Conformational Study of *N*-Nitroso-2,6-diphenylpiperidines and *N*-Nitroso-2,6-diphenylpiperidin-4-ones by Molecular Mechanics Calculations, X-ray Crystallography, and ^{1}H and ^{13}C NMR Spectroscopy

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Molecular geometries of several *N*-nitroso-2,6-diphenylpiperidines and *N*-nitroso-2,6-diphenylpiperidin-4-ones were calculated by the molecular mechanics (MM2) method with added parameters for the *N*-nitroso group and by X-ray crystallography and ^{1}H and ^{13}C NMR. We found that these molecules adopt either a chair conformation with two phenyl groups at the axial positions or a distorted boat-like conformation. Contrary to the earlier literature suggestions, a diequatorial chair conformer is destabilized by the $A^{(1,3)}$ strain resulting from a steric interference of the planar NNO moiety with the neighboring equatorial substituents. The X-ray crystal structures showed diaxial orientation of the phenyls in two compounds, assuming the chair conformations and boat-like piperidine ring geometry in three other nitrosamines. The ^{1}H and ^{13}C NMR spectra exhibited similar conformational preferences in solution to that predicted by the MM2 calculations. Most of the compounds derived from the symmetrically substituted amines appeared to be almost conformationally homogeneous, whereas the conformational equilibria of unsymmetrically substituted nitrosamines are rather complex.

Introduction

N-Nitrosamines have drawn considerable interest in recent years due to their strong carcinogenic and mutagenic properties.[1] Many biochemical and physicochemical investigations have been directed toward establishing their structure–activity relationships.[2] Since the molecular geometry and conformational behavior critically influence the biological activity, the stereochemistry of *N*-nitrosamines has been extensively studied by different experimental and computational methods.[3] Particularly, various NMR techniques have been widely applied to these compounds to explain their conformational preferences.[4]

N-Nitrosopiperidines are the fundamental members of this class of compounds. The nitroso group introduced at the nitrogen atom profoundly affects the conformation of the piperidine ring and the orientation of substituents. A strong steric interaction of the planar *N*-nitrosamino group with the nearly coplanar equatorial substituents at C-2 and C-6 is of primary importance here. This kind of interference, called allylic (or pseudoallylic) 1,3-strain ($A^{(1,3)}$), is often observed in the six-membered rings, including exo- and endocyclic double bonds in alkenes, enamines, *N*-acylpiperidines, and related systems.[5,6] Due to this effect, *N*-nitroso-*cis*-2,6-dimethylpiperidine (**2b**) exists in solution almost exclusively in a diaxial chair conformation.[7] The methyl substituents are forced to occupy the axial positions because the energy barrier to N–N rotation is high (ca. 23 kcal/mol)[8] and the $A^{(1,3)}$ strain prevails over a diaxial interaction between these groups. Similar conformational preferences might be expected for other *N*-nitrosopiperidines with bulky 2,6-substituents. Contrary to this expectation, Jeyaraman and co-workers, on the basis of the NMR study of several *N*-nitroso-*cis*-2,6-diphenylpiperidines and *N*-nitroso-*cis*-2,6-diphenylpiperidin-4-ones, have recently excluded the possibility of a diaxial orientation of the phenyl substituents.[9] They have assumed that both *Z* and *E* stereoisomers, resulting from hindered N–N rotation and being in equilibrium, exist in solution in chair conformations with the phenyl groups in equatorial positions. However, a closer examination of their ^{1}H NMR data reveals a significant nonequivalence of the vicinal coupling constants exhibited by the H-2 and H-6 benzylic protons,

