indicates the difference in the frequency factor of the Arrhenius equation. The greater polar nature is deduced from the greater $\rho^+(k_1)$ value. The greater Kk_2 value for each phenylthio radical suggests that the reaction of indene is highly exothermic, owing to the release of the strain energy of the five-membered ring, or that the adduct radical of indene having cis planar conformation is more stable than that for the slightly angular trans adduct (dihedral angle of *trans*-β-methylstyrene is 12°).[26] Some of above factors cooperate in order to control the reactivity of indene.

Experimental Section

Indene and *cis*- and *trans*-β-methylstyrenes (Aldrich Chemical Co.) were distilled under reduced pressure before use. Disulfides were purified by recrystallization from ethanol. Cyclohexane used as a solvent was of spectrophotometric grade.

Xenon flash photolysis apparatus was of standard design;[27] the flash duration and energy of the xenon lamps (Xenon Corp., N-851C) were ca. 10 μs and 130 J, respectively. Flash photolysis of the disulfides was performed in a 10-cm cylindrical cell with light of wavelength longer than 350 nm, which does not excite the olefins. Kinetic observations were made with a continuously monitored light source and photomultiplier detection. The oxygen concentration in cyclohexane was calculated from Henry's law using the partial oxygen pressure.[28]

Registry No. *p*-$BrC_6H_4S\cdot$, 31053-90-4; *p*-$ClC_6H_4S\cdot$, 31053-91-5; $C_6H_5S\cdot$, 4985-62-0; *p*-*t*-$C_4H_9C_6H_4S\cdot$, 81372-23-8; *p*-$CH_3C_6H_4S\cdot$, 31053-92-6; *p*-$CH_3OC_6H_4S\cdot$, 31053-93-7; *p*-$NH_2C_6H_4S\cdot$, 31053-95-9; *cis*-β-methylstyrene, 766-90-5; *trans*-β-methylestyrene, 873-66-5; indene, 95-13-6.

(26) Kobayashi, T.; Arai, T.; Sakuragi, H.; Tokumaru, K.; Utsunomiya, C. *Bull. Chem. Soc. Jpn. 1981, 54*, 1658.

(27) Porter, G.; West, M. A. In "Techniques of Chemistry"; Weissberger, A. Ed.; Wiley: New York, 1974; p 367.

(28) Murov, S. I. "Handbook of Photochemistry"; Marcel Dekker: New York, 1973; p 89.

Stereoelectronic Effects in Tertiary Amine Nitrosation: Nitrosative Cleavage vs. Aryl Ring Nitration

Richard N. Leoppky* and Witold Tomasik

Department of Chemistry, University of Missouri, Columbia, Missouri 65211

Received June 7, 1982

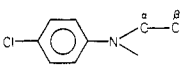
The nitrosation (acetic acid) of *N*-(4-chlorophenyl)pyrrolidine gives at least 30% *N*-(4-chloro-2-nitrophenyl)pyrrolidine while the corresponding aryldibenzylamine gives no nitration and only nitrosative dealkylation at nitrogen. This difference in reaction site has been probed with *N*-(4-chlorophenyl)diethylamine. This substance undergoes competitive ring nitration to *N*-(4-chloro-2-nitrophenyl)diethylamine (50%) and nitrosative dealkylation to (4-chlorophenyl)ethylnitrosamine (50%). The former compound nitrosates further to give (4-chloro-2-nitrophenyl)ethylnitrosamine. This substance denitrosates to give the corresponding secondary amine. The reactivity differences result from stereoelectronic factors controlling the amine nitrogen unshared pair delocalization into the aryl ring. This interpretation is supported by ^{13}C NMR data and mechanistic arguments.

As the awareness that certain environmental chemicals cause cancer has grown, so has the realization that prevention or, at least, reduction of the disease prevelance can be attained through a knowledge of the chemistry of carcinogen production and transformation. Tobacco products and smoke, for example, are known to contain variable trace quantities of nitrosamines,[1] substances that are recognized as potent animal carcinogens.[2] In a fundamental study of nitrosation of nicotine in aqueous acid, Hecht and co-workers[3] found a number of unusual trace nitrosamine products to be formed from the pyrrolidine ring in addition to those major ones, which were produced in accord with expectations from previous studies of tertiary amine nitrosation.[4] With the exception of Hecht's work, there has been no published thorough investigation of heterocyclic tertiary amine nitrosation despite the ubiquity of such compounds in the environment.

To initiate our study of heterocyclic tertiary amine nitrosation we began by investigating the reaction of *N*-(4-chlorophenyl)pyrrolidine (1) with nitrous acid at 80–90 °C. While this reaction gives a complex array of products, the characterization and chemistry of which will be the subject of a forthcoming publication from our laboratory, we found a major product to be *N*-(4-chloro-2-nitrophenyl)-pyrrolidine (2). Aryl ring nitration accompanying tertiary amine nitrosation certainly has precedent and is not new.[4,5] In this case, however, it was unexpected because *N*-(4-chlorophenyl)dibenzylamine (3) apparently gave only nitrosative debenzylation and no aryl ring nitration.[4]

In this paper we present the results of our investigation into this apparent discrepancy. We have reinvestigated the nitrosation of 3 and found the initial report to be

Table I. ^{13}C NMR Chemical Shifts for Amines (ppm)



compd[a]	1	2	3	4	α	β
1	147.0	112.9	129.0	120.7	48.1	25.9
4	147.0	113.3	129.3	120.6	45.0	12.6
3	148.4	114.2	129.0	122.1	55.0	

[a] Ph C_1-C_4: 138.8, 129.0, 127.0, 127.3

(1) Hecht, S. S.; Ornaf, R. M.; Hoffman, D. *J. Natl. Cancer Inst.* **1974**, *54*, 1237.

(2) Magee, P. N.; Montesano, R.; Preussman, R. In "Chemical Carcinogens", Searle, C. E., Ed.; American Chemical Society: Washington, D.C., 1976; pp 461–625.

(3) Hecht, S. S.; Chen, C. B.; Ornaf, R. M.; Jacobs, E.; Adams, J. D.; Hoffman, D. *J. Org. Chem.* **1978**, *43*, 72.

