Di-*tert*-butyl peroxyoxalate (DBPO) was prepared by Bartlett's method.[8]

DMBI was prepared from 2-phenylbenzimidazole according to literature procedure:[6a,b,13] mp 97–98 °C (lit.[6b] mp 97.5–98.5 °C); $^1$H NMR ($CDCl_3$) $\delta$ 7.4–7.75 (m, 5 H), 6.4–6.6 (m, 2 H), 6.6–6.9 (m, 2 H), 4.95 (s, 1 H), 2.55 (s, 6 H). Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.33; H, 7.18; N, 12.49. Found: C, 79.92; H, 7.28; N, 12.35.

Solvents benzene[14] and acetonitrile[15] were purified by standard procedures. Tetrahydrofuran (Aldrich, HPLC grade) was freshly distilled over $Na/(C_6H_5)_2CO$. Dimethylformamide (Aldrich, HPLC grade) was used as received.

**General Procedure for the Reduction of α-Nitro Sulfones.** A solution of α-nitro sulfone (0.050 M), internal standard (0.02 M), and DMBI (0.05 M) was placed in a reaction ampule, degassed by three freeze–thaw cycles, sealed under vacuum, and thermostated at 61 °C for the time specified. The ampule was then opened and the mixture analyzed by GLPC (4 ft × $^1/_4$ in. glass column packed with 10% FFAP on Chromosorb W (AW-DMCS, 60–80 mesh) or a 20 ft × $^1/_4$ in. glass column packed with 5% OV-101 on Chromosorb W (AW-DMCS, 100–120 mesh)). GLPC analyses were carred out with a HP 5840A gas chromatograph interfaced to a HP 5840A integrator.

Products were identified by a comparison of their retention time, GLPC/mass spectra, and GLPC/IR spectra with those of authentic samples.

When DBPO was used as initiator, the reactions were carried out at room temperature and under laboratory lighting. For the reaction in the presence of oxygen, the ampule was sealed under atmospheric pressure and thermostated at 61 °C for 23 h.

**General Procedure for the Preparative Reactions.** A solution of α-nitro sulfone (2 mmol), DMBI (2.2 mmol), and AIBN (0.14 mmol) in 20 mL of distilled THF was placed in a reaction tube, degassed by three freeze–thaw cycles, sealed, and thermostated at 61 °C for 24 h. After the tube was opened, the mixture was diluted with 50 mL of anhydrous ethyl ether and filtered. The solid was washed with $Et_2O$. The solid (salt from DMBI) was recovered. The filtrate was treated with a dilute ethereal iodine solution to destroy excess DMBI. The solution was again filtered and the filtrate evaporated. The residue was purified by column chromatography (silica gel) eluted with ether, which uppon evaporation gave the pure nitroalkane. The purity was higher than 95% as checked by GLPC. The product was identified by comparison of its $^1$H NMR and IR spectra with those of the authentic material.

**Reduction of Isolated 1,3-Dimethyl-2-phenylbenzimidazolium Benzenesulfinate to DMBI.** The reisolated 1,3-dimethyl-2-phenylbenzimidazolium benzenesulfinate (0.40 g, 0.11 mmol) obtained from the preparative reduction was dissolved in a minimum amount of methanol (3 mL), and sodium borohydride (0.10 g) was added in small portions to the stirred solution. The solvent was removed under reduced pressure. Water (5 mL) was added to the residue, which was then filtered and washed with water. The precipitate was recrystallized from 95% ethanol and dried: yield 81%; mp 90–91.5 °C). A comparison of the mixture melting point with the melting point of authentic DMBI was identical.

(13) Craig, J. C.; Ekwuribe, N. N.; Fu, C. C.; Walker, K. A. M. *Synthesis* **1981**, 303.
(14) Vogel, A. I. *Textbook of Practical Organic Chemistry*; Longman: Birmingham, AL, 1956.
(15) Walter, M.; Ramaley, L. *Anal. Chem.* **1973**, *45*, 165.

