(1) Part 9: L. A. Errede, P. D. Martinucci, and J. J. McBrady, *J. Org. Chem.*, in press.

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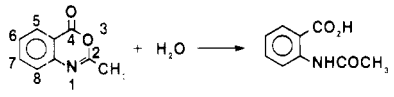
increase in reactivity when the solvent was a weak proton acceptor such as benzene but that the corresponding addition of water caused no significant change in selectivity and even a decrease in reactivity when the solvent was a good proton acceptor such as pyridine. We were surprised to observe also that the alternate reaction, i.e., hydrolysis of 1 in pyridine, is unusually slow even when water is added in large excess relative to 1 and ammonia. Since one would expect at first glance that the rate of hydrolysis would increase in pyridine rather than decrease, we decided to study the hydrolysis of 1 in organic solvents more fully. Our purpose was to learn how hydrogen bonding of water with itself, with the solvent, and with added solutes affects the rate of this apparently simple reaction that produces a weak acid product 2 from a weak base (1) as indicated below.

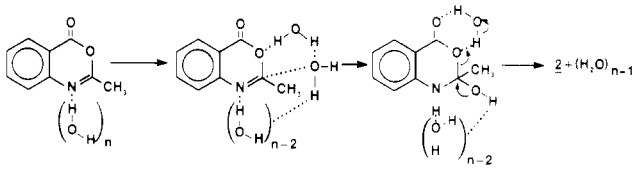


1 2

The facile hydrolysis of acetylanthranil (1) in water to give the corresponding *o*-acetamidobenzoic acid (2) was reported by Bredt[2] and by Bogert[3] as early as 1900, but its mechanism was not elucidated until 1971. The investigation of Williams and Salvadori,[4] who carried out this hydrolysis in buffered aqueous solutions enriched with ^{18}O, showed that (1) the reaction is stoichiometric, (2) it involves nucleophilic attack at C-2 in aqueous acid solution but at C-4 in aqueous base, (3) the kinetics is pseudo-first-order, and (4) the rate constant, k, attains a minimum value at pH 6.8. This minimum represents the intersection of two lines of unit slope, negative and positive, which relate log K as a function of pH in buffered aqueous acid and base solutions, respectively. Subsequently Bolotin et al.[5] showed that the reactivity and selectivity are altered in accordance with theory by ring substituents that affect the relative electrophilicities at C-2 and C-4. Recently, Cremin and Hegarty[6] reported that the rate of hydrolysis is increased 250-fold at pH 6.8 by a carboxyl group located in the 8-position, where it can exert intramolecular acid catalysis that enhances susceptibility to nucleophilic attack at C-2 (and/or C-4). On the other hand, they noted that the rate of hydrolysis in aqueous base is decreased 4-fold by a carboxylate group in the 5-position, where it presumably can exert steric or electronic repulsion to the negatively charged nucleophile approaching the 4-position.

Although kinetic studies of the hydrolysis of 1 in organic solvents have not been reported, the manner in which water associates with proton-acceptor, S, and -donor, SH, solvents has been studied extensively by IR and NMR spectroscopy.[7,8] Takahashi and Li[9] reported that termolecular complexes of the type S·HOH·S are the dominant species when water is dissolved in a large excess of proton-acceptor solvent such as acetone, tetrahydrofuran, or dimethylformamide. They also noted, however, that solvated clusters of the type $S\cdot(H_2O)_n\cdot S$ are also present and that their proportion increases with water concentration. It was shown by others[10-12] that in neutral solvents such as benzene, hexane, and dichloroethane, which are neither proton acceptors or donors, water is present primarily as ring clusters of the type $(H_2O)_n$, where n is 1, 2, 3, and 4, held together by hydrogen bonding. Although the dominant "n-mer" species depends somewhat on the choice of neutral solvent, usually it is the trimer in equilibrium with much smaller amounts of the others.[12]

Scheme I



One can expect therefore that association with a proton-acceptor solvent will decrease the activity of water, provided that the dielectric constant of the solvent is not so high as to favor dissociation into ionic species via the equilibrium

$$S\cdot HOH\cdot S \rightleftarrows S\cdot H^+ + {}^-OH\cdot S$$

as this should increase the rate of interaction with 1 in accordance with the acid and base mechanisms reported by Williams and Salvadori.[4] One would also expect that the rate constant for reaction of 1 with S·HOH·S would be smaller than that for the corresponding reaction with $S\cdot(H_2O)_n\cdot S$, the latter of which can associate with 1 in a multidentate mode and then produce 2 via a "von Grotthus-like" mechanism,[1] illustrated in Scheme I, in the same manner that it does in aqueous solution. If this is true, then the rate constant for reaction with $(H_2O)_n$ in a neutral solvent should be about equal to that in water at pH 6.8 and greater than that in either a proton-acceptor or -donor solvent with low dielectric constant. Since the product of hydrolysis, 2, is a strong proton donor, one would also expect that the accumulation of this product would affect the reaction kinetics accordingly. It was decided therefore to study the hydrolysis of 1 in terms of these variables, namely, the choice of organic solvent, the initial concentration of water, and the concentration of acidic protons, either added or accumulated.

Effect of Solvents and Added Solutes

The results of this investigation are summarized in Table I, which confirms that the choice of solvent does indeed have a marked effect on the rate of hydrolysis. The conversions of 1 to product 2 at room temperature were monitored by proton NMR, except for the hydrolysis in benzene, which was followed by weighing the accumulated insoluble product.