(4) Smith, P. A. S.; Loeppky, R. N. *J. Am. Chem. Soc.* **1967**, *89*, 1147.

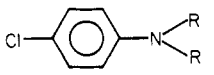
(5) Hodgson, H. H.; Kershaw, A. *J. Chem. Soc.* **1930**, 277.

0022-3263/83/1948-2751$01.50/0

entirely accurate. The nitrosation chemistry of *N*-(4-chlorophenyl)diethylamine (**4**) serves as a simple model for the similar chemistry of **1** and is reported. We have found that **4** undergoes competitive ring nitration and nitrosative dealkylation. The nitration product subsequently undergoes nitrosative dealkylation, another unexpected process. Stereoelectronic effects are invoked to explain these differences, and a possible mechanism for ring nitration is given.

Results

The *N*-arylamines **1**, **3**, and **4**, which were used as substrates in this research, are known compounds and were

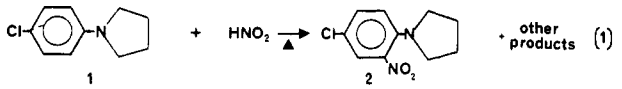


1, R = $-(CH_2)_4-$
3, R = $-CH_2C_6H_5$
4, R = $-CH_2CH_3$

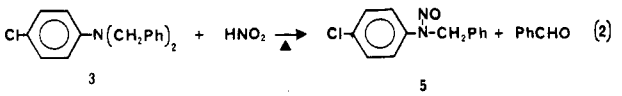
prepared by literature methods. The ^{13}C NMR chemical shifts for the aryl carbons of these amines differ and are given in Table I. Amines **1** and **4** undergo relatively rapid photooxidation, and we took precautions to store and use them in the dark under argon.

The nitrosation reactions of **1**, **3**, and **4** were conducted under Ar at temperatures of 85–90 °C in glacial acetic acid. A threefold excess of sodium nitrite per mol of amine is added in water over a 5-min period. Normally the mixture was stirred for 2 h at 85–90 °C prior to workup. In several cases the course of the reaction was followed by using HPLC. In this situation aliquots were removed and quenched in cold methanol, and the products were determined by HPLC with the aid of external standards.

The reaction of the *N*-arylpyrrolidine **1** with nitrous acid gave *N*-(4-chloro-2-nitrophenyl)pyrrolidine (**2**) in 30% yield in 2 h (eq 1). None of the starting material remained,



1 2 (1)



3 5 (2)

and there are a number of other products that primarily result from side-chain degredation after ring opening and will be described separately. In contrast to this, the reaction of the *N*-aryldibenzylamine **3** with nitrous acid under the same conditions gave (4-chlorophenyl)benzylnitrosamine (**5**) in 99% yield (HPLC) (eq 2). It has previously been reported that this reaction gave **5** and benzaldehyde (70%).[4] Since these prior yields were based on isolation of the aldehyde, we considered it worthwhile to confirm the previous observation using modern instrumentation.

The nitrosation of the diethylamine derivative was more complex than **3** but much simpler than **1**. At the end of the 1.5-h reaction time, the products consisted of (4-chlorophenyl)ethylnitrosamine (**6**) (54%), *N*-(4-chloro-2-nitrophenyl)diethylamine (**7**) (2.3%), (4-chloro-2-nitrophenyl)ethylnitrosamine (**8**) (25%), *N*-(4-chloro-2-nitrophenyl)ethylamine (**9**) (0.5%), and no starting material. The material balance at this time was 82% and experienced a general decline from 100% at 17 min to 75% at 4 h. The time course of the product yields are given graphically in Figure 1, and the transformations are summarized in Scheme I. Within 4 min there were nearly equal yields (50 ea.) of nitrosamine **6** and nitro compd. **7**. The nitro compound yield then decreased as it was converted into the nitrosamine **8** by nitrosative dealkylation. It is interesting that the yield of this nitrosamine reaches a maximum (25%) and declines slightly as it is slowly denitrosated in the acetic acid reaction medium to the secondary amine **9**. The secondary amine could have arisen by another route. Secondary amines can be intermediates in tertiary amine nitrosation.[4] While we believe **9** is a likely intermediate in the formation of **8**, we have evidence that its appearance in the final reaction mixture results from denitrosation of **8**. The yield of **8** decreases while that of **9** increases (Figure 1). HPLC analysis of the reaction mixture prior to 60 min failed to reveal detectable quantities of **9**. When **8** was heated in glacial acetic acetic acid (85–90 °C) for 3 days, a 69% yield of **9** resulted. Although the reaction is neither as extensive nor as fast, the denitrosation of **8** in HOAc–"HNO_2" has been observed independently. It is likely that the denitrosation only becomes significant after the consumption of much of the "HNO_2" by thermal decomposition or reaction.

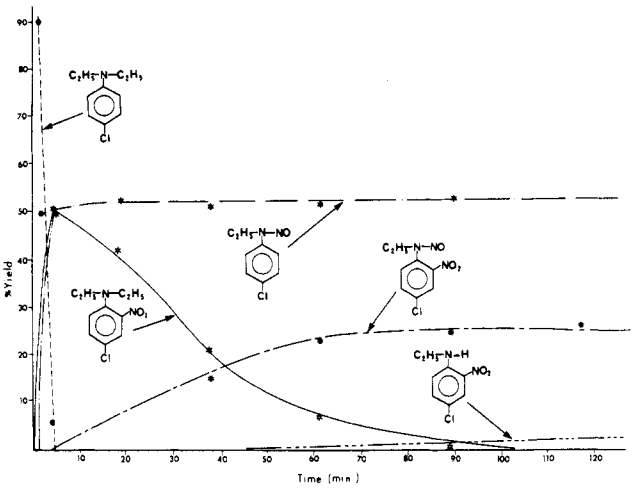
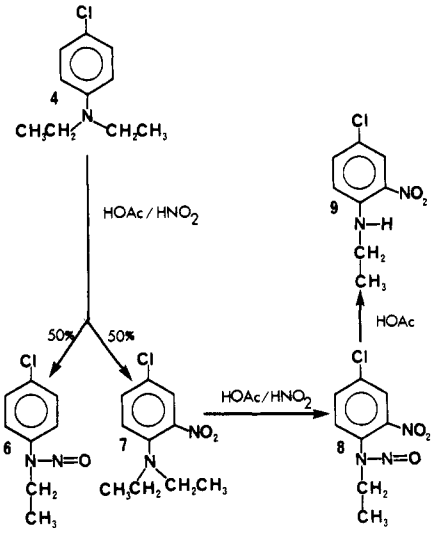


