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New Method for the Facile Reduction of α-Nitro Sulfones to Nitroalkanes via an Electron-Transfer–Hydrogen Atom Abstraction Mechanism

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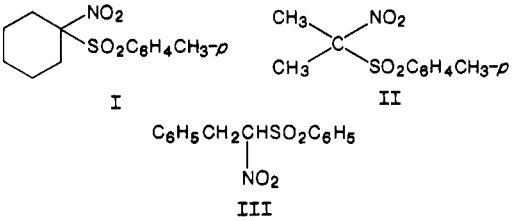
The mechanism for the reduction of several α-nitro sulfones with 1,3-dimethyl-2-phenylbenzimidazoline (DMBI) was investigated. The reduction proceeds by a free-radical chain process where the initiation step and one of the propagation steps involve single electron transfer reactions. The synthetic utility of the reduction was investigated.

α-Nitro sulfones are potentially useful substrates in organic synthesis. (Arylsulfonyl)nitromethane and its alkylated derivatives easily undergo C-alkylation to form mono- or dialkylated α-nitro sulfones.[1] While the sulfonyl group may be replaced by other groups via a free-radical chain substitution,[2] synthetically it is also desirable to replace the sulfonyl group by a hydrogen atom. Only two methods for achieving this transformation have been reported. One involves the use of sodium hydrogen telluride.[3] Only one substrate was used to demonstrate this process, and no mechanistic investigations were carried out, although an electron-transfer process was proposed for the desulfonylation. The other reducing agent that has been investigated is *N*-benzyl-1,4-dihydronicotinamide (BNAH). When the reduction was carried out in benzene under prolonged irradiation using a large excess of the reagent (≥6 molar equiv), moderate yields of nitroalkanes could be obtained.[1] A radical chain mechanism was proposed for the transformation by analogy to the reduction of activated nitroalkanes. Almost simultaneously it was reported that α-nitro sulfones were easily reduced to the corresponding nitroalkanes by BNAH in dimethylformamide at room temperature.[4] A radical nonchain mechanism was proposed. However, neither experimental nor mechanistic details were given.

During the course of the investigation of the reduction of nitroalkanes by organotin hydrides,[5] we carried out the reductions of several α-nitro sulfones by BNAH and compared them with the tin hydride reductions. Contrary to the published report,[4] reduction products were only produced (e.g., >4%) when the reaction was carried out under prolonged irradiation (72 h, 200-W incandescent lamp). Under these conditions, moderate yields (25–59%) of the corresponding nitroalkanes could be realized.[5] In a related study,[6c] 1,3-dimethyl-2-phenylbenzimidazoline (DMBI) was found to be a more reactive electron-transfer reducing agent than BNAH, and it was therefore expected that the reduction of α-nitro sulfones by DMBI would also be more facile.

α-Nitrocyclohexyl *p*-tolyl sulfone (I), α-nitroisopropyl *p*-tolyl sulfone (II), and (2-nitro-2-(phenylsulfonyl)-ethyl)benzene (III) were chosen as model compounds for tertiary and secondary α-nitro sulfones.



I II III

The reduction of α-nitrocyclohexyl *p*-tolyl sulfone (I) by DMBI was carried out in several solvents. The product (nitrocyclohexane) yield was affected by the addition of an initiator (azobisisobutyronitrile, AIBN, or di-*tert*-butyl peroxyoxalate, DBPO) or an inhibitor (*p*-dinitrobenzene,

(1) Wade, P. A.; Hinney, H. R.; Amin, N. V.; Vail, P. D.; Morrow, S. D.; Hardinger, S. A.; Safe, M. S. *J. Org. Chem.* **1981**, *46*, 765.

(2) See, for example: (a) Kornblum, N.; Boyd, S. D.; Ono, N. *J. Am. Chem. Soc.* **1974**, *96*, 2580. (b) Zeilstra, J. J.; Engberts, J. B. F. N. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 954.

(3) Suzuki, H.; Takaoka, K.; Osuka, A. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1067.

(4) Ono, N.; Tamura, R.; Tanikoga, R.; Kaji, A. *J. Chem. Soc., Chem. Commun.* **1981**, 71.

(5) Unpublished results from this laboratory.

