Synthesis, Structure, and Conformational Dynamics of Bridgehead-Substituted Nitrosamines. Di-1-adamantylnitrosamine and Di-1-norbornylnitrosamine

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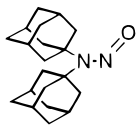
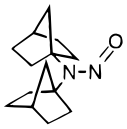
The synthesis of two bridgehead-substituted nitrosamines, di-1-adamantylnitrosamine (**1**) and di-1-norbornylnitrosamine (**2**), is described, and their solid state crystal structures are reported. Large bridgehead substituents increase the NNO angle of the nitrosamine (compared to that found for dimethylnitrosamine) without deconjugating the NNO π system significantly. This structural change correlates with a red-shifted optical absorption, a diminished N,N rotational barrier, and a greater ease of oxidation of these hindered nitrosamines than is observed for dimethylnitrosamine. The electronic basis of these structure/function correlations is examined. It is concluded that **1** is more strained than *N*-nitroso-2,2,6,6-tetramethylpiperidine (**3**) which is more strained than **2** and that a raised (in energy) NO n* orbital is primarily responsible for the extreme properties of the former.

Introduction

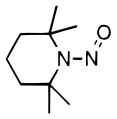
How alkyl substituents influence dialkylnitrosamine properties is the focus of this report. Understanding nitrosamine substituent effects in more detail broadens our knowledge of this important organic functional group which serves as a versatile synthetic progenitor to a variety of other N,N-bonded functionalities and whose biochemical properties are of importance to the field of chemical carcinogenesis.[1] Here, we present the preparation of two new sterically hindered bridgehead-substituted nitrosamines, di-1-adamantylnitrosamine (**1**) and di-1-norbornylnitrosamine (**2**), and report their structures and properties.



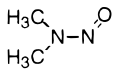
Ad_2NNO, **1**



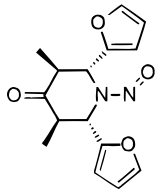
Nor_2NNO, **2**



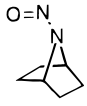
TEMPNO, **3**



Me_2NNO, **4**



DFDMPNO, **5**



ABHNO, **6**

Nitrosamines possess a four-electron, three-atom π system similar to that of an amide. Like an amide nitrogen, the nitrosamine amino nitrogen prefers a planar geometry (or very nearly so) and possesses chemically distinct alkyl substituents *syn* and *anti* to the in-plane oxygen. Interchange of these substituents requires activation energies of 20−24 kcal mol^{-1}, slightly higher than observed for the analogous process in amides. Unlike amides, nitrosamines possess a high-lying in-plane NO lone pair combination orbital. This n* orbital, although not thought to be the HOMO, plays an important role in nitrosamine excitation and oxidation and should be sensitive to the size of the alkyl substituents. Of particular interest here is how substituent size affects the NNO electronic structure and, correspondingly, nitrosamine electronic properties. It is plausible that twisting of the NNO π system and/or opening of the NNO angle occurs when substituents on N become large. Unfortunately, a lack of nitrosamine structural data has left the structural details of this issue unresolved. General trends in nitrosamine optical properties, ease of oxidation, and N,N rotational barriers as a function of substituent size are known (vide infra) and are consistent with either nitrosamine π twisting or NNO angle opening or both. The preparation *and* crystal structure determination of bridgehead-substituted nitrosamines **1** and **2** now allows us to correlate nitrosamine structure and properties directly for a small set of substrates.

Results

Synthesis. Title substrates **1** (Ad_2NNO) and **2** (Nor_2NNO) were prepared by nitrosation of the corresponding amines **7** and **8** (Scheme 1). Amine **7** (Ad_2NH) was initially prepared by a known literature sequence[2] involving permanganate oxidation of $AdNH_2$ to $AdNO_2$, reductive coupling of $AdNO_2$ with bromoadamantane to yield Ad_2NO, and finally subsequent reduction of Ad_2NO to **7**. This sequence suffered from a poor yield and a required laborious chromatographic purification of the nitroxide (∼10%) in the second step. A better route to **7** was devised by Dervan and McIntyre[3] involving pyrolysis of 1-bromoadamantane and 1-adamantamine. We used this reaction to prepare multigram quantities of **7** in a single step of 86% yield. While amine **7** did not react with nitrous acid under standard conditions, presumably

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(1) For reviews see (a) Challis, B. C.; Challis J. A. In *Supplement F: The Chemistry of Amino, Nitroso, and Nitro Compounds and Their Derivatives*; Patai, S., Ed.; Wiley: New York, 1982; Part 2, Chapter 26. (b) *Nitrosamines and Related N-Nitroso Compounds*; Leoppky, R. N., Michejda, C. J., Eds.; American Chemical Society: Washington DC, 1994.

(2) Morat, C.; Rassat, A. *Bull. Chem. Soc. Fr.* **1971**, *3*, 891 and references therein.

(3) McIntyre, D. K. Ph.D. Thesis, California Institute of Technology, 1982. We thank Prof. Dervan for alerting us to this work.