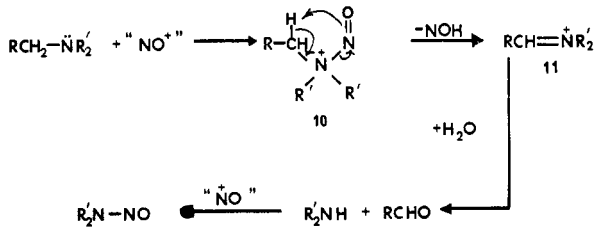
Figure 1. Percent yield of the products shown given as a function of time (min) as determined by HPLC.

Scheme I



Each of the products from **3** was separated from the reaction mixture after an appropriate time by column chromatography. With the exception of **8** all products are known compounds and their characterization is given in the Experimental Section. Both chemical and spectral

Scheme II



data are consistent with the structure assigned to compound 8 ($C_8H_8ClN_3O_3$). The nitrosamine nature of this substance is suggested by a positive Griess test and and by its ^1H NMR spectrum, which exhibits ethyl groups in two different environments (CH_2 δ 3.97 (q), CH_3 1.15 (t); CH_2 4.63 (q), CH_3 1.50 (t)). Close inspection of the aromatic-H region of the spectrum also gave evidence that 8 was a mixture of stereoisomers. This part of the spectrum clearly shows the abc pattern of C_6, C_5, and C_3 protons that we have come to associate with the 2-nitro-4-chlorophenyl system. The upfield region of this part of the spectrum shows two doublets (a and a') in intensity ratios of 42:58 at δ 7.11 and 7.44, respectively, and this intensity ratio matches that seen in the ethyl portion of the spectrum. The *E* isomer (ethyl and N=O syn)[6,7] is the more abundant, and this permits the assignment of the δ 7.44 doublet to it. The C-3 and C-5 hydrogens have identical chemical shifts in the two isomers (δ 8.08 and 7.73, respectively) at 60 MHz but can be resolved at 300 MHz. It appears that the steric requirements of the *o*-nitro group in this compound are such that the N–NO group and the aromatic ring are not coplanar. The steric requirements of the benzene ring face are not as great as the edge, and we see this reflected in the *Z*:*E* isomer ratio in this compound. The mass spectrum of 8 gave a molecular ion at 229 and peaks characteristic of M – NO (199) and M – C_2H_5 (200) as well as others.

Discussion

The behavior of *N*-(4-chlorophenyl)diethylamine (4) toward nitrous acid on the one hand seems reasonable in a general sense but, on the other hand, exhibits several surprises when compared to the known nitrosation chemistry of *N*-aryldibenzylamines.[4] First, 4 undergoes competitive ring nitration and nitrosative dealkylation at almost comparable rates while 3 experiences no ring nitration and only nitrosative dealkylation. Second, the nitro derivative of 4 (7) undergoes nitrosative cleavage while *N*-(4-nitrophenyl)dibenzylamine has been reported to be inert toward this reaction under the same conditions.[4] The lack of reactivity in the latter compound was associated with strong delocalization of the amine nitrogen unshared pair induced by the highly electron-withdrawing *p*-nitro substituent. The *o*-nitro group in 7 is certainly capable of the same powerful electronic effect, yet we observe the reasonably facile nitrosative dealkylation of this compound. Finally, it is relatively rare to witness nitrosamine denitrosation (conversion of 8 to 9) under the nitrosation conditions employed here (no halide ions or other strong nucleophiles (excepting amines) in this aqueous acetic acid). We believe that these interesting observations can be explained by interplay of steric and electronic factors in each case.

The differences in the nitrous acid chemistry of amines 1 and 4 compared to that of 3 can be attributed to a structural perturbation that either facilitates the nitrosative dealkylation or increases the rate of attack on the aromatic ring. A mechanism for tertiary amine nitrosative dealkylation (Scheme II) was first advance in 1967, and work since that time has largely substantiated this hypothesis, but there are examples where ring strain[8] or heterocyclic substituents[9] induced a different mode of nitrosamine formation. A recent kinetic investigation of the reaction has been published by Gowenlock et al.[10] These researchers produced evidence that the loss of NOH is rate limiting above pH 3.8 and is preceded by a rapid equilibrium nitrosation–denitrosation. The loss of NOH is proposed to occur by a syn cyclic transition state, and this product-determining step is subject to control by steric factors when there are competing routes of elimination.[4] Electronic effects appear to exert relatively little influence on the course of NOH elimination.

It could be argued that the relative amounts of nitrosation and nitration result from the different abilities of the benzyl and ethyl groups to be "cleaved from nitrogen". A comparison of the pH-independent rate constants for nitrosative dealkylation of triethylamine and tribenzylamine shows the former to be 17 times more reactive than the latter.[10] These rate constants, however, are composed of two relevant terms, the NOH elimination rate constant and the equilibrium constant for formation of the nitrosammonium ion. Relative basicities suggests that the latter is likely to be larger for the triethylamine. The relative rates of nitrosative dealkylation of 3 (benzyl) and 4 (ethyl) are probably not significantly different from tribenzylamine and triethylamine. Since the benzyl compound nitrosates more slowly than triethylamine, it is unlikely that the relative amount of nitrosative dealkylation compared to nitration results from differences in the proclivity of 3 and 1 toward nitrosative dealkylation. This hypothesis can be argued from another perspective as well.