# AM1 Study of the Protonation of Pteridine-Related Tetraazanaphthalenes

Julio Anguiano and Javier Fernández Sanz

*Department of Physical Chemistry, Faculty of Chemistry, University of Sevilla, 41071 Sevilla, Andalucia, Spain*

Jaume Vilarrasa*

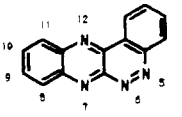
*Department of Organic Chemistry, Faculty of Chemistry, University of Barcelona(III), 08028 Barcelona, Catalonia, Spain*

*Received November 30, 1987*

All the possible non-N-bridged diazinodiazines (13 structures) and their protonated forms (36 structures) have been calculated by means of the recently developed AM1 SCF-MO method, after a critical evaluation of its performance. Some remarkable points—pteridine is predicted to be the strongest base of the series; compound 4 should be preferably protonated at N1—and some reasonable rules to explain the basicity differences are disclosed.

It is known that $pK_a$ values of pteridines, quinazolines, and related polyazanaphthalenes are masked by the covalent hydration phenomenon:[1] due to the spontaneous addition of water or protic solvents to polar double bonds, some $pK_a$ values found in the literature for these molecules belong in fact to their hydrates or solvates. To know which are or could be the more basic and/or nucleophilic nitrogens of these heterocyclic systems is a subject of current interest.[2]

In this connection, it is also worth noting that in a very recent experimental work,[3] which deals with the addition of hydrogen chloride to quinoxalino[2,3-*c*]cinnoline (1) to afford exclusively its 10-chloro derivative, the N12-protonated form was postulated as a key intermediate, despite the fact that MNDO calculations[4] on this system predicted that "it is protonation at N7 which yields the cation of lowest heat of formation".[3] This last result is strange, since it is well-known that pyridazine (1,2-diazine) is a stronger base than pyrazine (1,4-diazine) and that cinnoline (1,2-diazanaphthalene) is also stronger than quinoxaline (1,4-diazanaphthalene).[5]



1

(1) For a review on the subject, see: Albert, A. *Adv. Heterocycl. Chem.* **1976**, *20*, 117.
(2) Lowe, P. A. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds. (Katritzky, A. R., Rees, C. W., General Eds.); Pergamon: Oxford, 1984; Vol. 2, p 581. Pfleiderer, W. *Ibid.* Vol. 3, p 261. Castle, R. N.; Phillips, S. D. *Ibid.* Vol. 3, p 329.
(3) Glidewell, C.; Shepperd, T.; Smith, D. M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 507. Glidewell, C.; Shepperd, T.; Smith, D. M. *Tetrahedron Lett.* **1983**, *24*, 3151.
(4) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899, 4907.
(5) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon: Oxford, 1985.

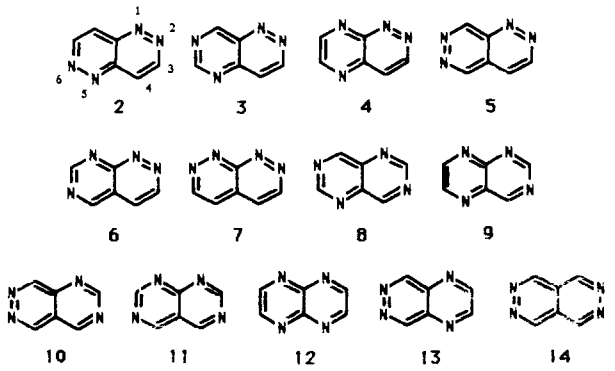
0022-3263/88/1953-3900$01.50/0 © 1988 American Chemical Society