The kinetics of hydrolysis of 1 in benzene saturated with water in room temperature (expt 2), like that for hydrolysis in water[4-6] or for hydrolysis of powdered 1 exposed to air saturated with water vapor,[1] is pseudo-first-order.[13] Although the rate of reaction in water at pH 6.8 is greater than that observed in benzene (k = 0.0011/min), owing to the low solubility of water in benzene at 25 °C (0.031 mol/L), the corresponding second-order rate constants

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Table I. Hydrolysis of Acetylanthranil (1) in Organic Solvents at Room Temperature

expt no.	composition of solution at $t = 0$: solvent	$[1]_0$	$[2]_0$	$[H_2O]_0$	added solute, 0.5 M	time to point of inflection, t_i, h	pseudo-second-order rate constants, L/mol·min: before inflection, k_b	after inflection, k_a
1	water (pH 6.8)			55			0.040[a]	
2	benzene	0.49	<0.01	0.031[b]			0.034[c]	
3	CD_3SOCD_3	0.42	0.08	2.56		0		0.045
4	CD_3SOCD_3	0.42	0.08	0.61		0.5	0.011	0.040
5	CD_3COCD_3	0.42	0.08	0.57		7	0.0020	0.010
6	$DCON(CD_3)_2$	0.44	0.06	0.57		15	0.0021	0.0073
7	pyridine	0.48	0.02	3.5		5	3.5×10^{-4}	11×10^{-4}
8	pyridine	0.48	0.02	1.1		7.5	1.4×10^{-4}	6.3×10^{-4}
9	pyridine	0.48	0.02	0.60		45	0.9×10^{-4}	5.2×10^{-4}
10	pyridine	0.48	0.02	0.41		65	0.8×10^{-4}	5.1×10^{-4}
11	pyridine	0.48	0.36	1.1		0.8	8.8×10^{-4}	0.0057
12	pyridine	0.48	0.02	0.60	HCl	0		0.10
13	pyridine	0.46	0.04	0.66	proton sponge	135	3.6×10^{-4}	0.0018
14	pyridine	0.40	0.10	0.70	Dabco	672	2.3×10^{-5}	4.4×10^{-5}
15	$DCCl_3$	0.44	0.06	0.19[b]			0.0052[d]	
16	CD_3CN	0.43	0.07	0.91			0.0012	

[a] Calculated from pseudo-first-order rate constant at pH 6.8 that was reported by Williams.[4] [b] Solvent was saturated with H_2O during hydrolysis run. [c] Calculated from pseudo-first-order rate constant from kinetic data determined gravimetrically. [d] Calculated from pseudo-first-order rate constant from kinetic data determined by NMR.

calculated for conversion in water ($k = 0.040$ L/mol·min)[4] and in benzene ($k = 0.034$ L/mol·min) are about the same. This suggests that a neutral organic solvent, i.e., a solvent that is neither a proton donor nor a proton acceptor, influences the hydrolysis of 1 primarily by limiting the concentration of the coreactant, which is relatively insoluble in these solvents.

Hydrolysis in a proton-donor solvent, SH, is affected positively by hydrogen bonding with the heterocyclic nitrogen atom of 1 to give 1·HS, which would enhance the electrophilicity at the adjacent 2-position of 1, and also is affected negatively by hydrogen bonding with water to give $SH{\cdot}OH_2$, which would interfere with nucleophilic attack at the 2-position. The net effect on reactivity would be the resultant of these two opposing factors. It was observed that the pseudo-first-order rate constant for hydrolysis of 1 in chloroform saturated with water at room temperature (0.19 M, expt 15) is $k = 9.9 \times 10^{-4}$/min.[13] The second-order rate constant calculated therefrom is $k = 0.0052$ L/mol·min, which is about sevenfold smaller than that in benzene (expt 2) or water. Hydrolysis of 0.5 M 1 in acetonitrile that was 0.6 M with respect to water (expt 16) is second order; i.e., the classical plot of log $[H_2O]/[1]$ as a function of time is a straight line.[13] The rate constant ($k = 0.0012$ L/mol·min) calculated from the slope of this line is even smaller than that for hydrolysis in chloroform. That the order of reactivity in these solvents is benzene > chloroform > acetonitrile is consistent with the point of view that the decrease in reactivity is attributable to formation of $SH{\cdot}OH_2$ as a function of the solvent's ability to serve as a proton donor, which would decrease accordingly the "activity" of the solvated water.

Hydrolysis in a proton-acceptor solvent, S, proved to be more complicated than expected. The plot of log $[H_2O]/[1]$ as a function of time in these solvents exhibited a sharp inflection at some time, t_i, as shown in Figure 1, in which is plotted the data for interaction of 1 (0.5 M) with water (0.6 M) in hexadeuteriodimethyl sulfoxide (expt 4), in hexadeuterioacetone (expt 5), in heptadeuteriodimethylformamide (expt 6), and in pyridine (expt 9). It was noted that the time required to reach the observed inflection point at t_i in a given solvent (that initially was 0.6 M with respect to water) appeared to be a linear function of the log of the corresponding second-order rate constants

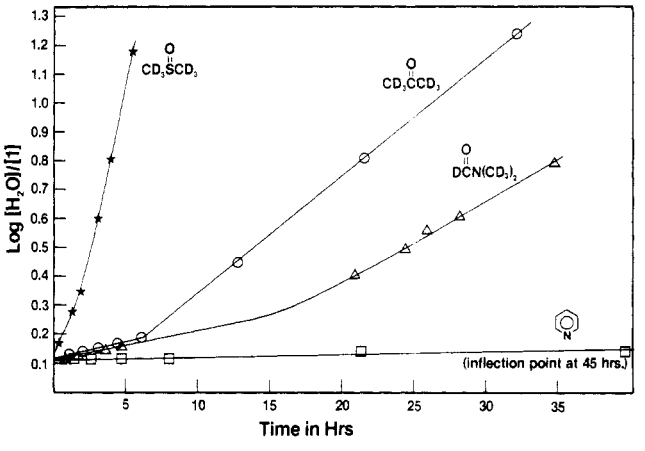

Figure 1. Interaction of 1 (0.5 M) and H_2O (0.6 M) in proton-acceptor solvents.

"before" (k_b) and "after" (k_a) this event.[13] Thus, these linear relationships are given approximately by the equation

$$t_i = -(44 - 22 \log k_b) = -(30 - 22 \log k_a)$$

This relationship shows that this phenomenon is not a spurious happening but is in fact a function of the physical and/or chemical properties of the solvent.