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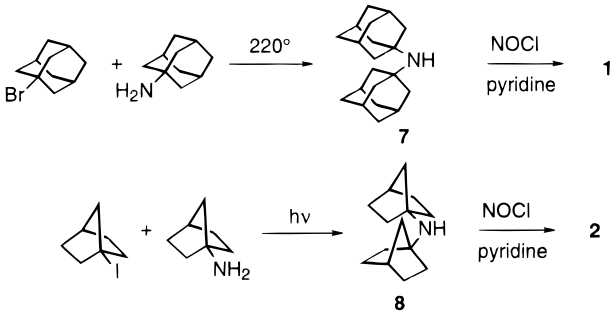
Table 1. Selected Data from Dialkylnitrosamine Structures

properties[a]	Ad_2NNO (**1**) crystal	Nor_2NNO (**2**) crystal	Me_2NNO (**4**) gas[8]	Me_2NNO (**4**) crystal[9]	DFDMPNO (**5**) crystal[10]
			Distances (Å)		
N−O	1.245(2)	1.241(3)	1.234(2)	1.260(6)	1.242(5)
N−N	1.326(2)	1.326(3)	1.344(2)	1.320(6)	1.320(5)
C−N *syn*	1.531(2)	1.484(3)	1.460(2)	1.461(7)	1.493(6)
C−N *anti*	1.522(2)	1.482(3)	1.460(2)	1.465(7)	1.453(6)
			Angles (deg)		
NNO	117.9(2)	115.7(2)	113.6(2)	114.3(3)	115.1(4)
CNN *syn*	121.2(1)	121.7(2)	120.3(3)	122.6(4)	119.7(3)
CNN *anti*	110.6(1)	113.1(2)	116.4(3)	117.4(4)	115.4(3)
CNC	128.2(1)	124.7(2)	123.2(2)	120.0(4)	123.1(3)
$\alpha_{av}(N)$[b]	120.0	119.8	120.0	120.0	119.4
			Twist Angles (deg)		
CN,NO *syn*	0.4(3)	0.4	0.0	0.0	6.0
CN,NO *anti*	−178.1(2)	173.2(2)	180.0	180.0	171.2

[a] Estimated standard deviations in the least significant figure are given in parentheses. [b] The average angle at the amino nitrogen atom.

Scheme 1



because of steric hindrance, its nitrosation was achieved with NOCl under Back and Barton conditions[4] to give nitrosamine **1** in 92% yield.[5]

Nitrosamine **2** proved more difficult to synthesize. A pyrolytic reaction analogous to that used in the preparation of **1** failed to give any di-1-norbornylamine (**8**). On the basis of work by Kropp and co-workers[6] involving irradiation of 1-iodonorbornane in methanol to give 1-methoxynorbornane in good yield, we tried photolysis of 1-iodonorbornane in the presence of 1-norbornylamine in CH_2Cl_2. This reaction gave only 1-chloronorbornane. However, when a neat melt of 1-nobornylamine and 1-norbornyl iodide was photolyzed, amine **8** formed in low yield (12% isolated). Unreacted starting materials were recovered from this reaction, making the conversion 22%. We were not able to scale up this reaction beyond 0.5 g of iodide because of ensuing problems with declining transparency of the sample as the photoreaction proceeds, so this step has remained laborious. Nevertheless, repetitive runs have allowed the preparation of gram quantities of **8**. Subsequent nitrosation of **8** by NOCl/pyridine to give target nitrosamine **2** occurred in 86% yield.

X-ray Structures. Both nitrosamine **1** and **2** are crystalline solids which we have analyzed by X-ray diffraction.[3,4] From cooled ethereal solutions, **1** crystallized as pale yellow needles and **2** crystallized as rectangular plates. Figure 1 shows ORTEP diagrams of **1** ($R = 0.036$, $R_w = 0.044$) and of **2** ($R = 0.052$, $R_w = 0.060$).

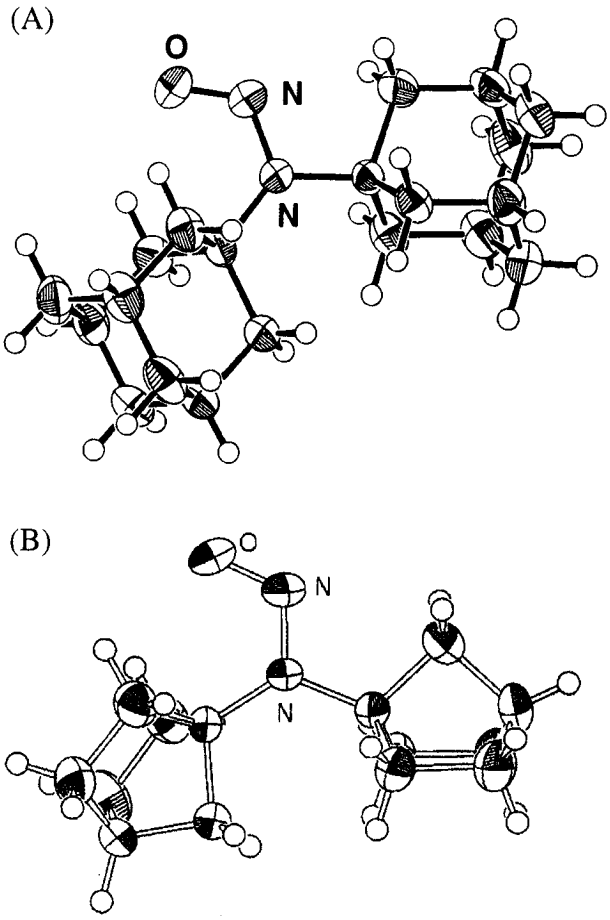


Figure 1. ORTEP diagrams of (A) di-1-adamantylnitrosamine (**1**) and (B) di-1-norbornylnitrosamine (**2**) (50% thermal ellipsoids).