**Table I. Proton Affinities of 15 as Predicted by AM1, 3-21G, and 6-31G* Calculations**

| | 15 | 15-H$^+$ | PA, kcal/mol |
|---|---|---|---|
| AM1 ($\Delta H_f$) | 51.5 kcal/mol | 196.4 kcal/mol | 222.3 |
| 3-21G[a] | −185.846 13 au | −186.231 75 au | 242.0 |
| 6-31G*//3-21G[a] | −186.910 24 au | −187.285 13 au | 235.2 |
| MP3/6-31G*//3-21G[a] | −187.496 88 au | −187.859 62 au | 227.6 |
| MP4/6-31G*//3-21G[a] | −187.506 21 au | −187.868 56 au | 227.4 |
| ZPE difference (calcd) | | | −9.2 |
| ZPE difference (corr) | | | −8.1 |

[a] Total energy in atomic units (au); 1 au = 627.5 kcal/mol.

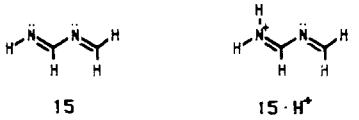
To gain insight into these two questions—the first one of broader scope, the second one more specific—we have carried out for the first time a systematic study of the relative energies of all the possible (non-N-bridged) diazinodiazines, from 1,2,5,6-tetraazanaphthalene (**2**) to 2,3,6,7-tetraazanaphthalene (**14**), and their protonated forms by means of the AM1 method.[6] The series includes pteridine (**9**)[7] and 1,2,5,8-tetraazanaphthalene (**4**), the parent structure of **1**.




## Results and Discussion

**Reliability of AM1.** A previous step was to evaluate the performance of the AM1 method concerning heterocyclic species. Former work by us has shown that AM1 is very suitable for the prediction of the heats of formation ($\Delta H_f$) of azines and benzazines and for their proton affinities (PAs),[8] provided that a correction term of ca. 9 kcal/mol is added to the calculated $\Delta H_f$ values of neutral and protonated molecules for each pair of vicinal nitrogens with nonbonding valence electrons. This correction term had to be introduced because of the *systematic* underestimation by AM1 of the electron repulsion between vicinal lone-pair nitrogen atoms.

Another previous point that we posed ourselves was to evaluate whether the AM1 underestimation of the lone-pair electron repulsion between peri nitrogens (i.e., nitrogens with "parallel lone pairs" such as those found in the all-planar 1,3-diazabutadiene structure (**15**) or in 1,8-naphthyridine) is also significant or not. To solve this question, we calculated the minimum-energy points of **15** and its N1-protonated conjugate acid (**15**-H$^+$) by means




of the AM1 method and of ab initio methods at the 3-21G,[9] 6-31G*,[10] MP3/6-31G*//3-21G,[10] and MP4(SDQ)/6-31G*//3-21G[10] levels. As demonstrated,[8] ab initio calculations with the split-valence 3-21G basis set give PAs for heterocyclic azines that *systematically* lie 18–20 kcal/mol above the available experimental results; the results for **15** and **15**-H$^+$ (see Table I) show the expected pattern,[8] since the 3-21G calculated PAs lie 20 kcal/mol above the AM1 PAs. Moreover, inclusion of the correlation energy at the 6-31G* level gives PAs values of ca. 227.5 kcal/mol; if zero-point energy (ZPE) and thermal corrections were taken into account,[11] our best ab initio calculations would predict a PA value for **15** of 227.5 (±0.1)−8.1 (±0.2) + 1.5 ≈ 221 kcal/mol.

Thus, it appears that the predicted AM1 value (222.3 kcal/mol) for the protonation of **15** is reliable, with a probable "error" of 1–2 kcal/mol. It means that the repulsion between the nitrogen lone pairs of **15** is not (significantly) underestimated or, at least, that the possible "defects" of the method are compensated in such cases.

In summary, the level of confidence of AM1 is very good, bearing in mind the usual errors of all methods. Only a correction term is needed: 9 kcal/mol must be added to each computed $\Delta H_f$ value to obtain correct absolute energies for those species with two neighboring nitrogens.