As discussed by Gutman,[14] two important solvent properties that affect hydrogen bonding in donor-acceptor molecules are the solvent "donicity", DN (i.e., the ability of the solvent molecule to donate its electron pair) and the dielectric constant, ϵ. Those solvents, S, with DN greater than that of water (DN > 18.0) ensure that virtually all of the solvated water molecules are present as S·HOH·S in equilibrium with very small amounts of $S{\cdot}(HOH)_n{\cdot}S$, as noted by Takahashi and Li.[9] This would serve to lower the "activity" of water accordingly. On the other hand, dissociation of these solvated complexes into the corresponding ionic species, $S{\cdot}H^+$ and $^-OH{\cdot}S$, would be expected to increase with ϵ. This in turn would serve to increase the reactivity, as noted by Williams and Salvadori[4] for hydrolysis of 1 in water.

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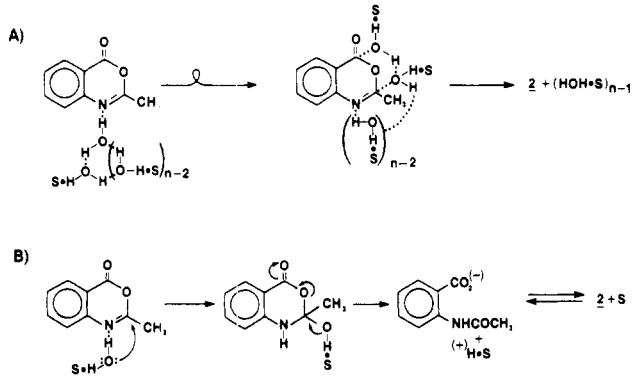
Scheme II. Hydrolysis in Strong Proton-Acceptor Solvents



Consistent with the above expectations, it was observed that in those solvents with DN > 18.0, i.e., in pyridine (DN = 33.1, ϵ = 12.3), in dimethylformamide (DN = 26.6, ϵ = 36.1), and in dimethyl sulfoxide (DN = 29.8, ϵ = 45.0), both log k_b and log k_a are linear functions of ϵ, i.e., log $k_b = -4.81 + 0.063\epsilon$ and log $k_a = -4.12 + 0.062\epsilon$, and the corresponding t_i decreases accordingly (i.e., t_i (in h) = $60 - 1.29\epsilon$).

The rate of hydrolysis in acetone (DN = 17.0, ϵ = 20.7), however, is significantly higher than expected on the basis of these relationships in terms of ϵ, probably because its donicity is lower than that of water. This difference in ability to serve as a proton acceptor would displace the solute–solvent equilibrium in favor of S·$(H_2O)_n$·S, which would be expected to react faster with 1 than does S·HO-H·S, as discussed in the introduction.

There is yet another solvent-related factor that can affect the rate of hydrolysis, namely, the molecular bulk of the solvent molecule, S, that associates with water by hydrogen bonding. Earlier kinetic studies with ammonia[1] and with amines[15] have shown that steric hindrance markedly affects the selectivity and rate of interaction with 1. The results obtained in these studies are consistent with a reaction sequence which involves association of the solvated coreactant RN(H·S)$_2$ with the heterocyclic nitrogen atom of 1 to form 1·HNRH·S, followed by intramolecular nucleophilic attack at the adjacent C-2 position, which is impeded by the presence of the methyl substituent, i.e., the larger the bulk of R and associated S, the slower the rate of reaction. It is reasonable to expect that the same might be true for hydrolysis; i.e., interchange with solvent gives 1·HOH·S, which rearranges via intramolecular nucleophilic attack at C-2 to give product 2 as shown in Scheme IIB.

If this is true, then it should be possible to decrease markedly the rate of hydrolysis by addition of a difunctional tertiary amine solute that is a stronger proton acceptor than the solvent, even if the molecular weight of the added solute is about the same as that of the solvent. Presumably the higher affinity for the hydrogen atoms of water should favor association with an equivalent amount of the difunctional solute NRN to give S·(HOH·NRN)$_n$·S in equilibrium with 1·(HOH·NRN)$_n$·S, thereby amplifying the apparent bulk of the mixed association complex by a factor of about n. This amplification should produce a corresponding decrease in the rate of conversion to product 2. As a test of this hypothesis, pyridine (pK_a = 5.19), the most basic member of the set of solvents investigated in this study but the one with the lowest dielectric constant, was chosen as the test solvent, and 1,4-diazabicyclo-[2.2.2]octane, known also by its acronym[16] Dabco or as "triethylenediamine" (pK_a = 8.68),[17] was chosen as the test additive because of its relatively rigid structure, which should minimize any effects of steric hindrance, and because of its relatively low molecular weight for a bifunctional aliphatic tertiary amine, which should ensure that any observed large retarding effect on hydrolysis rate would be attributable to n-mer formation rather than to the bulk of the test solute per se.

Accordingly, the interaction of 1 (0.4 M), water (0.7 M), and Dabco (0.5 M) in pyridine at room temperature to give product 2 was monitored by proton NMR (expt 14). The kinetic behavior of this conversion was qualitatively the same as that observed for hydrolysis in the absence of Dabco, as shown in Figure 6, but the rate constants for this conversion, before and after the corresponding inflection point t_i, were decreased markedly from about $k_b = 1 \times 10^{-4}$ L/mol·min and $k_a = 5 \times 10^{-4}$ L/mol·min without Dabco (expt 9) to $k_b = 2.3 \times 10^{-5}$ and $k_a = 4.4 \times 10^{-5}$ with Dabco (expt 14). Moreover, the time required to reach the inflection point, t_i = 672 h in the presence of Dabco, was considerably longer than that (t_i = 140 h) expected on the basis of the observed retarded rate constants.[13] These results support the point of view that the apparent bulk of the mixed complex associated with the heterocyclic nitrogen atom of 1 has a marked effect on the rate of conversion to product 2.