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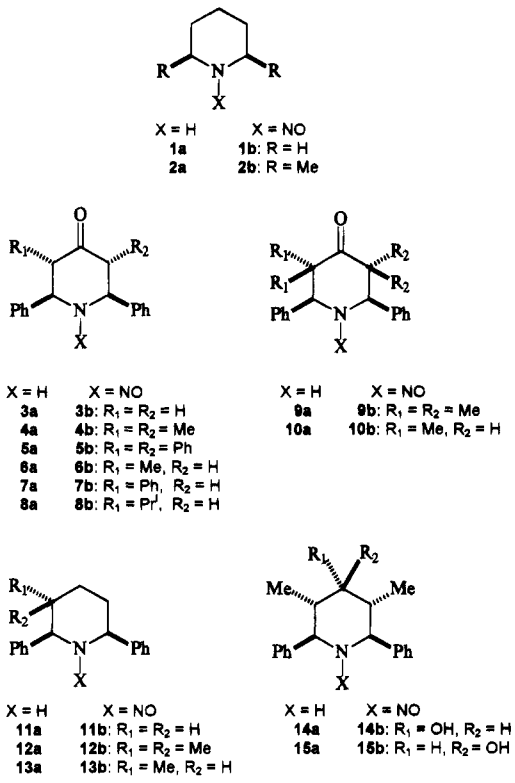
Chart 1



which in our opinion suggests a contribution from the ring conformers of a lower than C_s symmetry, i.e., non-chair ones, rather than the twisting of the chair "on the syn side only" proposed by the above authors. Recently reported X-ray crystallographic structures of two compounds from this class remain in line with this supposition.[10] Moreover, a separation of the resonances due to *syn* and *anti* benzylic protons vary in a broad range, e.g., for some compounds they differ by 1.5 ppm and merge for other ones, which may indicate different and more complex conformational equilibria than those assumed by the aforementioned authors.

The above considerations and doubts prompted us to reexamine the stereochemistry of the title compounds. For this purpose we prepared *N*-nitrosamines **3b**–**15b** from the corresponding amines **3a**–**15a** (Chart 1). The conformational preferences of the molecules were studied by molecular mechanics (MM2) calculations, and the results were compared with those obtained from X-ray crystallographic analysis. Finally we measured and analyzed the high-resolution ^{1}H and ^{13}C NMR spectra to establish the solution conformations. The results undoubtedly showed preference for the diaxial chair and distorted boat conformers, structures rather uncommon for the six-membered ring compounds, whereas the diequatorial chair conformer appeared to be very unstable for the majority of compounds from this class.

Results and Discussion

2,6-Diphenylpiperidin-4-ones **3a**–**10a** were obtained by a Mannich condensation of benzaldehyde with the appropriate ketone and ammonia according to the literature procedures.[9,11] Their configurations, as shown above, are known from ^{1}H NMR and crystallographic data.[12] The piperidines **11a**–**13a** were prepared by Wolff–Kishner reduction of the corresponding piperidinones. The N-nitrosation of the amines **3a**–**15a** gave the *N*-nitrosamines **3b**–**15b**.

Table 1. Relative Steric Energies (kcal/mol) of the Conformers Calculated by the MM2 Method

compd	CA	CE	B1	B2	B3	B4
2b	0.0	2.11	3.16	2.51		
3b	0.0	4.72	2.10	2.64	2.69	4.68
4b	1.48	0.70	0.0	0.43	2.01	4.02
5b	0.0	4.30	0.61	1.24	2.85	4.68
***Z*-6b**	0.0	2.70	2.43	0.38	3.45	3.49
***E*-6b**	0.03	2.61	1.77	0.72	1.36	5.41
***Z*-7b**	0.20	3.64	0.98	0.72	3.01	1.66
***E*-7b**	0.0	3.78	0.40	1.33	0.91	3.73
***Z*-8b**	0.01	3.81	3.03	1.27	4.28	3.36
***E*-8b**	0.0	3.60	2.44	1.48	1.96	5.33
9b	1.30	2.59	0.40	1.00	0.0	1.49
***Z*-10b**	0.10	4.96	3.38	4.83	4.79	2.77
***E*-10b**	0.0	4.23	2.40	4.78	4.66	4.32
11b	0.0	1.35	2.11	2.58	2.33	4.12
***Z*-12b**	0.32	1.96	3.20	4.94	4.85	3.12
***E*-12b**	0.0	1.30	2.16	4.56	4.23	4.88
***Z*-13b**	0.06	0.18	2.32	0.80		3.69
***E*-13b**	0.0	0.07	1.74	1.13	1.12	
14b	3.70	0.0	2.53	2.96	4.51	
15b	5.49	0.0	1.00	1.44	2.34	