Two factors, electronic and steric, determine the relative rates of NOH elmination for the diethyl and dibenzyl cases. If NOH elimination is endothermic, it is probably only modestly so, and the degree of C–H bond breaking is little more than 50% at a maximum. It is likely that the reaction is exothermic because tribenzylnitrosammonium tetrafluoroborate is thermally unstable above −20 °C in ether and the internal competitive nitrosative elimination of NOH from substituted tribenzylamines gives a Hammett ρ value of only −0.17.[4] Therefore, electronic factors associated with heterolytic C–H bond fission and stabilization of the incipient imminium ion are likely to be of little importance in this reaction. To the degree that they are, they should favor the more rapid elimination of NOH in the dibenzyl case. Steric factors will be important in determining the activation energy for syn cyclic elimination of NOH. The dibenzylarylnitrosammonium ion will have a slightly higher ground-state energy than its diethyl counterpart because of steric crowding around the tetrahedral nitrogen. The transition-state energy will be even greater in the dibenzyl case due to the fact that benzyl–ethyl eclipsing is of significantly higher energy than methyl–ethyl eclipsing (diethyl case). The activation energy for NOH elimination from the dibenzylarylnitrosammonium ion is likely, therefore, to be slightly greater than that for the diethylarylnitrosammonium ion.

Our experiments show that the benzyl compound 3 undergoes exclusive nitrosative dealkylation in contrast

(6) Karabatsos, G. J.; Taller, R. A. *J. Am. Chem. Soc.* **1964**, *86*, 4373.
(7) Pregosin, P. S.; Randall, E. W. *J. Chem. Commun.* **1971**, 399.
(8) Loeppky, R. N.; Smith, D. H. *J. Org. Chem.* **1976**, *41*, 1578.
(9) Loeppky, R. N.; Outram, J. R. *Tetrahedron Lett.* **1982**, in press.
(10) Gowenlock, B. G.; Hutchinson, R. J.; Little, J.; Pfab, J. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1110.

to its ethyl and pyrrolidine analogues. We conclude, from the experiments above, therefore, that it is highly unlikely that an enhanced rate of nitrosative debenzylation is responsible for the relative nitrous acid chemistry of 1 and 4 compared to 3. We must add, however, a qualification to this conclusion. If radicals or radical cations intervene in the nitrosative dealkylation reaction, oxidative debenzylation might occur very readily. This possibility is suggested by the work of Singer, who showed that small yields of "ω - 1 oxidation products" are formed from the acidic nitrosation of tributylamine and *N*-cyclohexylmorphine in addition to the normal products. Singer proposed that the nitrosammonium ion **10** undergoes homolytic fission in competition with NOH elimination. The resulting radical cation abstracts intramolecular hydrogen atoms to give the "ω – 1 oxidation" products. The main pathway to products, however, appears to be the route shown in Scheme II. The formation of a nitrogen-centered radical cation either by nitrosammonium ion N–NO bond dissociation or direct electron transfer from the amine to NO^+ could lead to preferential debenzylation through facile intermolecular benzylic C–H abstraction to give an iminium ion **11**. We have at present, however, no evidence in support of the possible involvement of this pathway.

The differential chemistry of **3** (and **1**) and **4** must result from factors associated with the mechanism of the nitro compound production. The precise composition of the nitrosating mixture produced from acetic acid and nitrite at 80–90 °C is not known at present. It is likely to contain an assembly of nitrosating agents (HNO_2, N_2NO^+, NOAc, and N_2O_3), which we will collectively call NO^+. It will also contain NO, NO_2, and possibly some HNO_3. These substances are produced according to the well-known reactions given in eq 3 and 4. Despite the probably formation of

$$3HNO_2 \xrightarrow{\Delta} HNO_3 + 2NO + H_2O \quad (3)$$

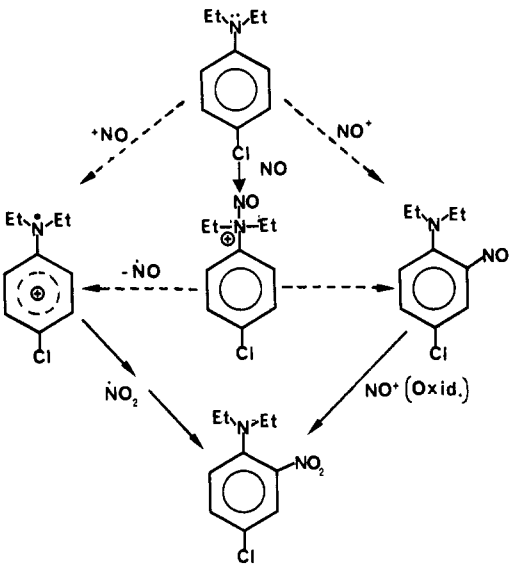
$$2HNO_2 \xrightarrow{\Delta} NO + NO_2 + H_2O \quad (4)$$

some nitric acid in the nitrosation mixture, it is unlikely that the nitration proceeds through NO_2^+. The formation of significant quantities of this species occurs only at high acidity.

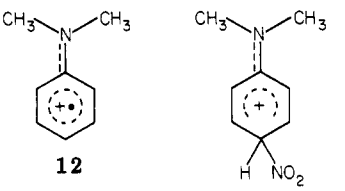
It has been recognized for years that nitrite catalyzes the nitration of the aromatic amines, phenols, and ethers. The explanation for this catalysis has been used to explain nitration under nitrosation conditions and involves *C*-nitrosation followed by oxidation of the nitroso compound to the nitro compound.[12] *C*-Nitrosation is much more regioselective than *C*-nitration, and this has been used as a tool to distinguish it from classical *C*-nitration. It is interesting that *C*-nitroso compounds are often not isolated from aromatic amine nitrosations; rather the corresponding nitro compounds are.[5]

Several recent publications have shown that the nitrite-catalyzed nitration of electron-rich aromatic rings can occur by a route that does not involve the oxidation of the *C*-nitroso compound.[15,16] An alternative mechanism advanced by Giffney and Ridd[13] for the nitrite-catalyzed

Scheme III



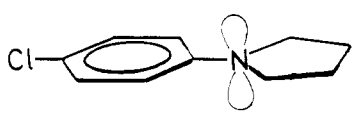
nitration of *N*,*N*-dimethylbenzenamine involves the nitrosoammonium ion **10**. This species dissociates to generate NO and the radical cation **12**. Subsequent reaction



12 **13**

with NO_2, formed from reduction of NO_2^+ by NO, gives the well-known intermediate **13** and leads to the nitro compound. We believe that the nitro compounds **2** and **7** are formed either via *C*-nitrosation followed by oxidation or by a pathway similar to the Giffney–Ridd mechanism[13] where NO_2 is produced from the thermal decomposition of N_2O_3 in the nitrosation mixture (see Scheme III).