**AM1 Calculations of Diazinodiazines 2–14.** The heats of formation of **2**–**14** and of all their N-protonated species are collected in Table II, second column. The protonation position is pointed out by means of N1-H, N2-H, etc. After the addition of either 0, 9, or 18 kcal/mol to the AM1 value, depending on the case, to obtain the so-called "AM1 corr" value, the corresponding "PA corr" arises from PA = $\Delta H_f$(base) + $\Delta H_f$(H$^+$) − $\Delta H_f$(base-H$^+$), using the experimental value of 367 kcal/mol[12] for $\Delta H_f$(H$^+$). For the sake of concision, the PA values are put in the same table, in rows **2**(N1-H), **2**(N2-H), and so on, but, as is obvious, these values correspond to reactions **2** → **2**(N1-H), **2** → **2**(N2-H), etc. The calculated dipole moments are included in the last column, while the optimized geometrical parameters can be obtained on request. It is to be noted that in all these calculations we have only assumed that all atoms were coplanar and symmetry conditions do operate.

(6) Dewar, M. J. S.; Zoebisch, E. C.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(7) For earlier calculations of pteridine, see: Gready, J. E. *J. Comput. Chem.* **1984**, *5*, 411. Gready, J. E. *THEOCHEM* **1985**, *25*, 1. Also see Neiman (Neiman, Z. *J. Heterocycl. Chem.* **1974**, *11*, 7) for CNDO/2 and MINDO/1 calculations of the pteridine protonation site.

(8) Fernández, J.; Anguiano, J.; Vilarrasa, J. *J. Comput. Chem.*, in press. The predicted PA values are only a few kilocalories per mole below the available experimental ones. Also see: Fos, E.; Vilarrasa, J.; Fernández, J. *J. Org. Chem.* **1985**, *50*, 4894.

(9) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939. Binkley, J. S.; Frisch, M. J.; DeFrees, D. J.; Raghavachari, K.; Whiteside, R. A.; Schlegel, H. B.; Fluder, E. M.; Pople, J. A. GAUSSIAN 82, Carnegie-Mellon University, Pittsburg, PA.

(10) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213. For the Moller–Plesset treatment of the electron correlation, see: Moller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618. Binkley, J. S.; Pople, J. A. *Int. J. Quantum Chem., Symp.* **1976**, *10*, 1. Krishnan, R.; Frisch, M. J.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 4244.

(11) The 3-21G ZPE corrections were calculated to be 42.0 kcal/mol for **15** and 51.2 kcal/mol for **15**-H$^+$ (i.e., the calculated ZPE difference was 9.2 kcal/mol). Since extensive comparisons with experiment have shown that the corresponding harmonic frequencies are 10–20% too large, with a mean error of ca. 12%, a more realistic ZPE difference value could be 8.1 ± 0.2 kcal/mol (for a review, see: Hess, B. A.; Schaad, L. J.; Cársky, P.; Zahradnik, R. *Chem. Rev.* **1986**, *86*, 709). On the other hand, thermal corrections, from 0 to 298 K, are expected to be small (around 1.5 kcal/mol, as calculated for related examples: Meot-ner, M.; Liebman, J. F.; Del Bene, J. E. *J. Org. Chem.* **1986**, *51*, 1105). Overall corrections (differential ZPE plus thermal corrections) of 6–8 kcal/mol are rather common for similar protonations (see ref 12 and Hehre et al.: Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley-Interscience: New York, 1986).

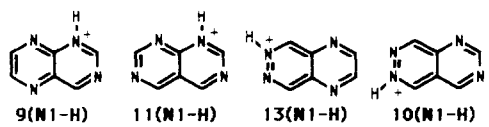
(12) Cf.: *Gas Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic: New York, 1979; Vol. 2.