Selected bond lengths and angles for these nitrosamines, along with those for **4** (gas phase[7] and crystal[8] structures) and **5**[9] (crystal structure), are compiled in Table 1.

Conformational Dynamics. At 298 K, the ^1H NMR spectrum of **1** showed distinct adamantyl groups: one group *syn* and one *anti* to the nitroso oxygen. At elevated

(4) Back, T. G.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 924.

(5) Also see ref 3 for nitrosation of amine **7** to nitrosamine **1**.

(6) (a) Kropp, P. J.; Jones, T. H.; Poindexter, G. S. *J. Am. Chem. Soc.* **1973**, *95*, 5420. (b) Kropp, P. J.; Poindexter, G. S. *J. Am. Chem. Soc.* **1974**, *96*, 7142.

(7) (a) Rademacher, P.; Stølvik, R.; Lüttke, W. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 806. (b) Rademacher, P.; Stølvik, R. *Acta Chem. Scand.* **1969**, *23*, 660.

(8) Krebs, B.; Mandt, J. *Chem. Ber.* **1975**, *108*, 1130.

(9) Sukumar, N.; Ponnuswamy, M. N.; Thenmozhiyal, J. C.; Jeyaraman, R. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1069.

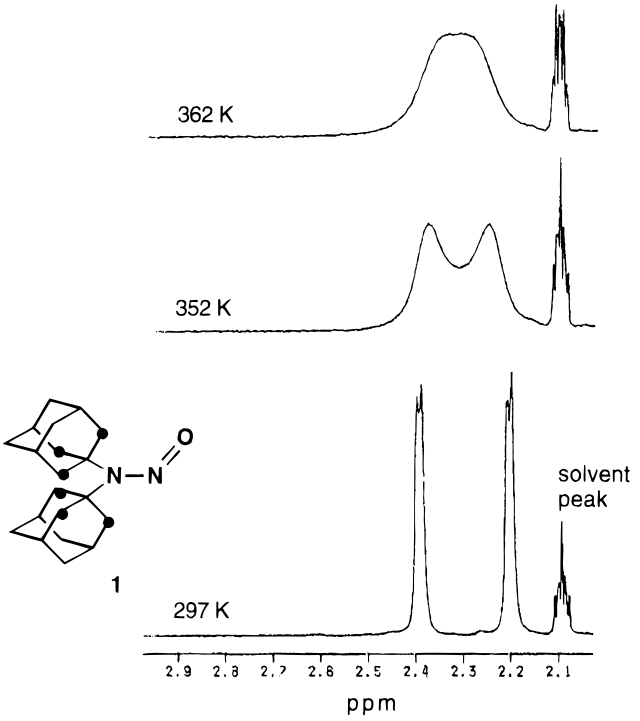


Figure 2. Partial ^{1}H NMR spectrum of di-1-adamantylnitrosamine (**1**) at 297, 352, and 362 K in toluene-d_8. Proximal (●) methylene proton signals are monitored.

temperature, the peaks at δ 2.4 and 2.2 in toluene-d_8 (tentatively assigned as the proximal *syn* and *anti* methylene protons of **1**) changed reversibly (Figure 2). Above 362 K, the adamantyl groups of **1** interchanged fast on the NMR timescale, giving rise to a single, averaged set of adamantyl protons. From the ^{1}H NMR data, T_c = 362 K, and an isomerization barrier ($\Delta G^{\ddagger}_{362}$) of 18.0 ± 0.2 kcal/mol (using $\Delta\nu$ = 44.8 Hz) for substituent interchange in nitrosamine **1** has been calculated.[10]

The analogous isomerization barrier for nitrosamine **2** was measured by variable temperature (VT) ^{13}C NMR spectroscopy in bromobenzene-d_5.[11] In these experiments, the two CH bridgehead ^{13}C NMR signals at δ 33.59 and 33.12 (identified by DEPT experiments) of **2** were monitored. The data analysis yielded T_c = 410 K and $\Delta G^{\ddagger}_{410}$ of 21.1 ± 0.2 kcal mol^{-1} (using $\Delta\nu$ = 22.5 Hz) for norbornyl group interchange.

UV-vis and CV Data. Nitrosamines possess n,π* transitions, typically from 350−370 nm. The UV-vis spectrum for **1** in CH_3CN showed an absorbance with λ_m 390 nm, while that for **2** showed a peak with λ_m 378 nm. These data, along with other selected nitrosamine λ_m values, are compiled in Table 2.