Regardless of which pathway is taken to the nitro compound, there is substantial literature evidence that it is only produced in tertiary amine nitrosation reactions when the N-bound aryl group has sufficient electron density to activate the ring toward electrophilic aromatic substitution.[4,5] Because of aryl substituents in compounds **1**, **3**, and **4** are always the same (Cl^- and $(RCH_2)_2N$–), it is not at first apparent that the aryl rings in these amines have significantly different electron densities and differential capabilities toward supporting electrophilic aromatic substitution, but we believe this to be the case. We propose that the relatively bulky N-bond benzyl groups sterically interfere with the delocalization of the nitrogen unshared pair and reduce the electron density of the aromatic ring compared to the amines **1** and **4**. Ideally, the aryl-bound amine nitrogen will be sp^2 hybridized providing the unshared pair is orthogonal to the aryl ring plane so that it may interact with benzene ring π system and increase its electron density (see depiction **14** below).

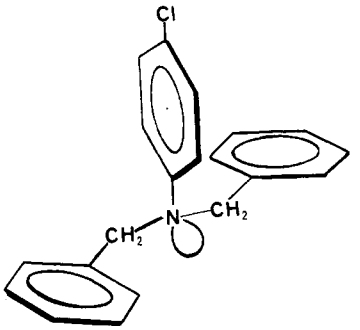


14

The pyrrolidine **1** is particularly well suited to adopt this arangement because the alkyl groups are "tied back" in the

(11) Singer, G. M. in "*N*-Nitroso Compounds: Analysis, Formation, and Occurence"; Walker, E. A., Griciute, L., Castegnaro, M., Borzsonyi, M., Eds.; IARC: Lyon, France, 1980; IARC Sci. Pub. No. 31, p 139.
(12) Challis, B. C.; Lawson, A. J.; *J. Chem. Soc. B* **1971**, 770.
(13) Giffney, J. C.; Ridd, J. H. *J. Chem. Soc., Perkin Trans. 2*, **1979**, 618.
(14) Ross, D. S.; Humard, G. P.; Blucher, W. G.; *J. Chem. Soc., Chem. Commun.* **1980**, 539.
(15) Al-Omran, F.; Fujiwara, K.; Giffney, J. C.; Ridd, J. H.; Robinson, S. R. *J. Chem. Soc., Perkin Trans. 2* **1981**, 518.
(16) Main, L.; Moodie, R.; Schoefield, K. *J. Chem. Soc., Chem. Commun.* **1982**, 48.

five-membered ring and there is little to no interference with the ortho hydrogens. The similar chemistry and properties (vide infra) of the diethylamine 4 suggest that it has nearly the same nitrogen geometry as 1. Models, however, show the benzyl groups interfere with the aryl ortho hydrogens, and a rotation around the aryl–nitrogen bond is necessary to minimize repulsive steric interactions as shown in depiction 15. The nitrogen adopts a more



15

tetrahedral geometry to "move" the benzyl groups farther from the ortho hydrogens, and the unshared pair axis is now twisted and tilted from its maximal overlap position. This necessarily decreases the electron density in the benzene ring.

Support for this argument comes from the substrate ^{13}C NMR spectra given in Table I. The aryl ring carbon shifts for 1 and 4 are nearly identical. The aryl ring carbon resonances are well-known to be influenced by ring electron density and thus remote substituents.[17] The C_2 and C_4 positions move downfield as the electron density provided by the C_1 substituents decreases. For example, δ C_4–HNAc = 123.1 and C_4–NH_2 = 119.2. The data of Table I show that C_4 is 1.4 and 1.5 ppm more upfield for 1 and 4, respectively, than it is in 3, and a similar observation can be made for C_2. The aryl ring of 3, therefore, is less electron rich than 1 and 4. Similar effects could act to destabilize the transition state for electrophilic attack on the aryl ring of 3 compared to 4 and 1 and thereby slow its rate to the point where it is not competitive with nitrosative dealkylation.

A similar rationale can be used to explain why *N*-(4-chloro-2-nitrophenyl)diethylamine (7) undergoes nitrosative dealkylation to produce 8 while *N*-(4-nitrophenyl)-dibenzylamine is unreactive under similar conditions.[4] The base-weakening effect of an *o*-nitro group will be at least as great as that of a *p*-nitro substituent as long as steric factors do not interfere with delocalization of the nitrogen unshared pair into the aromatic ring. It appears, however, that this is occurring and a stereoelectronic effect is responsible for the reactivity difference here as well. Models show steric crowding of the *N*-ethyl group in 8 by the *o*-nitro group. The amine nitrogen unshared pair axis twists from its position perpendicular to the ring plane, and the electron density at nitrogen increases, permitting the nitrosation such as that observed for 8. Denitrosation reactions of nitrosamines are normally not encountered in acetic acid solutions. The denitrosation reaction normally occurs in strong acids and requires good nucleophiles such as halide ions. The mechanism of this reaction for arylalkylnitrosamines has been studied by Williams and his group and involves protonation of the amine nitrogen followed by nucleophilic attack at the nitroso nitrogen with N–N bond fission.[18,19] In the absence of a trap for the NO–Nu (Nu is nucleophile), the reaction is reversible. In our case we presume that the nucleophile is acetate or acetic acid (or perhaps water). The thermal decomposition of NO–Nu apparently drives the reaction to the right.

We believe that the relatively facile denitrosation of 8 suggests that there is not good overlap between the π orbital system of the ring and the NNO group due to steric factors. This lack of conjugation will weaken the NNO bond and make it more succeptable to cleavage. The aryl ring, however, will be exerting a strong inductive withdrawal and will mimic to some extent of a carbonyl bound to the amino nitrogen. *N*-Nitroso amides undergo more facile denitrosation than their nitrosamine counterparts.[19] We believe, through the use of reaction coordinate analysis, that a nitrosamine or other *N*-nitroso compound with an attached electron-withdrawing group has less need for acid catalysis (proceeds more easily in weaker acids) and involves more N–NO bond breaking.