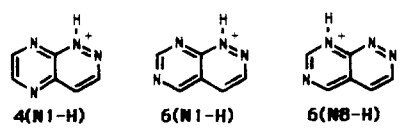
Table II. AM1-Calculated Heats of Formation,[a] PAs,[a] and Dipole Moments[b] for Diazinodiazines

| | AM1 | AM1 corr | PA corr | $\mu_D$ |
|---|---|---|---|---|
| 2 | 109.8 | 128 | | 0.00 |
| 2(N1-H) | 283.4 | 292.5 | 202.5 | |
| 2(N2-H) | 285.0 | 294 | 201 | |
| 3 | 98.2 | 107 | | 1.79 |
| 3(N1-H) | 273.0 | 273 | 201 | |
| 3(N2-H) | 270.9 | 271 | 203 | |
| 3(N5-H) | 261.5 | 270.5 | 203.5 | |
| 3(N7-H) | 262.2 | 271 | 203 | |
| 4 | 105.0 | 114 | | 3.72 |
| 4(N1-H) | 271.9 | 272 | 209 | |
| 4(N2-H) | 277.1 | 277 | 204 | |
| 4(N5-H) | 273.8 | 283 | 198 | |
| 4(N8-H) | 268.4 | 277.5 | 203.5 | |
| 5 | 109.3 | 127 | | 3.75 |
| 5(N1-H) | 286.2 | 295 | 199 | |
| 5(N2-H) | 287.0 | 296 | 198 | |
| 5(N6-H) | 279.1 | 288 | 206 | |
| 5(N7-H) | 277.6 | 288.5 | 207.5 | |
| 6 | 103.6 | 112.5 | | 4.29 |
| 6(N1-H) | 270.9 | 271 | 208.5 | |
| 6(N2-H) | 278.8 | 279 | 200.5 | |
| 6(N6-H) | 269.6 | 278.5 | 201 | |
| 6(N8-H) | 262.6 | 271.5 | 208 | |
| 7 | 114.5 | 132.5 | | 6.10 |
| 7(N1-H) | 284.4 | 293.5 | 206 | |
| 7(N2-H) | 288.7 | 298 | 201.5 | |
| 8 | 87.3 | 87 | | 0.01 |
| 8(N1-H) | 251.3 | 251 | 203 | |
| 8(N3-H) | 252.3 | 252 | 202 | |
| 9 | 93.9 | 94 | | 2.38 |
| 9(N1-H) | 250.2 | 250 | 211 | |
| 9(N3-H) | 256.1 | 256 | 205 | |
| 9(N5-H) | 263.0 | 263 | 198 | |
| 9(N8-H) | 255.4 | 255.5 | 205.5 | |
| 10 | 97.9 | 107 | | 2.58 |
| 10(N1-H) | 263.8 | 273 | 201 | |
| 10(N3-H) | 265.9 | 275 | 199 | |
| 10(N6-H) | 265.3 | 265 | 209 | |
| 10(N7-H) | 266.8 | 267 | 207 | |
| 11 | 92.0 | 92 | | 2.50 |
| 11(N1-H) | 248.8 | 249 | 210 | |
| 11(N3-H) | 255.4 | 255.5 | 203.5 | |
| 12 | 101.2 | 101 | | 0.01 |
| 12(N1-H) | 262.4 | 262.5 | 205.5 | |
| 13 | 99.4 | 108.5 | | 4.28 |
| 13(N1-H) | 270.3 | 279 | 196.5 | |
| 13(N6-H) | 265.6 | 265.5 | 210 | |
| 14 | 108.8 | 127 | | 0.00 |
| 14(N1-H) | 280.6 | 289.5 | 204.5 | |

[a] In kilocalories per mole. [b] In debyes.