Effect of Water Concentration

In the preceding section, we noted that the rate constants, k_a and k_b, for hydrolysis in acetone were significantly greater than those expected on the basis of its dielectric constant, ϵ; i.e., from the observed empirical relationships, log $k = A + B\epsilon$. Since these relationships were established by using data recorded for solvents with "donicity" much greater than that for water (DN = 18), we suggested that perhaps this higher-than-expected activity might be attributed to the inadequate "donicity" of acetone (DN = 17), which is lower than that for water. It is reasonable to expect that the proportion of partially solvated water clusters, S·$(H_2O)_n$·S, in equilibrium with totally solvated water, S·HOH·S, would be significantly greater in solvents with DN less than that of water than it is in solvents with DN greater than that of water. We postulated that the rate constant for reaction of 1 with S·$(H_2O)_n$·S is much greater than that for reaction with S·HOH·S, because the former can associate easily with 1 in a multidentate mode that leads quickly to product 2 via the "von Grotthus-like" mechanism outlined in Scheme IIA, whereas the totally solvated water associates with 1 in a monodentate mode via solvent interchange and then undergoes product formation much more slowly via the rearrangement mechanism outlined in Scheme IIB.

If this postulation is correct, then it follows that the observed second-order "rate constant" for hydrolysis in a given solvent should in fact be a function of the water concentration, since Takahashi and Li[9] have shown that the proportion of S·$(H_2O)_n$·S in equilibrium with S·HOH·S increases with water concentration. It was decided therefore to study the effect of initial water concentration $[H_2O]_0$ on hydrolysis rate, using a solvent with high donicity and low dielectric constant to minimize ionization of S·HOH·S. Accordingly the rate of conversion of 1 (0.5 M) to 2 at room temperature was monitored by proton NMR

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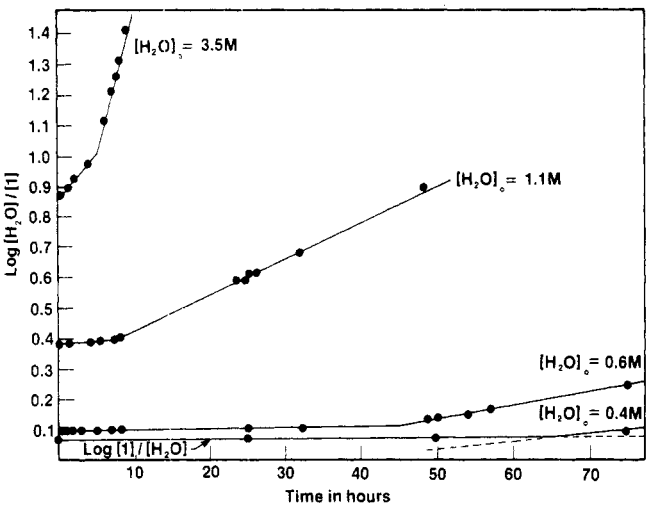


Figure 2. Hydrolysis of 1 (0.5 M) in pyridine at room temperature as a function of initial water concentration $[H_2O]_0$.

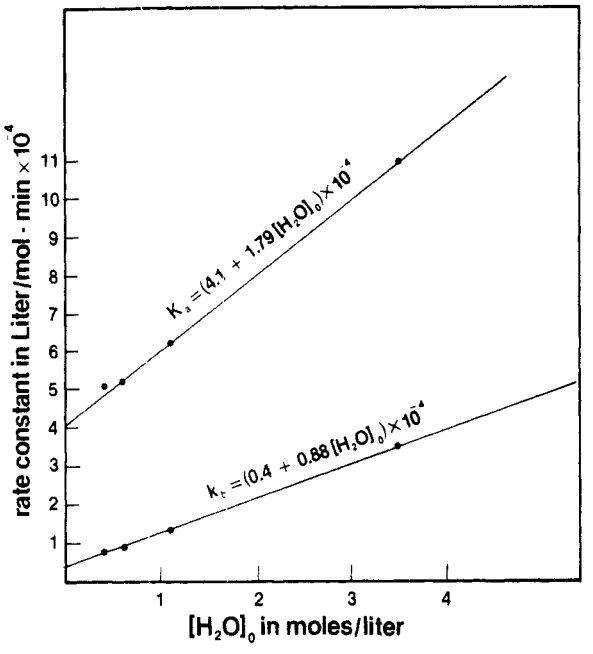


Figure 3. Pseudo-second-order rate constant in pyridine as a function of initial concentration of water.

in a set of time studies in which the $[H_2O]_0$ in pyridine was 0.41 M (expt 10), 0.60 M (expt 9), 1.1 M (expt 8), and 3.5 M (expt 7). Again each plot of the log of the ratio of reactants as a function of time exhibited a sharp inflection at a time t_i, as shown in Figure 2. The log of the observed rate constants before and after these points of inflection increased linearly with the initial water concentration, $[H_2O]_0$, as shown in Figure 3. Again it was observed that the corresponding time required to reach this point of inflection, t_i, in pyridine is a linear function of log k_b and log k_a,[13] which under these experimental conditions is given approximately by the equation

$$t_i = (840 - 220 \log K_b) = -(680 - 220 \log K_a)$$

This implies that t_i is markedly sensitive to water concentration.

Similar results were observed with a solvent with high dielectric constant. Thus, the hydrolysis of 1 (0.5 M) in Me_2SO (ϵ = 45) that was 0.6 M with respect to water exhibited an inflection point at 0.5 h (expt 4); the observed rate constants before and after this event were k_b = 0.011 and k_a = 0.040 L/mol·min. In contrast, no point of inflection was noted when this hydrolysis was made to occur in Me_2SO that was 2.5 M with respect to water (i.e., t_i = 0) and the observed initial rate constant was k = 0.045 (expt 3).