Molecular Geometry. The molecular structures of the nitrosamines were calculated by the molecular mechanics (MM2) method.[13] Some additional parameters needed to deal with the NNO group were added to the original Allinger parametrization, as described earlier,[14] and now the method has been further improved and extended to accommodate the aryl-substituted compounds. Table 1 shows the relative steric energies of the conformers corresponding to the calculated energy minima. The method correctly predicts the existence of *N*-nitrosopiperidine (**1b**) in the chair conformation and shows that for **2b** the diaxial chair form is ca. 2 kcal/mol more stable than the diequatorial one. Generally six conformers (Chart 2), can be expected for the symmetrically substituted title compounds and 12 for the unsymmetrically substituted ones (six for each *Z* and *E* stereoisomer), two chairs **CA** and **CE** with phenyl groups in diaxial and diequatorial positions, respectively, and four distorted boat **B2**–**B4** conformers. The contributions from two other possible boat forms **B5** and **B6** are negligible, since the calculated steric energy of **B5** is enormously high (ca. 5 kcal/mol higher than that of the lowest energy conformer) and the calculations showed that there is no energy minimum for **B6**. It is noteworthy that, in the case of symmetric compounds, conformers **B1** and **B2** (also **B3** and **B4**) differ only in the orientation of the nitroso oxygen (*syn* or *anti* to the neighboring equatorial phenyl group). Analogously, the conformers of unsym-

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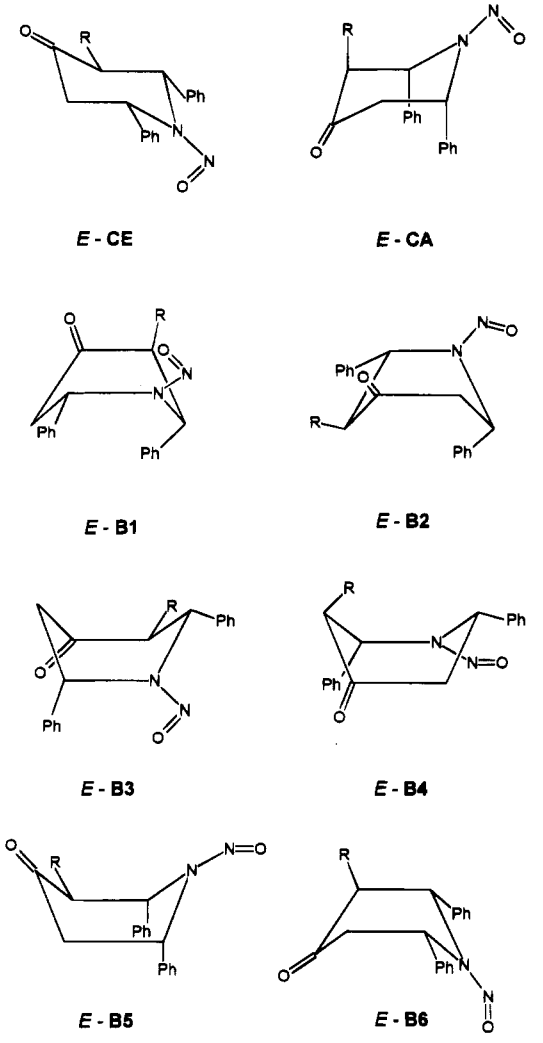
Chart 2



metrically substituted nitrosamines *E*-**B1** and *Z*-**B2**, *E*-**B3** and *Z*-**B4** and vice versa are related by the opposite configuration of the nitrosamino group.

For the majority of the compounds, including the simplest ones **3b** and **11b**, the **CA** form is the most stable structure, whereas the **CE** conformer is of much higher energy as a consequence of the $A^{(1,3)}$ strain. The most important exceptions are compounds **4b** and **9b**, predicted to favor the **B1** or **B3** boat conformations, and **14b** and **15b**, expected to prefer the **CE** form.