Electrochemical oxidation of nitrosamines **1** and **2** by cyclic voltammetry (CV) gave chemically irreversible waves at 25 °C, showing that the respective radical cations decay in less than 1 ms under these conditions.[12] The peak oxidation potentials (E_p^{ox}) observed for **1** and **2** were 1.45 and 2.00 V vs SCE, respectively, at 200 mV s^{-1} in CH_3CN (0.1 M nBu_4NClO_4). At −45 °C, the cyclic voltammogram of **2** became chemically reversible with

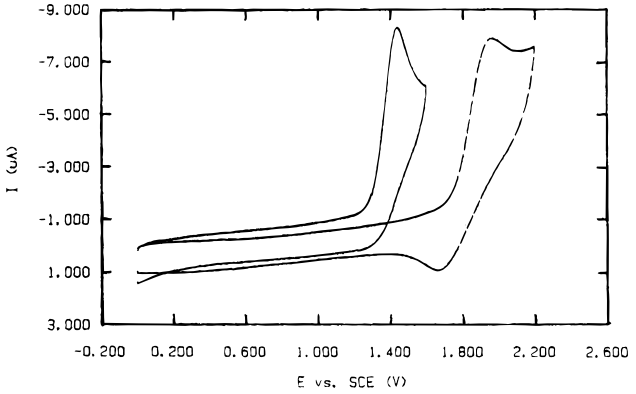


Figure 3. Cyclic voltammogram of Ad_2NNO (**1**) (solid) at 25 °C in CH_3CN (0.1 M nBu_4NClO_4) and of Nor_2NNO (**2**) (dashed) at −65 °C in PrCN (0.1 M nBu_4NClO_4).

Table 2. Selected Nitrosamine N,N Rotation Barriers, λ_m Values, and E_{pa} Values

compound	$\Delta G^{\ddagger}$ (kcal mol^{-1})	λ_m[e] (nm)	E_p^{ox} (V vs SCE)[f]
Ad_2NNO (**1**)	18.0[a]	390	1.45
TEMPNO (**3**)	19.6[b]	388	1.82
Nor_2NNO (**2**)	21.1[c]	378	2.00
$(iPr)_2NNO$	23.5[d]	366	1.91
$(Me)_2NNO$ (**4**)	23.0[d]	352	2.13

[a] In toluene-d_8. [b] In C_2Cl_4 (ref 23). [c] In PhBr-d_5. [d] In $PhNO_2$-d_5 (ref 23). [e] In CH_3CN. [f] Anodic peak potential vs SCE in CH_3CN (0.1 M nBu_4NClO_4) at 25 °C and 200 mV/s.

$E^{\circ\prime}$ = 1.86 V vs SCE. Figure 3 shows some typical CV data recorded for **1** and **2**.

Discussion

Crystal Structures. Relatively few nitrosamine crystal structures are known. This is surprising in view of the chemical and biological importance of this functional group. Previously reported nitrosamine X-ray structures include those for dimethylnitrosamine[8] (**4**) (at low temperature), *N*-nitroso-2,6-di-2-furyl-3,5-dimethyl-4-piperidinone[9] (**5**), *N*,*N*′-dinitroso-1,8-diazadecaline[13] (DNDD), and 3-phenyl-*N*-nitrosopyrrolidine[14] (PNNP). Here, we consider the structural characteristics of sterically hindered **1** and **2** compared to those of **4** and **5** (Table 1).[15]

All nitrosamines in Table 1, regardless of the size of substituents, have similar NO and NN bond lengths (using an average of the rather different gas phase and crystal NO lengths for **4**) and also have similar $C_{syn}NN$ angles. The structures differ, however, in CN bond lengths and in the other angles at the nitrogen atoms. The highly congested nitrosamine **1** has significantly longer CN bonds, larger NNO and CNC angles, and a smaller $C_{anti}NN$ angle than the others of Table 1. The structural trends are consistent with an anticipated steric effect of the substituents at the amino nitrogen of the nitrosamines. Thus, in-plane angular adjustment at the nitrogen atoms of R_2NNO in response to R's steric bulk seems to be the rule for the few structures which are currently known. Deviation from planarity at the amino

(10) This analysis is, strictly speaking, applicable for coalescence of pure singlet signals. The very small splitting of the peaks observed for **1** is not thought to introduce significant error in the measurement.

(11) Attempts to determine T_c for **2** by ^{1}H NMR in various deuterated solvents failed because of overlapping signals.

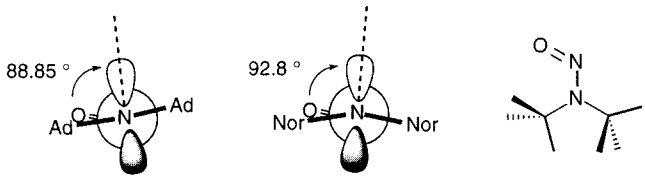
(12) Nitrosamine radical cation reaction paths will be the subject of further publications now under preparation.

(13) Willer, R. L.; Lowe-Ma, C. K.; Moore, D. W.; Johnson, L. F. *J. Org. Chem.* **1984**, *49*, 1481.

(14) Polónski, T.; Milewska, M. J.; Katrusiak, A. *J. Am. Chem. Soc.* **1993**, *115*, 11410.