In conclusion, we have established that aromatic dialkylamines undergo competitive aryl nitration and N-nitrosation. N-Nitrosation can also follow nitration. The relative amounts of these processes is principally determined by stereoelectronic factors involving the delocalization of the amine unshared pair by the aryl ring. ^{13}C NMR chemical shifts of the 2 and 4 carbons in the ring are good indicators of the degree of unshared pair delocalization when compared to calculated values. We hypothesize that these shifts can be used to predict the extent of aryl ring nitration in such compounds. Denitrosation of nitrosamines in weak acids can be facile for nitrosamine bearing electron-withdrawing groups. This observation and its possible practical significance suggest further work on the mechanism of denitrosation.

Finally, we believe the results and interpretation presented here are of potential utility in the area of environmental carcinogenesis not only for the reasons stated above but because they lead to a better understanding of the nitrosation pathways open to an activated arylamine.

Experimental Section

Caution: Nitrosamines are potent animal carcinogens. A workable safety protocol can be obtained by writing the principal author.

High-performance liquid chromatography (HPLC) was performed on a Waters gradient instrument employing a WISP autosampler and UV detector operating at 254 nm. The HPLC employed a Du Pont Zorbax reversed-phase ODS column. Gas chromatography was performed on a Hewlett-Packard (HP)5880A Level 4 gas chromatograph and data system employing $^1/_8$-in packed glass columns. The data from both the HPLC and GC were fed into the HP system that performed the peak integration. HPLC employed external standards for quantitation. GLC employed internal standards. Mass spectrometry was performed on a Du Pont 292 instrument. NMR spectra, Bruker Hx90 (^{13}C, 22.6 MHz) and Nicolet 300 CH (300 Mz), were obtained from Varian EM360 (^1H (300 MHz), ^{13}C (75.4 MHz)) instruments. Infrared spectra were obtained on a Perkin-Elmer 237 spectrometer. Chemicals were obtained from Commercial sources.

Preparation of Amines. *N*-(4-Chlorophenyl)pyrrolidine (1) was prepared by the reduction of *N*-(4-chlorophenyl)succinimide with diborane according to the method of Brown:[20] yield 95%; mp 85–86 °C (lit.[21] mp 85 °C). *N*-(4-Chlorophenyl)dibenzylamine (3) was prepared by the benzylation of 4-chlorobenzeneamine;[4] yield 69%; mp 104–105 °C (lit.[4] mp 101–103 °C). *N*-(4-Chloro-

(17) Stothers, J. B. In "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972; p 197.

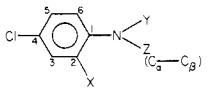
(18) Biggs, I. D.; Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* **1975**, 107.

(19) Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* **1977**, 128.

(20) Brown, H. C.; Hein, P. *J. Org. Chem.* **1973**, *38*, 912.

(21) Burger, B. (BASF) German Patent 812552, 1951; *Chem. Abstr.* **1953**, *47*, 3351h.

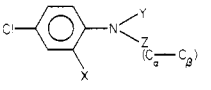
Table II. ^{1}H NMR Chemical Shifts (ppm)



compd	X	Y	Z	2	3	5	6	α	β
1	H	-(CH$_2$)$_4$-		6.43 (d)	7.15 (d)			3.2 (t)	1.97 (t)
2	NO$_2$	-(CH$_2$)$_4$-			7.73 (d)	7.31 (dd)	6.83 (d)	3.18 (t)	1.98 (t)
3	H	CH$_2$Ph	CH$_2$Ph	6.58 (d)	7.07 (d)			3.18 (t)	7.25 (s)
4	H	C$_2$H$_5$	C$_2$H$_5$	6.25 (d)	6.79 (d)			3.15 (q)	1.06 (s)
5	H	NO	CH$_2$Ph		7.41 (s)[a]			5.2 (s)	7.2 (m)
6	H	NO	C$_2$H$_5$		7.47 (s)[a]			4.03 (q)	1.15 (t)
7	NO$_2$	C$_2$H$_5$	C$_2$H$_5$		7.73 (d)	7.28 (dd)	6.98 (d)	3.08 (q)	1.08 (t)
8 *E*	NO$_2$	NO	C$_2$H$_5$		8.06 (d)	7.74 (dd)	7.44 (d)	3.99 (q)	1.16 (t)
8 *Z*	NO$_2$	NO	C$_2$H$_5$		8.09 (d)	7.71 (dd)	7.11 (d)	4.65 (q)	1.51 (t)
9	NO$_2$	H	C$_2$H$_5$		8.22 (d)	7.43 (dd)	6.85 (d)	3.38 (q)	1.04 (t)

[a] Chemical shift for C$_2$, C$_3$, C$_5$, and C$_6$.

Table III. ^{13}C NMR Chemical Shifts for Nitrosation Products



compd	X	Y	Z	1	2	3	4	5	6	α	β
2	NO$_2$	-(CH$_2$)$_4$-		141.41	136.67	125.99	119.92	132.97	117.08	50.53	25.72
5[a]	H	NO	CH$_2$Ph	141.0	121.0	129.4	126.0	129.4	121.0	47.4	
6[b]	H	NO	Et	140.5	120.7	129.9	128.0	129.9	120.7	39.2	11.8
7	NO$_2$	Et	Et	143.16	135.5	125.4	122.1	132.5	123.5	46.9	12.5
8 *E*	NO$_2$	NO	Et	133.13	145.29	128.37	125.69	135.26	133.75	41.8	11.4[c]
8 *Z*	NO$_2$	NO	Et	136.20	146.33	129.18	128.99	134.46	126.04	48.9	14.0[c]
9	NO$_2$	H	Et	144.1	131.5	125.9	119.9	136.3	115.2	37.9	14.3

[a] Ph (C$_2$-C$_4$: 131.6, 130.0, 127.5, 128.2). [b] *E* isomer. [c] Assignments tentative.

phenyl)diethylamine (4) was prepared by the ethylation of 4-chlorbenzeneamine yield 62%; mp 44 °C (lit.[22] mp 45.5–46.5 °C). ^{13}C NMR spectra for the starting amines are given in Table I while ^{1}H spectra are given in Table II.