Two X-ray determined structures of *N*-nitrosopiperidinones related to **4b** have been already reported.[10] The *o*-chloro analogue of **4b** shows the piperidine ring in a distorted boat **B1** conformation in accordance with the MM2 calculations. In addition we solved the crystal structures of the nitrosamines **5b** and **8b**−**11b**.[15,16] The simplest compound of the series, *N*-nitroso-*cis*-2,6-diphenylpiperidine (**11b**), crystallizes in two polymorphic forms, and in both of them the piperidine ring adopts the chair **CA** conformation with two axially oriented phenyl

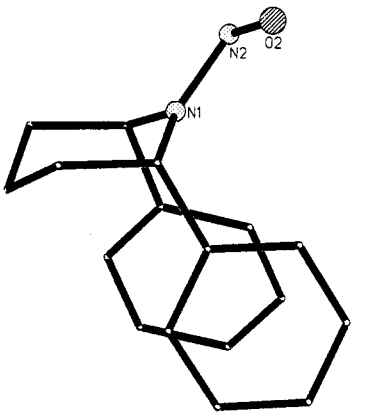


Figure 1. X-ray structure of **11b**.

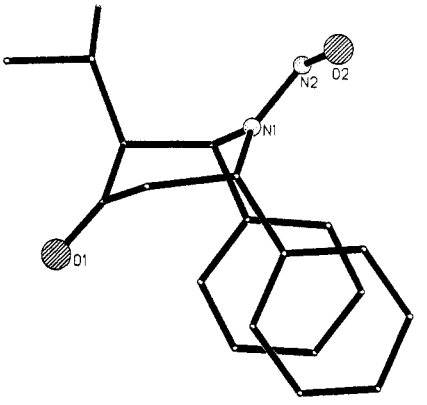


Figure 2. X-ray structure of **8b**.

groups (Figure 1) as predicted by the MM2 method. Also **8b** exists in the solid state in the **CA** form with three bulky substituents occupying axial positions (Figure 2). The solid state structures of **5b**, **9b**, and **10b** (Figure 3) are represented by the boat **B1** as the major conformer. The observed conformations of **5b** and **10b** presumably result from crystal packing forces, since the calculations showed preference of the **CA** form for these compounds.[17] This is in line with the NMR data pointing to a predominance of the **CA** conformer in solution, as will be discussed in the next section.

The calculated and observed geometries of **4b**, **5b**, and **8b**−**11b** (selected torsional angles) are compared in Table 2. Compounds preferring the boat **B1** or **B2** conformations in the crystal state or in solution are of special interest since six-membered ring molecules with an inherent preference for non-chair forms are rather rare.[18] Owing to their flexibility, the **B1** and **B2** conformers are more or less distorted from the perfect boat and the degree of the ring deformation depends on the substitution pattern; e.g., in **4b** the ring is only slightly twisted, whereas in **9b** it is severely distorted. All boat-type structures, derived from the MM2 calculations and the X-ray crystallography as well, are characterized by a smaller twisting about the N(1)−C(2) and a stronger

(15) The details of the X-ray structure of **11b** will be published elsewhere.

(16) The authors have deposited experimental details concerning the crystal structure determinations of **5b**, **8b**, **9b**, and **10b**, atomic coordinates, anisotropic atomic displacement parameters of non-H atoms, and lists of bond lengths and angles with the Cambridge Crystallographic Data Centre. The data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(17) A disorder was observed in the reported crystal structures. In **8b** and **11b** a single site in the crystal is occupied, with equal probability, by molecules having the nitroso group in two different orientations related to each other by ca. 180° rotation around the N−N bond. In **9b** and **10b** the NNO group is *syn* oriented to the equatorial phenyl in the more populated conformers (60 and 90%, respectively) and *anti* in the less populated ones. A single site in the crystal of **5b** is occupied by molecules assuming the **B1** and **B3** conformations (77 and 23%, respectively).