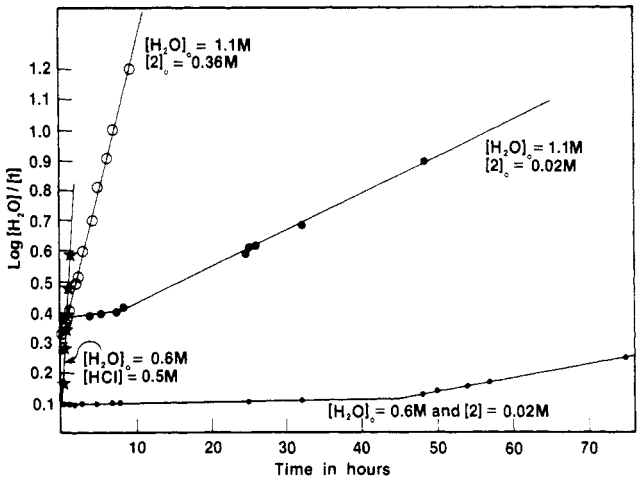


Figure 4. Effect of proton-donor solutes on hydrolysis of 1 (0.5 M) in pyridine at room temperature.

These results show that the observed rate constants are in fact "pseudo-second-order" rate constants, which increase with "water" concentration, i.e., with S·$(H_2O)_n$·S in proton-acceptor solvents, with $(H_2O)_n$·HS in proton-donor solvents and with $(H_2O)_n$ in neutral solvents. That the observed rate constant for reaction with H_2O in benzene is about the same as that observed for hydrolysis in water at pH 6.8 suggests that interaction in both media involved multidentate association with $(H_2O)_n$ clusters, where n is some interger above two or three as noted in Scheme I, and that the product formation thereafter is equally facile despite the great differences in the bulk phase of the two media.

Effect of Acidic Solutes

In view of the observations of Williams and Salvadori[4] that the mechanism and the rate of hydrolysis in water are dependent upon pH, it was reasonable to suspect that the accumulation of the acidic product 2 as a function of percent conversion of 1 was responsible for the sharp change in rate constant at some point t_i as illustrated in Figures 1 and 2. This suspicion was reinforced by the observations that this point of inflection occurred at about the same percent conversion of 1 to 2 when the acid product was very soluble in the reaction medium but that no inflection was exhibited when the acid product was insoluble in the reaction medium. It was postulated, therefore, that the inflection occurred when the available $[H^+]$ reached a critical concentration established by the equilibria with solvent and solutes.

It was decided to test this hypothesis by comparing the kinetic results at two levels of added product 2 in pyridine at room temperature. Accordingly, the rates of interaction of 1 (0.48 M) with water (1.1 M) in pyridine solutions that initially were 0.02 M (expt 8) and 0.36 M (expt 11) with respect to 2 were monitored by proton NMR. The kinetic results, plotted in Figure 4, show that k_b and k_a were 6.3- and 9.0-fold greater, respectively, at the higher level than at the lower level of added 2 and that the corresponding time to reach the point of inflection, t_i, was shortened from 7.5 h at the lower level to 0.8 h at the higher level.

When hydrolysis of 1 was made to occur in pyridine to which had been added an equivalent amount of HCl in the form of pyridine hydrochloride (expt 12), t_i was eliminated completely, as shown in Figure 4, and the pseudo-sec-

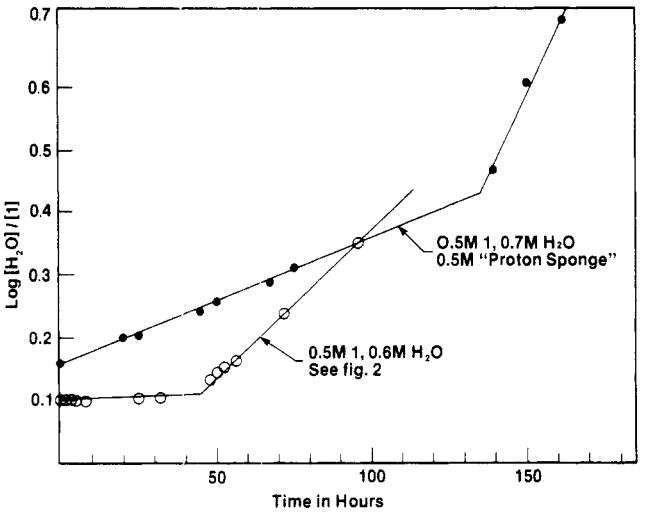


Figure 5. Effect caused by presence of 0.5 M 1,8-bis(dimethylamino)naphthalene on the hydrolysis of 1 in pyridine at room temperature.