(6) DMBI was first employed by Chikashita et al. to reduce α-halo ketones[6a] and α,β-unsaturated carbonyl compounds.[6b] The authors proposed a S_N2 hydride transfer mechanism for α-halo ketones. However, we have shown[6c] that the reaction proceeds via a SET–hydrogen atom abstraction mechanism similar to the reduction by BNAH.[6d] (a) Chikashita, H.; Ide, H.; Itoh, K. *J. Org. Chem.* **1986**, *51*, 5400. (b) Chikashita, H.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1747. (c) Tanner, D. D.; Chen, J. Abstracts of the 3rd North American Chemical Congress, Toronto, ON, June 1988; paper ORGN 414. (d) Tanner, D. D.; Singh, H. K.; Kharrat, A.; Stein, A. *J. Org. Chem.* **1987**, *52*, 2142.

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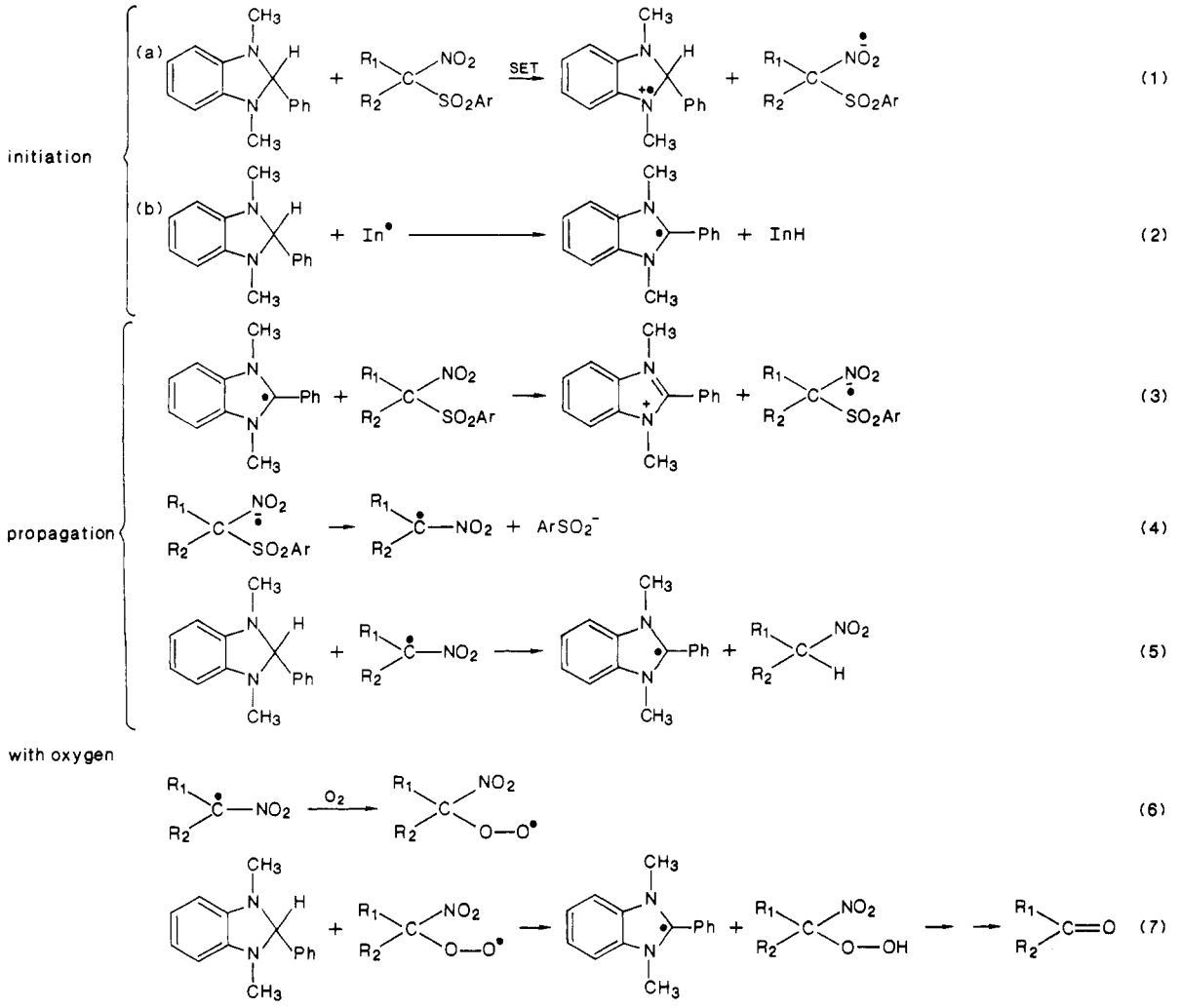
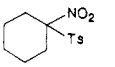
Scheme I