(15) The DNDD and PNNP structures are not considered in this discussion because the former is a bis(nitrosamine) and the latter has rather large associated errors.

nitrogen is negligible for **1** and **4**, very slight for **2**, and slight for **5**. We speculate that increased effective electronegativity of the 1-norbornyl bridgehead group[16] may account for the slightly nonplanar amino nitrogen of **2** and that ring strain associated with having an sp^2 center in a six-membered ring accounts for the slight pyramidalization in **5**.[17] It appears that large alkyl substituents in R_2NNO do not result in significant deconjugation (twisting) of the NNO π system.[18] For example, the dihedral angle between the amino nitrogen lone pair orbital axis (which bisects the RNR angle) and the NNO plane deviates from 90° by only 1.2 and 2.8° in nitrosamines **1** and **2**, respectively (as shown in the exaggerated Newman projections) and by only 0.0 and 1.4° for crystal structures **4** and **5**, respectively. Lastly, it is noted that structures **1**, **2**, and **4** show geared conformations at the α C atoms, such that the nitroso O atom straddles two β C_{syn} atoms as depicted below.



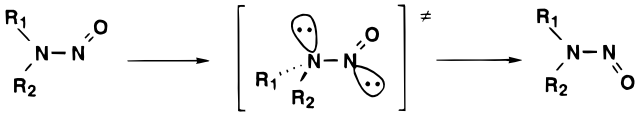
The angular trends at the nitrogen atoms in the crystal structures of Table 1 are consistent with simple expectations of steric strain minimization.[19] As R increases in size, the NNO angle increases. In turn, opening the NNO angle should have important electronic consequences to a nitrosamine's optical properties and its ease of oxidation.

UV-vis and Electrochemistry. The "large" NNO angle in **1** necessitates a strong N,O lone pair,lone pair antibonding interaction in this nitrosamine and raises the energy of the corresponding n* orbital. The effect is evident in **1**'s UV-vis spectrum which shows a red shifted n,π* transition compared to the other nitrosamines of Table 2. It is, of course, incorrect to equate state energy changes directly with orbital energy changes, but trends in the optical spectra of a series of similar molecules will generally correlate with the relevant orbital energy changes. In this regard, it is interesting to note that for nitrosamines in general, the NO n* orbital of mention may not be the HOMO for the molecule even though the n,π* excitation is clearly the lowest energy optical transition for nitrosamines. For example, calculations at both semiempirical and ab-initio levels suggest the HOMO of Me_2NNO is the NNO π orbital with the NO n* orbital being close but lower in energy.[20]

Although the NO n* orbital may not be the HOMO for most nitrosamines, it is generally these electrons which nevertheless are the most easily excited or removed from nitrosamines. Masui and co-workers have shown by ESR spectroscopy that $\mathbf{3}^{\bullet+}$ is a σ (rather than π) radical[21] illustrating that, at least adiabatically, electron loss from **3** gives the NO n* radical cation. In accord with Masui's results, our calculations (6-31G*/UHF) of $Me_2NNO^{\bullet+}$ predict its positive spin density to be concentrated in the NO n* orbital, consistent with the matrix ESR spectrum of this species observed by Mishra and Symons.[22] Thus, combined theoretical and experimental analyses suggest that orbital reordering accompanies nitrosamine adiabatic oxidation.

Consider also the CV data for the nitrosamines of Table 2. Unfortunately, only oxidation peak potentials (E_p^{ox}) are available for this series because, with the exception of **2** and **3** in cold solution, the cyclic voltammograms of these substrates are chemically irreversible. Given this limitation, we cannot draw quantitative thermodynamic conclusions about the relative ease of oxidation because E_p^{ox} values are influenced by the rate of decay of the radical cation formed. Nevertheless, the qualitative trend in the Table 2 data of lower E_p^{ox} values for more hindered nitrosamines is clear and is consistent with the n* oxidation of the nitrosamines.

N,N Rotation Barriers. The isomerization process which interchanges the alkyl groups of Me_2NNO requires roughly 23 kcal mol^{-1}.[23] The mechanism is thought to involve rotation about the NN bond (as shown) rather than inversion at the nitroso nitrogen; calculations predict the latter to require roughly 4 times the activation energy of the former.[24]



A priori, how large alkyl substituents at N will affect the nitrosamine N,N rotational barrier is not obvious. Bulky alkyl groups in R_2NNO structures are expected to strain both the planar ground state conformation (via eclipsing of R_{syn} and O) and the bisected transition state (by hindering R_2N pyramidalization). However, the low isomerization barriers for **1** and **2** clearly illustrate that ground state strain is more important than transition state strain for these nitrosamines, consistent with previous correlations made for a series of α-branched heterocyclic nitrosamines.[25] The data of Table 2 support such a general correlation. The lowest barrier for alkyl substituent interchange in a nitrosamine of which we are aware is 16.5 kcal mol^{-1} for **6**.[26] In **6**, angular destabilization of the ground state and stabilization of the transition state facilitate the isomerization. The barrier of 18.0 kcal mol^{-1} for **1** is also atypically low, the lowest, in fact, so far reported for a nonheterocyclic nitrosamine.

(16) Wiberg, K. B.; Lowry, B. R. *J. Am. Chem. Soc.* **1963**, *85*, 3188.