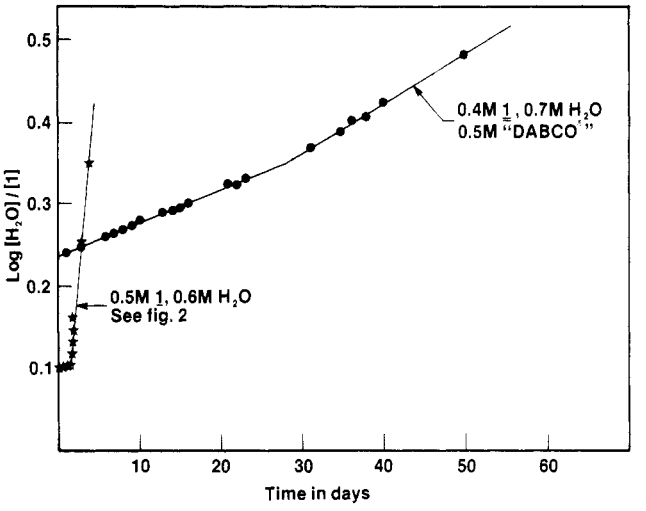


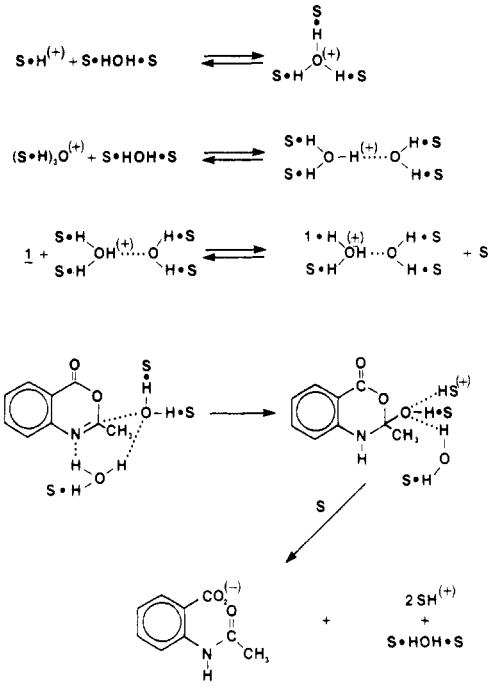
Figure 6. Effect caused by presence of 0.5 M 1,4-diazabicyclo-[2.2.2]octane on the hydrolysis of 1 in pyridine at room temperature.

ond-order rate constant was increased about 200-fold over the observed rate constant under the same hydrolysis conditions in the absence of added HCl (expt 9).

If one accepts the premise that the inflection of t_i in the plot of log $[H_2O]/[1]$ as a function of time in proton-acceptor solvents is attributable to the accumulation of the acid product **2**, then one would expect that t_i would be increased considerably if a solute were added that could hold tenaciously the protons supplied by the hydrolysis product. Such a compound is 1,8-bis(dimethylamino)-naphthalene, which is referred to descriptively by the Aldrich Chemical Co. as "Proton Sponge". It was shown by Alder et al.[18] that this bis tertiary aromatic amine is remarkably basic with respect to protons (pK_a = 12.34) but only weakly nucleophilic with respect to more bulky electrophiles, owing to its highly strained peri-bis(dimethylamine) configuration. Accordingly the interaction of 1 (0.46 M), water (0.66 M), and "Proton Sponge" (0.5 M) in pyridine at room temperature (expt 13) was monitored by proton NMR. As expected, the time required to reach the inflection point, t_i, was extended threefold from 45 h in the absence of "Proton Sponge" (expt 9) to 135 h in its presence, as shown in Figure 5, despite that this additive caused about a fourfold increase in k_a and k_b from 1×10^{-4} and 5×10^{-4}, respectively (expt 9), to 3.6×10^{-4} and 18×10^{-4}, respectively (expt 13). It is interesting to note that the effect produced by the addition of Dabco as shown in Figure 6 is even greater than that produced by "Proton Sponge", despite that the latter retains protons much more tenaciously than the former. This enhanced effect with Dabco is attributed to associative telomerization with H_2O, as discussed in the above section.

In view of the observation that t_i is decreased considerably, or even eliminated, by addition of solute that contributes H^+ to the hydrolysis system, whereas t_i is increased considerably by addition of solutes that withdraw H^+ from the system, it is concluded that the inflection of t_i in the plot of log $[H_2O]/[1]$ as a function of t is caused by accumulation of H^+ to some stoichiometric concentration which depends on the interrelated equilibria with reactants and solvent. It is postulated that below this level hydrolysis occurs primarily via the "von Grotthus-type" mechanism shown in Scheme IIA, which involves interaction of 1 with $(H_2O{\cdot}S)_n$ that is in equilibrium with S·H-OH·S. After the critical amount of H^+ to permit protonation of 1 in significant concentration has been accumulated, hydrolysis via formation of 1·HOH·S in equilibrium

Scheme III



with S-HOH-S and subsequent rearrangement to give **2**, as outlined in Scheme III, becomes competitive with the von Grotthus mechanism outlined in Scheme IIA.

Summary and Discussion

The results obtained in these hydrolysis studies are consistent with a mechanism whereby acetylanthranil (1) reacts with a cluster of water molecules and/or solvated water molecules held together by hydrogen bonding, rather than with a single water molecule unfettered by its molecular environment. In a neutral solvent, i.e., one that is neither a proton donor or acceptor, this interaction involves the cluster $(H_2O)_n$, which can associate with 1 by hydrogen bonding at one or more of its three nucleophilic sites, especially the very nucleophilic heterocyclic nitrogen atom. This multidentate associated complex $1{\cdot}(H_2O)_n$ undergoes facile nucleophilic attack at C-2 or C-4 to give 2 via a von Grotthus like mechanism as outlined in Scheme I. The same mechanism obtains for hydrolysis in aqueous solution at pH 7, although the selectivity and rate of re-

action is influenced markedly above and below this neutral point as discussed by Williams and Salvadori.[4]

In proton-acceptor solvents, S, water is present primarily as S·HOH·S in equilibrium with a very small fraction as S·$(H_2O)_n$·S, both of which decrease the "activity" of water and slow the rate of interaction accordingly, unless the dielectric constant of the solvent is strong enough to effect ionization giving S·H^+ and $^-$OH·S. These ionic species enhance the rate of interaction, as discussed by Williams and Salvadori for hydrolysis of 1 in aqueous solution, and consequently mitigate the deactivating effect of solvation. The rate of interaction with S·$(H_2O)_n$·S is faster than that with S·HOH·S because the former, like $(H_2O)_n$, can associate easily with 1 by multidentate hydrogen bonding to give 2 as outlined in Scheme IIA, which is essentially the same as that suggested in Scheme I for reaction with $(H_2O)_n$ in neutral solvents. Reaction with completely solvated water, S·HOH·S, is slowed considerably because direct nucleophilic attack at C-2 or C-4 is hampered sterically by the added bulk of the two associated solvent molecules. Therefore interaction of 1 with this species is limited to the alternate route, which involves solvent exchange to give 1·HOH·S followed by intracomplex nucleophilic attack at the adjacent C-2 position as suggested in Scheme IIB. The rate of this rearrangement is inversely related to the bulk of the cluster held together by hydrogen bonding.