p-DNB). The results of these studies are listed in Table I. In order to observe the effect of changes in reaction conditions, the reactions were carried out in a manner such that incomplete reaction occurred. With the more reactive substrates where substantial but incomplete yields were obtained in relatively short times (<5 h), AIBN was not a good initiator to demonstrate the chain nature of the reaction since its half-life at 61 °C (~23 h) was too long to give appreciable decomposition. At lower temperatures, initiation with DBPO ($t_{1/2}$ = 24 h, 20 °C, C_6H_6; $t_{1/2}$ = 12 min, 20 °C, *i*-Pr_2O)[8] was more satisfactory.

In the absence of a radical initiator or inhibitor in solvents benzene and tetrahydrofuran, nitrocyclohexane was formed from I in relatively low yield. Although inhibition by *p*-DNB (an electron-transfer inhibitor)[7] was not appreciable, the reduction was initiated by AIBN. An electron-transfer free-radical chain sequence could be proposed for the mechanism of the initiated reductions. The uninitiated reduction no doubt proceeds by single electron transfer, SET, initiation, analogous to that proposed for BNAH and DMBI reduction of halo ketones.[6c,d] Direct evidence for the radical mechanism is obtained from the observation that the α-nitrocyclohexyl radical is intercepted by oxygen when the reduction is carried out in the presence of air. For example, when I and DMBI were heated in THF in the dark at 61 °C in the presence of atmospheric oxygen, two products, cyclohexanone (25.6%) and nitrocyclohexane (36.4%), were obtained. Similar

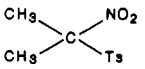
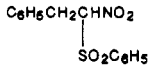
Table I. Reduction of α-Nitrocyclohexyl *p*-Tolyl Sulfone (I) by DMBI

		yield, %	
			
solvent	rctn condns[a]		
C_6H_6	61 °C, 24 h	15.7 ± 3	86.9 ± 0.9
	61 °C, 8% AIBN, 24 h	94.1 ± 4	9.2 ± 0.1
	61 °C, 5% *p*-DNB, 24 h	20.8 ± 0.8	80.6 ± 1.7
	61 °C, O_2, 24 h	30.2[b]	30.9
THF	61 °C, 24 h	22.4 ± 0.6	86.2 ± 5.1
	61 °C, 10% AIBN, 24 h	88.8 ± 2.3	14.5 ± 0.9
	61 °C, 6% *p*-DNB, 24 h	8.6 ± 0.3	103.7 ± 6.2
	61 °C, O_2, 24 h	36.4[c]	34.5
CH_3CN	61 °C, 5 h	51.8 ± 0.1	62.7 ± 10
	61 °C, 5% AIBN, 5 h	99.5 ± 1.5	0.0
	61 °C, 6% *p*-DNB, 5 h	30.4 ± 1.0	82.9 ± 10
	rt,[d] 3 h	48.5 ± 1.6	34.7 ± 1.7
	rt, 7% DBPO,[e] 3 h	86.8 ± 2.8	5.3 ± 0.3
	rt, 7% *p*-DNB, 3 h	11.4 ± 0.4	82.9 ± 4.1
DMF	61 °C, 5 h	79.5 ± 5.8	26.8 ± 3.2
	61 °C, 13 h	98.3 ± 0.5	0.0
	rt, 3 h	21.0 ± 1.1	72.6 ± 3.6
	rt, 6% DBPO, 3 h	101.0 ± 5.1	0.0
	rt, 4% *p*-DNB, 3 h	15.1 ± 0.8	90.0 ± 4.5

[a] Substrate:DMBI = 1:1. All the reactions are carried out in the dark except for the reduction at room temperature. [b] Cyclohexanone (39.4%) was also observed. [c] Cyclohexanone (25.6%) was also observed. [d] Room temperature. [e] DBPO = di-*tert*-butyl peroxyoxalate.

(7) Kornblum, N. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 734.
(8) Bartlett, P. D.; Benzing, E. P.; Pincock, R. E. *J. Am. Chem. Soc.* **1960**, *82*, 1762.