In comparing the PA values of Table II, it is seen that some protonations are especially favored, with values above 208 kcal/mol, and some others are relatively very unfavorable, with PAs below 200 kcal/mol. The cations formed more exothermically are the following:

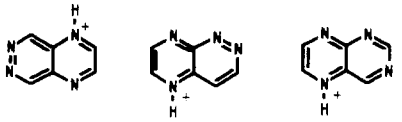


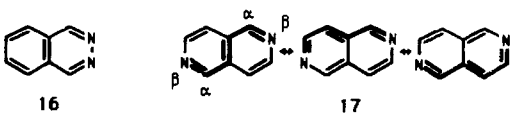

It is remarkable that pteridine is predicted to be the most basic member of the series, its protonation taking place at N1 to give 9(N1-H), a result that agrees with earlier STO-3G and 3-21G calculations of Gready;[7] this poses the question of whether the initial addition of water[1] to the 3,4-bond could be in fact a 1,4-addition, i.e., protonation at N1 followed by attack of water on C4, the more electron deficient carbon atom (+0.133 $e^-$ vs +0.130 $e^-$ for C2) of 9(N1-H). Secondly, it is to be noted that the more stable cation arising from 4 is that protonated at N1, the remaining positions being less favorable by more than 5 kcal/mol. From a more general viewpoint, it appears that five of the above species have peri nitrogens, which suggests that the proton is bonded more strongly when a second, appropriate nitrogen lone pair interacts with it, as could be expected since this is the conceptual basis of the so-called "proton sponges".[13] The two remaining species of the above set belong to another "class" that can be related to phthalazine (16); we had shown[8] that 16 is intrinsically much more basic than its isomers cinnoline, quinoxaline, and quinazoline.

Nevertheless, not every diazinodiazine with nitrogens in peri positions gives cations with the proton strongly linked to one of these peri nitrogens; for instance, the PA value for the protonation at N8 of 4 is only 203.5 kcal/mol, and that for pyrazinopyrazine (see 12) is 205.5 kcal/mol. In addition, not every diazinodiazine with two nitrogens as in 16 is a relatively strong base since, e.g., the PA value for protonation at N6 of 5 amounts to 206 kcal/mol and that for 14 is 204.5 kcal/mol. Thus, as expected, it appears that some factors disfavor the protonation on certain nitrogens.

To gain insight into these factors, a look to the three more unstable cations, with regard to the parent molecules, may help. These are




It is clear that having a para nitrogen is the worst situation for a given nitrogen atom. Another destabilizing factor, although not so significant, operates on β-nitrogens: it is the presence of a second β-nitrogen separated by five bonds, as depicted by 17. This is observed in comparing, e.g., 10(N6-H) to 10(N7-H), since N6 has no β-nitrogen atom opposite to it in the other ring while N7 has one. Another example is 14: whereas 16 is the most basic benzodiazine, 14 occupies an intermediate position within the diazinodiazine series. It is believed that N6 "deactivates" N2 whereas N7 "deactivates" N3, and vice versa. This is supported by the changes of total electron density when N2 of 14 is protonated: according to AM1, in the neutral molecule all the nitrogens of 14 have the same atomic net charge (−0.044 $e^-$), but after protonation of N2, the charge on N6 is +0.036 $e^-$ and on N7 is only +0.020 $e^-$. The relationship between positions 2 and 6, as depicted in 17, may be considered paratransannular; it may be named diagonal or diago.[14]




(13) Alder, R. W.; Bowman, P. S.; Steele, W. R. P.; Winterman, D. R. *J. Chem. Soc., Chem. Commun.* **1968**, 723.

(14) Since it is known that electron-donating groups at position 2 of naphthalene activate electrophilic attacks at positions 1 and 6 (see, e.g.: Koelsch, C. F. *Org. Synth.* **1940**, *20*, 18. Vona, J. A.; Merker, P. C. *J. Org. Chem.* **1949**, *14*, 1048), it is reasonable that electron-withdrawing groups at position 2 deactivate electrophilic attacks at the above-mentioned positions and, in the present particular case, that N2 deactivates N6 and vice versa. Obviously, this may be ascribed to the partial localization of double and single bonds in naphthalene and naphthalene derivatives (see 17).