Since reaction of 1 with S·$(H_2O)_n$·S is faster than that with S·HOH·S and the very small fraction of the former in equilibrium with the latter increases with water concentration as reported by Takahashi and Li,[9] the observed pseudo-second-order rate constant for hydrolysis increases markedly with initial concentration of water, below 2 M.

Since the product of hydrolysis of 1 is a weak acid, 2, which readily contributes protons that are known to enhance reactivity of 1, the mechanism of hydrolysis and the rate of conversion change sharply at some percent conversion, which appears to be related stoichiometrically to some characteristic amount with respect to the equilibria involving reactants, product, solvent, and other added proton acceptors or donor solutes. The cumulative effect of proton availability manifests itself in the plot of log $[H_2O]/[1]$ as a function of time. A sharp inflection occurs in this plot at some time, t_i, which is characteristic of the reactants–product–solvent system unless a strong proton-donor solute is added which shortens markedly t_i or a strong proton-acceptor solute is added which lengthens markedly t_i. It is assumed that this change in mechanism, associated with the point of inflection, involves protonation of S·HOH·S and subsequent more facile interaction with 1 to give 2, perhaps as suggested in Scheme III.

In contrast to the complicated results obtained in proton-acceptor solvents, the plot of log $[H_2O]/[1]$ as a function of time for reaction in a proton-donor solvent is quite normal; it shows no inflection or deviation from a straight line almost to complete conversion to product. The pseudo-second-order rate constant for reaction in these solvents, however, is smaller than that in benzene. The order observed in this study is benzene > chloroform > acetonitrile. It is believed that this decrease in reactivity in proton-donor solvents, SH, is also attributable at least in part to hydrogen bonding to form SH·OH_2, which impedes direct nucleophilic attack at C-2 and C-4, and the formation of 2 via rearrangement of 1·H_2O·HS as outlined in Scheme IIB.

The results observed in these kinetic studies of the interaction of 1 with water are consistent with those reported earlier[1] for the interaction of 1 with ammonia as summarized in the introduction. Reaction with ammonia neat or in neutral solvent is fourfold slower than the corresponding reactions with water, despite that ammonia is much more nucleophilic than water. The reason for this apparent anomaly is attributable to interaction with the clusters $(NH_3)_n$ and $(H_2O)_n$ rather than the respective individual molecules. In neutral solvents or neat, almost all of the nucleophilic centers in the ammonia cluster are associated with the adjacent molecule by hydrogen bonding so that almost none are available for interaction with the electrophilic centers in 1. In contrast, about half of the nucleophilic centers in the water cluster are not fettered by hydrogen bonding and therefore are exposed for interaction with 1 at either C-2 or C-4 after formation of the mixed 1·$(H_2O)_n$ complex as noted in Scheme I. Thus, reaction with water neat or in a neutral solvent is about 34-fold faster than the corresponding reactions with ammonia. The situation is reversed, however, for competitive reactions in strong proton-acceptor solvents with low dielectric constant, such as pyridine. In dilute solutions of these solvents, the nucleophilic centers of both coreactants are fully exposed. The relative rates for product formation, therefore, depend only on the relative rates that 1·HN·$(HS)_2$ and 1·HOH·S undergo intracluster nucleophilic attack at the adjacent C-2 position of 1. Since the unpaired electrons on nitrogen are more nucleophilic than the corresponding oxygen electrons, interaction with ammonia in pyridine is 53 times faster than interaction with water.[1]

The effects of hydrogen bonding and availability of the nucleophilic unpaired electrons within a cluster upon reaction rate with a bulky electrophile are also apparent when one compares the rate constants for interaction of 1 with ammonia in benzene and in pyridine solutions that contain added water. Addition of water to the benzene system causes a 500-fold increase in rate and a sharp change in selectivity.[1] These changes are attributed to formation of 1·$(NH_3)_n$·HOH, which leads immediately to *o*-acetamidobenzamide formation via nucleophilic attack at C-4, in contrast to 1·$(NH_3)_n$ association in the absence of water, which can only lead very slowly to 2-methylquinazolone formation as discussed previously.[1] On the other hand, addition of water to the pyridine system causes a twofold decrease in the rate of product formation without change in selectivity. This decrease is attributed to the solvent exchange equilibrium

$$1\cdot HN(H\cdot S)_2 + S\cdot HOH\cdot S \rightleftarrows (1\cdot H)(S\cdot H)_2N\cdot HOH\cdot S + S$$

which in effect substitutes the availability of strong nucleophilic unpaired nitrogen electrons for much less nucleophilic unpaired oxygen electrons. Consequently the rate for conversion of 1 to interaction products decreases accordingly.

Experimental Section

Materials. Acetylanthranil (1), mp 81–82 °C, was prepared as described previously.[19] It was stored in chunk form in a sealed flask to minimize interaction with atmospheric moisture since 1 undergoes hydrolysis to *o*-acetamidobenzoic acid (2) even in the solid state. Small samples were comminuted to a fine powder periodically and stored in a small vial for subsequent hydrolysis studies in organic solvents as needed. The ratio of 1 to 2 in the powdered sample at time zero of the hydrolysis study in solvent, S, was established by the initial corresponding ratio of the proton NMR integration values for the methyl group of 1 relative to that in 2 in the resultant 0.5 M solution of 1 + 2 in solvent S.

The position of the proton NMR signals for active hydrogen or water in these solvents, however, shifts downfield as a function of $[H_2O]$ (i.e., $\tau_w = \tau_0 - C[H_2O]$) and also as a function of the

(19) Part 1: L. A. Errede, *J. Org. Chem.*, 41, 1763 (1976).

mole fraction of OH attributable to **2** with respect to water (i.e., $\tau_x = \tau_w - CX$; see paragraph at end of this paper about Supplementary Material).

The solvents were obtained as commerical samples and were used as such without further purification. The proton spectra were recorded with either a Varian XL-100 or a Perkin-Elmer R32 spectrometer.