Nitrosation of *N*-(4-Chlorophenyl)pyrrolidine (1). The amine 1 under goes facile photooxidation. After its preparation it was stored in the dark under argon. Its nitrosation was conducted with degassed (Ar bubbled) reagents and solvents as follows. To a stirred solution of 1 (1.82 g, 10 mmol) in glacial acetic acid (25 mL) was added dropwise 2.1 g (30 mmol) of sodium nitrite dissolved in 5 mL of water at 85.90 °C within 8 min. After rapid cooling to 5 °C the mixture was added to 150 mL of cold methanol. The methanol, acetic acid, and water were removed on the rotary evaporator, and the half solid mass was digested with several portions of ether. The combined ether extracts were concentrated and chromatographed on 100 g of MN Kieselgel 60 with methylene chloride (750 mL) and then 30% methanol–methylene chloride. The first fraction (50 mL) gave 0.35 g (20%) of starting material (1), and the second 150 mL produced 0.54 g (24%) of *N*-(4-chloro-2-nitrophenyl)pyrrolidine 2. HPLC analysis of an aliquot of the reaction mixture prior to workup established the yield of this material to be 30%. The product 2 was recrystalized from 95% ethanol: mp 71–72 °C (lit.[23] mp 70–71 °C); MS, *m/e* 226 (22), 209 (54), 179 (100); see Table II for ^{1}H NMR. The characterization of the other products from this reaction will be presented in a forthcoming publication.

Nitrosation of *N*-(4-Chlorophenyl)diethylamine. *N*-(4-Chlorophenyl)diethylamine (4) (2.76 g, 15 mmol) was nitrosated in 40 mL of glacial acetic acid with 3.15 g (45 mmol) of sodium nitrite in 6 mL of water at 85–90 °C for 8 min. Aliquots (50 mL) were removed periodically, quenched, and then diluted to 10 mL with methanol. The samples were analyzed by HPLC using methanol as an eluant. The determined concentrations are plotted vs. time in Figure 1. The determinations involved the use of external standards prepared from the substances whose characterization is described below.

The data displayed in Figure 1 permitted the isolation and characterization of products near their maximum yield. The reaction was repeated on a 15 mM scale and stopped after 8 min. The workup was carried out as described for the nitrosation of 1. Evaporation of the ether gave 1.65 g (8.89 mmol) of crude (4-chlorophenyl)ethylnitrosamine, (6). Recrystallization from ethanol gave red crystals: mp 59 °C (lit.[24] mp 60–61 °C); for NMR see Table II. The mother liquor from the original crystallization was charomatographed on MN Kieselgel 60 (1:1 CH_2Cl_2:hexane) and produced 0.72 g of *N*-(4-chloro-2-nitrophenyl)diethylamine (7) as an oil (lit.[25] mp 32 °C); for NMR see Table II; MS, *m/e* 228 (28), 213 (100), 211 (61), 185 (15).

Nitrosation of *N*-(4-Chloro-2-nitrophenyl)diethylamine (7). A 0.35-g sample of 7 obtained from the preceding reaction was nitrosated under conditions identical with those described for *N*-(4-chlorophenyl)diethylamine (4). The workup procedure was the same, and chromatography on MN Kieselgur 60 produced an oil characterized as (4-chloro-2-nitrophenyl)ethylnitrosamine (8): MS, *m/e* 229 (13), 200 (100), 199 (72), 185 (99); see Tables II and III for NMR. The nitrosamine 8 was also obtained by unambiguous synthesis from 4-chloro-2-nitrobenzenamine by ethylation with ethyl bromide in benzene and 40% sodium hydroxide containing 5% (molar) tetrabutylammonium hydrogen sulfate (45 °C/10 h; yield of amine 95%) followed by nitrosation in glacial acetic acid with 25% excess $NaNO_2$ (25 °C). Purification employed chromatography on Kieselgur MN (20% hexane/CH_2Cl_2) followed by solvent stripping and bulb to bulb distillation at 115 °C (.05 torr). Anal. Calcd for $C_8H_8ClN_3O_3$: C, 41.84; H, 3.51; N, 18.3. Found: C, 41.79; H, 3.58; N, 18.16.

Denitrosation of (4-Chloro-2-nitrophenyl)ethylnitrosamine (8). (4-Chloro-2-nitrophenyl)ethylnitrosamine (8) (0.2 g, 0.87 mmol) was dissolved in 10 mL of glacial acetic acid and heated

(22) Thomas, D. G.; Billman, J. H.; Davis, C. E. *J. Am. Chem. Soc.* **1946**, *68*, 895.
(23) Nair, M. D.; Adam, R. *J. Am. Chem. Soc.* **1961**, *83*, 3518.
(24) Schmidt, E.; Fisher, H. *Chem. Ber.* **1920**, *53*, 1543.
(25) Holleman, M.; DeMooy, W. J. *Recl. Trav. Chim. Pays-Bas* **1915**, *35*, 30.

under argon for 3 days. The resulting mixture was chromatographed as described above, and 0.12 g (0.60 mmol; 69%) of *N*-(4-chloro-2-nitrophenyl)ethylamine (**9**) was isolated: MS (57), 185 (100); for NMR see Table II; mp 90.5 °C (lit.[26] mp 93 °C). In another experiment **8** was heated with acetic acid, water, and sodium nitrite in molar ratios corresponding to the nitrosation of 2 h. Chromatography permitted the isolation of a small amount of **9**. The presence of **9** in the original nitrosation mixture (after 2 h) of **4** was demonstrated by HPLC coinjection of **9**.

Nitrosation of *N*-(4-Chlorophenyl)dibenzylamine (3). *N*-(4-Chlorophenyl)dibenzylamine was nitrosated as described for **4**. HPLC analysis showed the reaction mixture to contain (4-chlorophenyl)benzylnitrosamine (**5**) (99%) as the sole product derived from **4**. Workup gave **5**, which was recrystallized from hexane: mp 55 °C (lit.[27] mp 57 °C); for NMR see Table II.