Table II. Reduction of α-Nitro Sulfones by DMBI in THF

substrate	rctn condtns[a]	RNO_2 yield, %
 II	61 °C, dark, 5 h	101.6 ± 5
	61 °C, dark, 3% *p*-DNB, 5 h	8.8 ± 2.0
	rt,[b] 3 h	36.7 ± 1.6
	rt, 10% DBPO, 3 h	61.0 ± 3.0
	rt, 6% *p*-DNB, 3 h	trace (<1%)
 III	90 °C, 0.5 h	73.6 ± 0.6
	90 °C, 3% AIBN, 0.5 h	83.6 ± 2.2
	61 °C, dark, 5 h	68.7 ± 6.8
	61 °C, dark, 4% *p*-DNB, 5 h	0.5 ± 0.1
	rt, 8 h	35.9 ± 3.4
	rt, 5% DBPO, 8 h	78.3 ± 6.8
	rt, 7% *p*-DNB, 8 h	1.7 ± 0.8

[a] Substrate:DMBI = 1:1. [b] Room temperature.

results were also obtained for the reduction in benzene (see Table I). The formation of ketones from the reaction of α-nitroalkyl radicals with oxygen substantiates the intermediacy of the α-nitroalkyl radical since this reaction is a well-documented process.[9] The general mechanism shown in Scheme I is proposed for the reduction of α-nitro sulfones by DMBI.

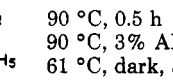
When the reduction was carried out in the more polar solvents acetonitrile and dimethylformamide, the thermal reduction in the absence of initiator became more facile. This is expected, considering the proposed reaction mechanism (Scheme I), since the increase in the solvent polarity accelerates the electron transfer (steps 1 and 3). The uninitiated reduction in CH_3CN can be inhibited by *p*-DNB to a limited extent. Initiation by AIBN could also be observed. In order to observe initiation and inhibition more clearly, we carried out the reduction at room temperature. A low-temperature initiator, di-*tert*-butyl peroxyoxalate (DBPO),[8] was used. Both inhibition and initiation were observed in CH_3CN while only initiation could be observed in DMF.

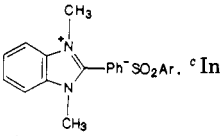
Reductions of α-nitro sulfones II and III were also carried out in THF to test the generality of the reduction by DMBI. The results are shown in Table II. The thermally initiated reduction of II is favored over that of I (see Tables I and II), no doubt due to the differences in the acceptor ability of the two nitro sulfones. Some indication that this is so was obtained from a comparison of the polarographic peak potentials of the current–voltage traces obtained on reduction of the two substrates: E_p for I was −0.78 V (vs SCE) while, for II, E_p was −0.72.[5] Although both reductions are irreversible, the peak potentials are indicative of the proposed order. At 61 °C, the reduction is strongly inhibited by *p*-DNB. Both initiation and inhibition could be observed when the reduction was carried out at room temperature.

The chain reduction by DMBI of all of the α-nitro sulfones is initiated with AIBN or DBPO in either of the four solvents and gives very good yields of their respective nitroalkanes. Although the reactivities of the substrates are qualitatively similar, small differences in their thermal reactivity or reaction in the presence of a particular inhibitor, *p*-DNB, are only quantitative, and these differences do not detract from the synthetic utility of the reduction.

In order to show the potential synthetic application of the present method, we reduced several α-nitro sulfones by DMBI on a preparative scale (Table III). The yields compared favorably with those obtained with BNAH.[1] One advantage of the present method is that the salt

Table III. Preparative Yield for the Reduction of Several α-Nitro Sulfones[a]

substrate	isolated yield, % nitroalkane	isolated yield, % salt[b]
I	92	90
III[c]	83	85
 IV	84	93

[a] Substrate:DMBI:AIBN = 1:1.1:0.07; THF, 61 °C, 24 h, degassed. [b] Salt:  [c] In another reaction run under the same conditions, except without AIBN, a quantitative conversion to nitroalkane was also obtained (GLPC).

1,3-dimethyl-2-phenylbenzimidazolium arenesulfinate ($DMBI^+ArSO_2^-$) can be easily separated from the reaction mixture, and it can be converted back to DMBI by reduction with sodium borohydride in methanol.

In conclusion, α-nitro sulfones are easily reduced by DMBI to give their corresponding nitroalkanes. A SET–hydrogen atom abstraction chain mechanism is proposed for the reduction. The structure of the substrate, solvent polarity, and temperature all affect the ease of the reduction.