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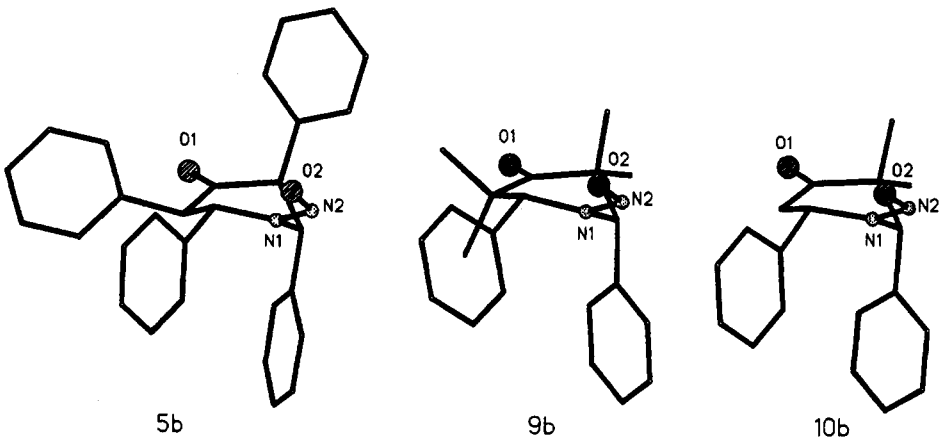
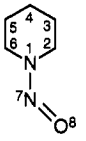


Figure 3. X-ray structures of **5b**, **9b**, and **10b**.

Table 2. Selected Torsional Angles for the Calculated and X-ray Structures of *N*-Nitrosamines

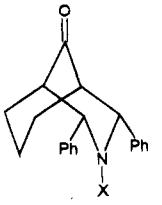


compd	struct	1234	1654	3216	3456	2345	2165	α[a]
4b	**B1**	48.1	54.7	−4.4	−12.2	−39.8	−47.4	4.2
	X-ray[b]	45.1	49.6	−1.6	−8.6	−40.7	−46.6	21.4
5b	**B1**	45.2	57.0	−3.1	−16.5	−48.2	−35.1	3.9
	X-ray	47.6	60.7	−9.2	−23.9	−45.5	−30.6	15.7
8b	***Z*-CA**	−53.6	48.5	60.4	−51.3	53.2	−56.8	1.0
	X-ray	−53.3	40.6	55.7	−48.9	54.4	−47.9	10.7
9b	**B1**	22.0	61.4	1.8	−40.0	−1.8	−44.7	4.5
	X-ray	32.6	59.2	−6.4	−35.4	−11.2	−40.4	20.0
10b	***E*-B1**	43.0	57.6	−5.7	−21.7	−28.8	−45.0	4.2
	X-ray	36.8	58.3	−0.5	−25.4	−23.2	−47.0	14.5
11b	**CA**	−54.8	50.9	58.4	−52.1	54.3	−56.6	2.3
	X-ray	−51.3	46.8	49.7	−53.6	55.6	−47.4	5.3

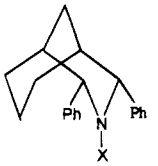
[a] The angle $\alpha = 180 - \phi(2617)$ characterizes distortion of the NNO group from planarity. [b] Data for *N*-nitroso-2,6-bis(2-chlorophenyl)-3,5-dimethylpiperidin-4-one taken from ref 10a.

twist about the C(4)−C(5) bond; however, they are still very far from the classical twisted boat conformation.[19]

Another important feature of these conformations is a marked nonplanarity of the amino nitrogen, which contrasts with a nearly coplanar arrangement of the nitrosamine system in the **CA** conformer. A much stronger pyramidal character of the amino nitrogen is expected for the diequatorial chair **CE** conformer; since the planar NNO group strongly interferes with the neighboring equatorial phenyls, its deviation from planarity is the only way to diminish the $A^{(1,3)}$ strain in this form. The X-ray structures of the bicyclic compounds **16b** and **17b** with the phenyl groups fixed in the equatorial positions confirm this supposition.[20] The nonplanarity of the NNO moiety is also evidenced by a bathochromic shift of the n−π^* electronic transition in the UV spectra of **16b** and **17b**.[21] The monocyclic nitrosamine **14b** behaves similarily; according to the MM2 calculations and the NMR spectra it adopts the **CE** conformation. Due to the apparent nonplanarity of the nitrosamine chromophore, **14b** shows the n−π^* absorbtion at considerably longer wavelengths [λ_{max} 381 nm (ϵ 55) in cyclohexane]



16a: X = H
16b: X = NO



17a: X = H
17b: X = NO

than simple nitrosamines [e.g. *N*-nitrosodimethylamine; λ_{max} 362 nm (ϵ 125)][22] and other compounds of this class [e.g., **11b** and **15b**; λ_{max} 368 (ϵ 70) and 369 nm (ϵ 52), respectively].