## Conclusions

(a) Pteridine, the parent ring of a well-known class of natural products, appears to be the strongest base within the diazinodiazine series. Taking into account that isomers are being compared, it is likely that this feature is maintained in condensed phase. The preferred protonation site of pteridine is N1.

(b) Pyrazino[2,3-*c*]pyridazine (**4**) is predicted to be protonated at N1. The energy differences among the cation protonated at N1 and the rest are so significant that, even in solution, protonation at N1 may be largely predominant. In the light of these results and former results from our work,[8] explanations offered by Glidewell et al.[3] concerning the reactivity of **1** should be partly revised.

(c) The basicity of any $\alpha$-nitrogen is quite enhanced when it has a peri nitrogen.

(d) The basicity of N2 or N3 of 2,3,*m*,*n*-tetraazanaphthalenes is larger than that of N1 or N2 of 1,2,*m*,*n*-tetraazanaphthalenes.

(e) The basicity of an $\alpha$-nitrogen is much lower when another $\alpha$-nitrogen (para) is present in the same ring.

(f) The basicity of a $\beta$-nitrogen is lower when another $\beta$-nitrogen lies in the opposite position of the other ring (diago).

**Registry No.** **2**, 6133-45-5; **2**·$H^+$, 115340-47-1; **3**, 6133-46-6; **3**·$H^+$, 115340-48-2; **4**, 254-96-6; **4**·$H^+$, 115340-49-3; **5**, 253-74-7; **5**·$H^+$, 115340-50-6; **6**, 254-62-6; **6**·$H^+$, 115340-51-7; **7**, 6133-50-2; **7**·$H^+$, 115340-52-8; **8**, 254-82-0; **8**·$H^+$, 115340-53-9; **9**, 91-18-9; **9**·$H^+$, 115340-54-0; **10**, 253-88-3; **10**·$H^+$, 115340-55-1; **11**, 254-64-8; **11**·$H^+$, 115340-56-2; **12**, 255-53-8; **12**·$H^+$, 115340-57-3; **13**, 254-95-5; **13**·$H^+$, 115340-58-4; **14**, 253-61-2; **14**·$H^+$, 115340-59-5; **15**, 82810-12-6; **15**·$H^+$, 115340-60-8; $H^+$, 12408-02-5.

# Acid-Catalyzed Hydrolysis of *N*-Hydroxyacetanilides: Amide Hydrolysis vs N–O Bond Heterolysis

Michael Novak,* Gayl A. Bonham, Linda K. Mohler, and Kristine M. Peet

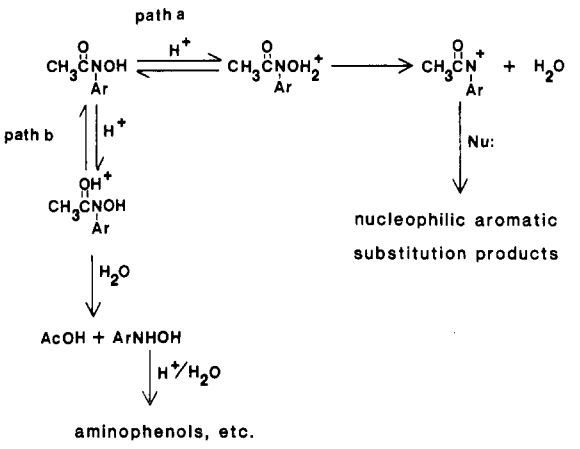
*Department of Chemistry, Miami University, Oxford, Ohio 45056*

*Received March 25, 1988*

Although it has been widely assumed that *N*-hydroxy-*N*-aryl amides decompose in acidic solution by acid-catalyzed N–O bond heterolysis, we have found that the *N*-hydroxyacetanilides **1a–e** largely decompose by the alternative amide hydrolysis pathway. The immediate products of hydrolysis, the hydroxylamines **2a–e**, can be detected by direct or indirect methods, but these materials also decompose via the Bamberger rearrangement under the reaction conditions. Only the *p*-EtO- and *p*-MeO-substituted *N*-hydroxyacetanilides (**1a** and **1b**) exhibit any sign of N–O bond heterolysis, and only as a minor component (ca. 7%) of the overall hydrolysis. No change in mechanism could be found for **1d** in $H_2SO_4$ solutions as concentrated as 9 M. The lack of reactivity of **1a–e** to N–O bond heterolysis is largely due to unfavorable protonation of the OH group. Protonation of the carbonyl oxygen is favored over the hydroxyl oxygen by ca. 7 orders of magnitude.