Experimental Section

Instrumentation. Gas chromatography/infrared (GLPC/IR) spectra data were obtained by using a Nicolet 7199 FT-IR instrument interfaced to a Varian series 3700 gas chromatograph. Gas chromatography/mass spectral (GLPC/MS) data were obtained by using a Varian Aerograph 1400 gas chromatograph coupled to an A.E.I MS-12 medium-resolution mass spectrometer with a Data General Nova 3DS-55 computer. The columns used for GLPC/IR and GLPC/MS were the same as those used for the quantitative analysis (vide infra).

Materials. The internal standard for GLPC, *p*-di-*tert*-butylbenzene (Aldrich), mp 78–79 °C (lit.[10] mp 80 °C), was recrystallized from ethanol and dried under vacuum (55 °C).

α,α′-Azobisisobutyronitrile (Aldrich) was recrystallized from ethanol/water and dried over P_2O_5 under vacuum, mp 101–102 °C (lit.[11] mp 103 °C).

α-Nitrocyclohexyl *p*-tolyl sulfone (I) and α-nitroisopropyl *p*-tolyl sulfone (II) were prepared by Kornblum's procedure.[12]

I: mp 136–137 °C (lit.[12] mp 135–136.5 °C); ^1H NMR ($CDCl_3$) δ 7.3–7.85 (m, 4 H), 2.5 (s, 3 H), 1.2–2.4 (m, 8 H), 2.6–2.8 (m, 2 H). Anal. Calcd for $C_{13}H_{17}NSO_4$: C, 55.11; H, 6.05; N, 4.94. Found: C, 54.98; H, 6.02; N, 5.06.

II: mp 110–111 °C (lit. 12 mp 109–110 °C); ^1H NMR ($CDCl_3$) δ 7.4–7.9 (m, 4 H), 2.55 (s, 3 H), 2.0 (s, 6 H). Anal. Calcd for $C_{10}H_{13}NSO_4$: C, 49.38; H, 5.39; N, 5.76; S, 13.18. Found: C, 49.45; H, 5.34; N, 5.61; S, 13.26.

(2-Nitro-2-(phenylsulfonyl)ethyl)benzene (III) and 1-nitro-1-(phenylsulfonyl)octane (IV) were prepared by the procedure of Wade.[1]

III: mp 85–86.5 °C (lit. 1 mp 86.5–87.5 °C); ^1H NMR ($CDCl_3$) δ 7.5–8.2 (m, 5 H), 7.35 (s, 5 H), 5.75 (dd, 1 H), 3.5–3.75 (m, 2 H). Anal. Calcd for $C_{14}H_{13}NSO_4$: C, 57.73; H, 4.50; N, 4.81. Found: C, 57.89; H, 4.58; N, 4.86.

IV: mp 53.5–55 °C (lit.[1] mp 53.5–54.5 °C); ^1H NMR ($CDCl_3$) δ 7.5–8.1 (m, 5 H), 5.5 (t, 1 H), 2.0–2.5 (m, 2 H), 1.0–1.5 (m, 10 H), 0.75–1.0 (m, 3 H). Anal. Calcd for $C_{14}H_{21}NSO_4$: C, 56.17; H, 7.07; N, 4.68. Found: C, 56.43; H, 6.88; N, 4.42.

(9) (a) Russell, G. A. *J. Am. Chem. Soc.* **1954**, *76*, 1595. (b) Kill, R. J.; Widdowson, D. A. *J. Chem. Soc., Chem. Commun.* **1976**, 755.

(10) *CRC Handbook of Chemistry and Physics*, 62nd ed.; CRC: Boca Raton, FL, 1981–1982.

(11) *Aldrich Catalog Handbook of Fine Chemicals*, 1986–1987.

(12) Kornblum, N.; Kestner, M. M.; Boyd, S. D.; Cattran, L. C. *J. Am. Chem. Soc.* **1973**, *95*, 3356.

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 ($CDCl_3$) δ 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

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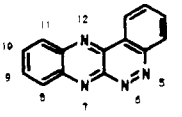
All the possible non-N-bridged diazinodiazines (13 structures) and their protonated forms (36 structures) have been calculated by means of the recently developed AM1 SCF-MO method, after a critical evaluation of its performance. Some remarkable points—pteridine is predicted to be the strongest base of 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]



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(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.
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