(17) Slight pyramidalization at the amino nitrogen of a nitrosamine is thought to be energetically easy. In fact, ab-initio calculations (6-31G*/MP2) on H_2NNO predict a very slightly pyramidal H_2N group in this molecule. See also: Harrison, J. A.; MacLagan, R. G. A. R.; Whyte, A. R. *Chem. Phys. Lett.* **1986**, *130*, 98.

(18) A slightly twisted, disordered nitrosamine structure is difficult to rule out from the crystal data, but the thermal parameters at the nitroso oxygen atom and the low *R*-values for structures **1** and **2** suggest that significant twisting is not taking place in these systems.

(19) However, we note that the $C_{syn}NN$ angle is rather invariant from structure to structure, suggesting that this parameter may have a steeper potential to variation than the other in-plane angles at nitrogen.

(20) Schaad, L. J.; Baker, C.; Beaird, D.; Blackstock, S. C. Manuscript in preparation.

(21) (a) Masui, M.; Nose, K.; Ohmori, H.; Sayo, H. *J. Chem. Soc., Chem. Commun.* **1982**, 879. (b) Masui, M.; Ohmori, H.; Ueda, C.; Nose, K.; Sayo, H. *Chem. Pharm. Bull.* **1983**, *31*, 3385.

(22) Mishra, S. P.; Symons, M. C. R. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1449.

(23) Lunazzi, L.; Cerioni, G.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7484.

(24) AM1/RHF (ref a) calculations on Me_2NNO give an N,N rotation path which is 79 kcal mol^{-1} lower in energy than a NNO linearization path. CNDO calculations give similar results (ref b). (a) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. (b) Battiste, D. R.; Davis, L. P.; Nauman, R. V. *J. Am. Chem. Soc.* **1975**, *97*, 5071.

(25) Harris, R. K.; Pryce-Jones, T.; Swinbourne, F. J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 476.

(26) Fraser, R. R.; Swingle, R. B. *Can. J. Chem.* **1970**, *48*, 2065.

If one assumes that ground state strain is the prevailing force which determines the relative N,N rotational barriers for the nitrosamines of Table 2, then one may rank the steric strain order in this series as **1** > **3** > **2**. This steric ordering of these tertiary alkyl-substituted nitrosamines is also supported by trends in their optical and electrochemical properties.

Conclusions

The synthesis and characterization of two bridgehead-substituted nitrosamines, di-1-adamantylnitrosamine **1** and di-1-norbornylnitrosamine **2**, are reported, and their solid state crystal structures are provided. The structure of **1** shows a large steric interaction between the 1-adamantyl groups and a larger NNO angle than observed in **2** or in Me_2NNO (**4**). The steric strain in **1** raises its energy (and that of its n* orbital) as reflected in its optical spectrum, its low N,N rotation barrier, and its ease of oxidation compared to other R_2NNO species. This strain is largely eased in **2**, as indicated by its smaller NNO angle, shorter wavelength UV-vis absorption, higher N,N rotation barrier, and higher E_p^{ox} value. Twisting of the nitrosamine π system is not a major structural manifestation in substrates **1** and **2**. Rather, the data show that for these hindered nitrosamines, the nitrosamine NO n* orbital energy is affected and this orbital influences many nitrosamine properties.

Experimental Section

General. Caution: ***All nitrosamines are potential chemical carcinogens, and special care should be taken in the handling and disposal of these substances.***[27]

An EG&G Princeton Applied Research Potentiostat/Galvanostat Model 273 was used to acquire electrochemical data. A four-necked cell (10 mL) equipped with a Pt disc (1.5 mm diam) working electrode, a Pt wire counter electrode, and an SCE reference electrode was routinely used for CV work. nBu_4NClO_4 (Kodak) was used as supporting electrolyte in CH_3CN (Aldrich HPLC grade) which was distilled from P_2O_5 before use. Nitrosyl chloride[28] and TEMPNO[29] were prepared according to literature methods. DEPT NMR experiments were used to establish the hydrogen multiplicity of the ^{13}C NMR signals.

Di-1-adamantylamine (7). Di-1-adamantylamine was prepared by the procedure of Dervan and McIntyre.[3] A thick-walled glass tube (20 cm long and 1.5 cm diam), closed on one end and narrowed at the other end, was filled with solid 1-adamantylamine (10.0 g, 0.0662 mol) and 1-adamantyl bromide (7.11 g, 0.0331 mol). After sealing the narrow neck under vacuum, the tube was placed in a metal can, buried in sand, and heated to 220 °C for 40 h. The mass inside the tube turned into a hard solid upon cooling to 25 °C. The solid was crushed with a mortar and pestle and dissolved in a mixture of ether (250 mL) and 20% aqueous NaOH (250 mL) by shaking in a separatory funnel. The ether layer was separated and shaken with 10% aqueous HCl solution (300 mL) to precipitate di-1-adamantylamine as the hydrochloride salt which was soluble in neither the ether nor aqueous layer. The precipitate was collected by filtration and washed once with water. The resulting white solid was shaken with a mixture of ether (200 mL) and 20% aqueous NaOH (200 mL) solution to regenerate di-1-adamantylamine in ether. The ether layer was separated and dried over anhyd K_2CO_3. After filtering off the drying agent and evaporating the solvent *in vacuo*, 8.10 g (86% yield) of di-1-adamantylamine (**7**) was obtained. Amine **7** can be further purified by crystallization from ether. Mp 196−197 °C (lit.[3] 196−197 °C; lit.[2] 201 °C). MS (EI, *m/z*): 286 (6, M + 1), 285 (28, M), 228 (100), 191 (22), 135 (83), 93 (19), 79 (23). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.99 (br s, 6H), 1.75 (br d, 12H), 1.59 (br s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.55 (C), 46.56 (CH_2), 36.65 (CH_2), 30.06 (CH). IR (CCl_4, cm^{-1}): 2935 s, 2855 s, 1480 m, 1450 s, 1353 m, 1295 s, 1117 m. Anal. Calcd ($C_{20}H_{30}N$): C, 84.13; H, 10.97; N, 4.90. Found: C, 84.03; H, 10.93; N, 4.93.