General Procedure for Hydrolysis of Acetylanthranil (1) in Organic Solvents. A sample of powdered **1** (0.04 g) was weighed into an NMR tube. Solvent (0.50 cm^3) was added by means of a microsyringe graduated into units of 0.01 cm^3 to produce a clear solution. A measured amount of water was then added by means of a microsyringe, graduated into units of 10^{-5} cm^3, and the initial time was noted. Tetramethylsilane (0.01 cm^3) was added as the internal reference and the first proton NMR spectrum was recorded immediately thereafter. The ratio [**1**]/[**2**] in the powdered sample taken for study and the ratio $[H_2O]/([1] + [2])$ were established from the relative integration values of τ for 1-CH_3, 2-CH_3, and active OH in this initial spectrum. Spectra were recorded periodically thereafter as needed to monitor the complete conversion of **1** to *o*-acetamidobenzoic acid (**2**). Usually the NMR tube was allowed to remain in the NMR probe (36 °C) during the first hour of hydrolysis or until hydrolysis was about 80% complete, whichever came first. Thereafter the NMR tube was stored at 22 °C until the next NMR spectrum was recorded.

The integration values for the sum of the methyl substituents 1-CH_3 and 2-CH_3 for each spectrum in the set of spectra recorded in order to monitor to completion the conversion of **1** to **2** were normalized to a common value of 50 units, which corresponded to 0.5 M with respect to solute (**1** + **2**) established gravimetrically. Accordingly, the units for concentration of unreacted **1** at time t were 0.01 of the corresponding integration value. Since the hydrolysis is known to be stoichiometric, the corresponding water concentration at time t was given by $[H_2O]_t = [H_2O]_0 - ([1]_0 - [1]_t)$. The values for log $[H_2O]/[1]$ were plotted as a function of t to establish the pseudo-second-order relationships shown in Figures 1 and 2 which were used to calculate k_b and k_a, the pseudo-second-order rate constants in L/mol·min before and after the observed point of inflection at t_i.

Registry No. **1**, 525-76-8.

Supplementary Material Available: Detailed procedures for hydrolysis time studies using CD_3CN, $CDCl_3$, and benzene as solvents and the plots of the data obtained thereby (8 pages). Ordering information is given on any current masthead page.

ESR Study of Persistent Thioaminyls, *N*-(Arylthio)-3,5-di-*tert*-butylphenylaminyls[1,2]

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Received February 5, 1980

N-(Arylthio)-3,5-di-*tert*-butylphenylaminyls (**2**) are generated by hydrogen-abstraction from *N*-(3,5-di-*tert*-butylphenyl)arenesulfenamides (**1**) and are investigated by means of ESR spectroscopy. When the sulfenamides were treated with lead dioxide in benzene, the solutions turn immediately dark blue or dark greenish blue (502–605 nm) and the colored solutions give a strong ESR signal due to **2**. The nitrogen hyperfine-splitting constants for **2** are in the range 9.52–9.64 G, and the g values are in the range 2.0057–2.0061. The spin densities in **2** are calculated by using the HMO and McLachlan HMO procedures, and the results are compared with the experimental results. The radicals **2** are very long-lived, even in the presence of oxygen, and can be isolated as hydrazine-type dimers (**3**) which dissociate into **2** at room temperature. The equilibrium constants for **3** ⇄ 2 **2** equilibria are measured in benzene, THF, chloroform, and acetone/benzene over a temperature range from 5 to 33 °C by means of ESR spectroscopy, and the following values are obtained: the equilibrium constants, 0.98×10^{-4}–4.59×10^{-4} M (in benzene at 27 °C); $\Delta H°$ and $\Delta S°$ for the equilibria, 13.3–13.8 kcal/mol and 29.0–29.2 eu (in benzene). These values are compared with literature values.

Although organic free radicals are generally recognized to be transient, there have been some exceptionally persistent free radicals.[3] For example, triarylmethyl radicals are in equilibrium with the isolable dimers in solution at room temperature,[4] and diphenylpicrylhydrazyl (DPPH),[5] nitroxides,[6] and verdazyls[7] can be isolated as pure crystals.

For the past few years, we have studied a type of thioaminyls, RNSR′, by ESR spectroscopy.[1] Since the aminyls bear a divalent sulfur atom adjacent to the radical center, they are significantly stabilized by the resonance contributions $-\dot{N}-\ddot{S}- \leftrightarrow -\ddot{N}^{-}-\dot{S}^{+}-$. Thus, these radicals are fairly persistent when they have no active hydrogen atoms (e.g., β hydrogen atoms). For the purpose of isolating this class of radicals, we have prepared some sterically protected thioaminyls. It has been found that *N*-(arylthio)-3,5-di-*tert*-butylphenylaminyls (**2**) are quite persistent, even in the presence of oxygen, and can be isolated as dimers (**3**) which dissociate into **2** at room temperature.

In this report we describe the generation of **2** and their ESR parameters, the isolation of **3**, the equilibrium constants for **3** ⇄ 2 **2** equilibria, and the thermodynamic

(1) Part 14 of the series "ESR Studies of Nitrogen-Centered Free Radicals." For part 13 see Y. Miura and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, **53**, 2395 (1980).

(2) For a preliminary report of this work see Y. Miura, Y. Katsura, and M. Kinoshita, *Chem. Lett.*, 409 (1977).

(3) For a review see A. R. Forrester, J. M. Hay, and R. H. Thomson, "Organic Chemistry of Stable Free Radicals", Academic Press, London and New York, 1968.

(4) M. Gomberg, *J. Am. Chem. Soc.*, **22**, 757 (1900).

(5) S. Goldschmidt and K. Renn, *Chem. Ber.*, **55**, 628 (1922).

(6) For a review see E. G. Rozantsev, "Free Nitroxide Radicals", translated from Russian by B. J. Hazzard, Plenum Press, New York and London, 1970.

(7) For a review see F. A. Neugebauer, *Angew. Chem., Int. Ed. Engl.*, 12, 455 (1973).

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