Acknowledgment. This research is supported by the National Cancer Institute, CA26914, DHHS. The authors wish to express their gratitude to the NCI and James M. Faulconer who assisted with the analysis. We also express our appreciation to the NSF (PCM-8115599) and the University of Missouri for providing funding for the 300-MHz NMR.

Registry No. 1, 4280-30-2; 2, 41173-36-8; 3, 15429-21-7; 4, 2873-89-4; 6, 1008-93-1; 7, 86309-90-2; 8, 86309-91-3.

(26) Behrens, M. H. *Recl. Trav. Chim. Pays-Bas* **1901**, *21*, 274.

(27) Carter, P.; Stevens, T. *J. Chem. Soc.* **1961**, 1743.

New Donors with Two-Electron Oxidation. Synthesis and Electrochemical Properties of Highly Conjugated Bis(4*H*-pyrans), Bis(4*H*-thiopyrans), and Bis(flavenes)

Chin H. Chen,* Jeffrey J. Doney, George A. Reynolds, and Franklin D. Saeva

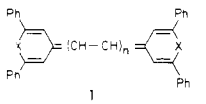
Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

Received November 16, 1982

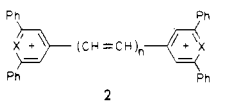
Highly conjugated $\Delta^{4,4'}$-bis(4*H*-pyrans), -(4*H*-thiopyrans), and -(flavenes) separated by four and six ethanediylidene groups were synthesized by condensing the bis Wittig–Horner reagent of tetraethyl 2-butene-1,4-diyldiphosphonate with the appropriate aldehydes. The bispyran separated by three ethanediylidene groups was prepared from the vinylogous pyranyl Peterson reagent generated in situ from 2,6-diphenyl-4-[(trimethylsilyl)ethenyl]-4*H*-pyran, which was synthesized from the corresponding acetylenic derivative by selective hydrogenation. The cyclic voltammograms of these highly conjugated donors are compared with those of the simple derivatives that are separated only by zero to two ethanediylidene groups. The two single-electron waves that are characteristic of the latter coalesce to one *two-electron* oxidation wave when the number of carbons in the extended conjugation separating the two pyranyl, thiopyranyl, and flavenyl moieties reaches eight. One of the extended bisthiopyrans studied, upon one-electron electrochemical oxidation, produces a 50:50 mixture of the neutral and the dicationic species in the presence of <10% of the cation radical species in methylene chloride.

Donors having *two* one-electron, reversible cyclic voltammetric oxidations are quite common.[1] The optimal peak potentials of the first wave for donors to form conducting mixed-valence charge-transfer complexes are believed to fall between $E^{\circ\prime} = 0$ and +0.4 V (vs. SCE).[2] Donor molecules with the unique electrochemical property of *one two-electron reversible* oxidation in this range, nevertheless, are extremely rare.[3] We are intrigued by the possibility that such a molecule D^0, once properly oxidized with a suitable acceptor A^0, might give rise to the kind of mixed-valence CT complexes (such as $D^0D^{2+} \cdot A_2^-$) that are conducive to a two-electron transport process through the molecular stack.

After our earlier studies of the synthesis and electrochemical properties of certain polyene-separated bispyrans and bisthiopyrans,[4,5] we noted that, by systematically extending the conjugation separating the two pyran and thiopyran moieties in **1**, we were able to make the two



1



2

one-electron, reversible oxidation waves coalesce to a single two-electron redox couple.[5] For example, the simple phenyl-substituted bisthiopyran **1** (X = S, $n = 0$) has $E_I^{\circ\prime}$ = +0.27 V and $E_{II}^{\circ\prime}$ = +0.48 V, with a separation of 210 mV, whereas the diethynylidenyl derivative **1** (X = S, $n = 2$) has $E_I^{\circ\prime}$ = +0.21 V and $E_{II}^{\circ\prime}$ = +0.34 V, with a separation of half-wave potentials of 130 mV (see Table II). We attributed this interesting phenomenon to the gradual decrease in energy in removing the second electron from the radical cation of **1**, because the dication **2** that is produced encounters less coulombic repulsion as the length of the conjugation separating the pyrylium or thiopyrylium functions increases. We envisaged that, by extending this conjugation *further* (i.e., $n > 2$), it should be possible to bring the two one-electron oxidation waves of **1** together

(1) Chen, C. H.; Reynolds, G. A. *J. Org. Chem.* **1980**, *45*, 2449. Chambers, J. Q.; Moses, P. R. *J. Am. Chem. Soc.* **1974**, *96*, 945. Engler, E. M.; Kaufman, F. B.; Green, D. C.; Compton, R. N.; Klots, C. E. *Ibid.* **1975**, *97*, 2921. Narita, M.; Pittman, C. U., Jr. *Synthesis* **1976**, 489. Perlstein, J. H. *Angew, Chem., Int. Ed. Engl.* **1977**, *16*, 519. Scott, B. A.; Kaufman, F. B.; Engler, E. M. *J. Am. Chem. Soc.* **1976**, *98*, 4342. Wudl, F.; Schafer, D. E.; Miller, B. *Ibid.* **1976**, *98*, 252. Hünig, S.; Ruider, G. *Justus Liebigs Ann. Chem.* **1974**, 1415.

(2) Torrance, J. B. *Acc. Chem. Res.* **1979**, *12*, 79.

(3) Chen, C. H.; Reynolds, G. A. *J. Org. Chem.* **1981**, *45*, 2449. Bard, A. J.; Phelps, J. *J. Electronal. Chem.* **1970**, *25*, App 2; **1976**, *68*, 313. Hünig, S.; Ruider, G. *Liebigs Ann. Chem.* **1974**, 1415.

(4) Reynolds, G. A.; Chen, C. H. *J. Org. Chem.* **1981**, *46*, 184.

(5) Reynolds, G. A.; Chen, C. H. *J. Heterocycl. Chem.* **1981**, *18*, 627.

0022-3263/83/1948-2757$01.50/0