Di-1-adamantylnitrosamine (1). The following reaction was carried out in an efficient hood according to a procedure by Back and Barton,[4] modified as follows. (This molecule has also been prepared by McIntyre and Dervan.[3]) A two-necked 100 mL round bottomed flask containing di-1-adamantylamine (0.700 g, 2.46 mmol) in 50 mL of ether−pyridine (1:1) was equipped with an N_2 bubbler. NOCl gas was delivered via Teflon tubing to a stirring solution of **7** until the reaction mixture turned cherry-red (∼10 min). The reaction mixture was stirred for another 10 min at 25 °C, and then a 1:1 mixture (30 mL) of water and ether was gradually added. After stirring another 5 min, the entire mixture was transferred to a separatory funnel. The organic layer was separated and washed with water (5 × 15 mL) to remove pyridine, dried over anhyd K_2CO_3, and concentrated *in vacuo* to give a yellowish solid which was crystallized from ether to yield 0.71 g of light yellow needles (92%). Mp 190−192 °C (lit.[3] 187−188 °C). UV-vis (CH_3CN, 4 mM) λ_m (nm) (log ϵ) 390 (0.284). IR (CCl_4, cm^{-1}) 2910 s, 1425 s, 1350 m, 1302 m, 1195 m, 1118 s, 1035 s, 970 s. ^1H NMR (300 MHz, $CDCl_3$) δ 2.4 (br s, 6H), 2.3 (br s, 6H), 2.17 (s, 3H), 2.06 (s, 3H), 1.65−1.75 (m, 12H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 69.2 (C), 68.9 (C), 43.7 (CH_2), 38.9 (CH_2), 36.3 (CH_2), 36.0 (CH_2), 30.3 (CH), 30.2 (CH). Anal. Calcd ($C_{20}H_{30}N_2O$): C, 76.39; H, 9.60; N, 8.90. Found: C, 76.02; H, 9.75; N, 8.69.

Di-1-norbornylamine (8). A neat mixture of 1-norbornylamine[30] (1.00 g, 9.00 mmol) and 1-iodonorbornane[31] (from 1-norbornyl lithium prepared according to Wiberg's procedure[16]) (0.500 g, 2.25 mmol) was packed in a quartz cuvette (5 mL) containing a magnetic stir bar. The cuvette was placed in a quartz water bath at 50 °C and irradiated by a focused beam from a 500 W Hg-Xe arc lamp with constant stirring for 7 h. The cell was rotated every hour to achieve uniform irradiation on all sides. The crude product was transferred from the cell by washing with 20 mL of a 1:1 4 N aqueous HCl−ether mixture into a separatory funnel. After extracting the ether layer with 4 N aqueous HCl (5 × 10 mL), the organic layer was dried over anhyd K_2CO_3 and evaporated *in vacuo* to give a brown liquid (0.213 g) identified as recovered 1-iodonorbornane (∼90% pure by GC). The combined aqueous layers were basified (pH ∼ 12) with solid sodium hydroxide at 0 °C and extracted with ether (3 × 10 mL). The combined ether extracts were dried over anhyd K_2CO_3 and evaporated to give a brown solid (0.833 g). Sublimation of this solid at 45 °C (0.1 mm Hg) for 16 h onto a water cooled cold finger gave a white solid (0.45 g) of pure 1-norbornylamine. The residue (0.357 g), enriched with di-1-norbornylamine (∼50%), was subjected to preparative thin layer chromatography (PTLC) as follows.

The residue was dissolved in ether, filtered to remove insoluble impurities, and charged onto two basic alumina 60 F_{254} PTLC plates (Merck, 20 cm × 20 cm, 1.5 mm thickness). The plates were eluted with a hexane-ether mixture (1:1). Three major bands were observed by UV detection (band no. 1, R_f = 0.12; no. 2, R_f = 0.50; no. 3, R_f = 0.88). The bands were cut and separately eluted with ether containing 0.25% methanol. Evaporation of solvent gave total solids weighing 97.4 mg (band no. 1), 56.7 mg (band no. 2), and 14.7 mg (band no. 3) which were identified by GC/MS as 1-norbornylamine, di-1-norbornylamine, and tri-1-norbornylamine, respectively. The net recovered yield of di-1-norbornylamine (**8**) was 0.0567

(27) For safe handling and disposal of nitrosamines, especially Me_2NNO (a known potent carcinogen) see Keefer, L. K.; Sansone, E. B.; Lunn, G. *Carcinogenesis* **1983**, *4*, 315.