It is widely assumed, with little supporting evidence, that *N*-hydroxy-*N*-arylacetamides decompose in acidic aqueous solution via N–O bond heterolysis to yield *N*-acetyl-*N*-arylnitrenium ions (Scheme I, path a).[1] Sulfuric, methanesulfonic, and carboxylic acid esters of such compounds have recently been shown to undergo uncatalyzed N–O bond heterolysis under various conditions to yield nitrenium ion species,[2-4] but the chemistry of *N*-hydroxy-*N*-arylamides in $H_2O$ has not been investigated in detail. Acid hydrolysis of the amide functionality followed by Bamberger rearrangement[5] of the resulting *N*-aryl-

**Scheme I**




hydroxylamines (Scheme I, path b) would also appear to be a viable reaction possibility in the absence of experimental data.

We have examined the hydrolysis of the *N*-hydroxyacetanilides **1a–e** in HCl solutions in the pH range 0.3–3.0 at 50 °C and found that these compounds undergo reaction primarily via path b to yield the corresponding hydroxylamines **2a–e**, which also decompose under these conditions, but which can be detected either directly by HPLC or UV spectroscopy or indirectly by product study comparisons. Path a is a minor contributor (<10%) to the hydrolysis of only **1a** and **1b**. Examination of the hy-

(1) See, for example: (a) Calder, I. C.; Creek, M. J.; Williams, P. J.; Funder, C. C.; Green, C. R.; Ham, K. N.; Tange, J. D. *J. Med. Chem.* **1973**, *16*, 499–502. (b) Calder, I. C.; Creek, M. J.; Williams, P. J. *Chem.-Biol. Interact.* **1974**, *8*, 87–90. (c) Calder, I. C.; Williams, P. J. *Chem.-Biol. Interact.* **1975**, *11*, 27–32. (d) Gemborys, M. W.; Gribble, G. W.; Mudge, G. H. *J. Med. Chem.* **1978**, *21*, 649–652. (e) Yoshioka, T.; Uematsu, T. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1377–1381.

(2) (a) Novak, M.; Pelecanou, M.; Roy, A. K.; Andronico, A. F.; Plourde, F. M.; Olefirowicz, T. M.; Curtin, T. J. *J. Am. Chem. Soc.* **1984**, *106*, 5623–5631. (b) Novak, M.; Pelecanou, M.; Pollack, L. *J. Am. Chem. Soc.* **1986**, *108*, 112–120. (c) Novak, M.; Pelecanou, M.; Zemis, J. N. *J. Med. Chem.* **1986**, *29*, 1424–1429. (d) Novak, M.; Roy, A. K. *J. Org. Chem.* **1985**, *50*, 571–580.

(3) Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1498–1499 and 2448–2449.

(4) Underwood, G. R.; Kirsch, R. B. *J. Chem. Soc., Chem. Commun.* **1985**, 136–138.

(5) (a) Bamberger, E. *Chem. Ber.* **1894**, *27*, 1347–1350, 1548–1557; **1895**, *28*, 245–251; **1900**, *33*, 3600–3622. (b) Sone, T.; Tokuda, Y.; Sakai, T.; Shinkai, S.; Manabe, O. *J. Chem. Soc., Perkin Trans. 2* **1981**, 298–302. (c) Kohnstam, G.; Petch, W. A.; Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* **1984**, 423–427.

0022-3263/88/1953-3903$01.50/0 © 1988 American Chemical Society