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g (12%). The recycling of unreacted starting material made the overall conversion 22%. Mp 51−52 °C. MS (EI, *m/z*): 205 (11, M), 176 (100), 148 (12), 95 (40). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.1−1.98 (br m, 2 H), 1.80−1.60 (br m, 5 H), 1.59−1.50 (br m, 8 H), 1.38 (br s, 8 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.63 (C), 45.80 (CH_2), 36.40 (CH_2), 34.66 (CH), 30.79 (CH_2). Anal. Calcd for $C_{14}H_{23}N$: C, 81.95; H, 11.22; N, 6.83. Found: C, 81.80; H, 11.21; N, 6.74.

Di-1-norbornylnitrosamine (2). The following reaction was carried out in an efficient hood according to a procedure originated by Back and Barton[4] and modified here as follows. To a three-necked 25 mL round bottomed flask attached to an argon bubbler was added di-1-norbornylamine (0.16 g, 0.780 mmol) dissolved in 12 mL of ether−pyridine (1:1). NOCl gas was bubbled (via Teflon tubing) through the stirring solution until the color turned to cherry-red (∼10 min). The mixture was stirred an additional 30 min and then transferred to a separatory funnel. The organic layer was washed with water (8 × 8 mL) to remove pyridine and dried over anhyd K_2CO_3. Evaporation of the ether layer *in vacuo* gave 0.151 g of **2** as a light yellow solid (83%) which gave a single spot by TLC (basic alumina/1:1 ether−hexane, $R_f = 0.65$). Further purification of di-1-norbornylnitrosamine was achieved by filtration of an ethereal solution of **2** through a plug of basic alumina and crystallization from ether. Mp 122−124 °C. MS (EI, *m/z*): 234 (3, M), 204 (54), 146 (11), 95 (100), 67 (40). UV-vis (acetonitrile, 3 mM) λ_{max} (nm) (log ϵ) 378 (0.124). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.61−2.50 (br m, 2H), 2.2 (br t, 1H), 2.16 (br t, 1 H) 2.13 (br s, 2H), 2.04−1.96 (br t, 2H), 1.94−1.75 (br m, 6H), 1.68−1.55 (br m, 2H), 1.54−1.43 (br t, 2H), 1.41−1.31 (br m, 2 H), 1.30−1.19 (br m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 74.73 (C), 71.93 (C), 45.67 (CH_2), 42.61 (CH_2), 34.84 (CH_2), 33.59 (CH), 33.12 (CH), 31.03 (CH_2), 30.50 (CH_2), 28.93 (CH_2). Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.80; H, 9.40; N, 11.96. Found: C, 71.68; H, 9.50; N, 11.88.

Variable Temperature ^{1}H NMR Analysis of Di-1-adamantylnitrosamine (1). Nitrosamine **1** (20 mg) dissolved in toluene-d_8 (0.5 mL) in a 5 mm NMR tube was analyzed by ^{1}H NMR (Bruker 300 MHz) at 307, 318, 329, 340, 351, 361, 362, 363, and 365 K. Spectrometer probe temperatures were controlled by nitrogen gas flow through the probe and a resistance coil heater. An ethylene glycol chemical thermometer was employed to measure probe temperature.[32] The two proximal adamantyl CH_2 peaks (δ 2.4 and 2.2), one *syn* and the other *anti* to the nitroso group, of nitrosamine **1** were monitored over the temperature range and were found to coalesce at 362 K. The peak separation ($\Delta\nu$) at 362 K was estimated by extrapolation from a linear $\Delta\nu$ vs T plot using data at 307, 318, 329, 340 K ($R^2 = 0.99$) to be 44.8 Hz. (Observed $\Delta\nu$ values changed by 7 Hz over the 307−340 K *T* range.) The resulting $\Delta G^{\ddagger}_{362}$ of isomerization was calculated[33] according to $\Delta G^{\ddagger}_{T_c} = RT_c\,[23 + \ln(T_c/\Delta\nu)]$ kcal mol^{-1} to be 18.0 kcal mol^{-1}. This value is considered to be accurate within ±0.2 kcal mol^{-1} (assuming < ±2 K error in *T* and <3 Hz error in $\Delta\nu$).

Variable Temperature ^{13}C NMR Analysis of Di-1-norbornylnitrosamine (2). A Bruker 300 MHz NMR spectrometer with a VT heating system was employed as in the case of **1**. Temperatures were measured by the NMR shift method using ethylene glycol peak positions as described above. A concentrated solution (120 mg in 0.5 mL) of di-1-norbornylnitrosamine **2** in bromobenzene-d_5 was used for analysis. The two bridgehead CH peaks at δ 33.59 and 33.12 were monitored by DEPT-135 ^{13}C NMR experiments at 306, 330, 350, 371, 392, 405, 409, 410, and 412 K. The observed T_c value was 410 K. The $\Delta\nu$ value at 410 was determined by extrapolation from a plot of $\Delta\nu$ vs *T* below 392 to be 22.5 Hz. These measurements yield $\Delta G^{\ddagger}_{410} = 21.1 \pm 0.2$ kcal mol^{-1} for nitrosamine **2** in bromobenzene-d_5.

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