The observed nonplanarity of the NNO system may be the source of some discrepancies between the calculated and observed geometries of nitrosamines as in the case of **15b**, which according to the NMR data favors the **B1** form, whereas the calculation places this 1.0 kcal/mol above the **CE** conformer. Also the energy of the **B1** form seems to be overestimated by the MM2 method, since its contribution to the conformational equilibria is greater than that expected from the calculated energy values. The pyramidalization of the amino nitrogen in **B1** and **CE** decreases the resonance energy of the system, and

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Table 3. ^{1}H NMR Spectral Data of *N*-Nitrosamines 3b–17b and Amines 3a–17a[a]

compd	solv	δ (*J*) *syn*-C_αH	δ (*J*) *anti*-C_αH	compd	solv	δ (*J*) C_αH
3b	$CDCl_3$	6.03 (6.3 and 7.8)	6.48 (5.3 and 6.1)	**3a**	$CDCl_3$	4.09 (4.1 and 11.3)
	CD_3OD	6.04 (6.3 and 6.8)	6.47 (5.9 and 6.3)			
4b	$CDCl_3$	5.21 (10.1)	6.16 (3.6)	**4a**	$CDCl_3$	3.62 (10.4)
	CD_3OD	5.33 (9.8)	6.23 (3.9)			
5b	$CDCl_3$	6.17 (7.6)	6.33 (6.4)	**5a**	$CDCl_3$	4.46 (10.6)
	CD_3OD	6.18 (7.8)	6.43 (5.4)			
Z-**6b**	$CDCl_3$	5.23 (10.2)	6.65 (2.7 and 7.0)	**6a**	$CDCl_3$	4.10 (3.3 and 11.5), 3.63 (10.4)
E-**6b**		6.05 (6.3 and 6.8)	5.93 (6.3)			
Z-**6b**	CD_3OD	5.25 (10.7)	6.70 (2.4 and 6.8)			
E-**6b**		6.13	5.92 (8.3)			
Z-**7b**	$CDCl_3$	6.19 (7.8)	6.54 (4.0 and 6.4)	**7a**	$CDCl_3$	4.32 (3.4 and 11.4), 4.24(10.6)
E-**7b**		6.18 (6.3)	6.55 (5.0)			
Z-**7b**	$CDCl_3$(−50 °C)	5.83 (10.3)	6.73 (2.9 and 6.4)			
E-**7b**		6.15 (6.3)	6.52 (5.9)			
Z-**7b**	CD_3OD	5.87 (10.3)	6.74 (3.4 and 6.8)			
E-**7b**		6.20 (5.9)	6.43 (8.8)			
Z-**8b**	$CDCl_3$	6.80 (2.4)[b]	6.42 (4.5 and 7.4)	**8a**	$CDCl_3$	4.10 (3.4 and 11.4), 3.99(10.5)
E-**8b**		6.08 (7.3)	6.59 (1.5)			
Z-**8b**	CD_3OD	6.69 (2.9)	6.46 (5.4 and 6.8)			
E-**8b**		5.99 (7.3)	6.56 (2.9)			
9b	$CDCl_3$	5.52	6.30	**9a**	$CDCl_3$	3.92
Z-**10b**	$CDCl_3$	6.41	6.34 (6.8 and 7.3)	**10a**	$CDCl_3$	4.05 (3.2 and 12.0), 3.82
E-**10b**		5.69 (8.8)	6.26			
Z-**10b**	CD_3OD	6.30	6.40 (6.8 and 8.3)			
E-**10b**		5.74 (7.3 and 9.9)	6.36			
11b	$CDCl_3$	6.14 (4.4 and 5.9)	6.11 (4.4 and 5.9)	**11a**	$CDCl_3$	3.86 (2.0 and 10.7)
	CD_3OD	6.04 (5.4)	6.00 (5.3)			
Z-**12b**	$CDCl_3$ (−50 °C)	5.83[c]	6.13 (5.0)	**12a**	$CDCl_3$	3.87 (2.9 and 11.2), 3.71
E-**12b**		6.28 (2.8 and 6.1)	5.50[c]			
Z-**12b**	CD_3OD	5.83[c]	6.13[c]			
E-**12b**		5.58 (6.3)	6.13[c]			
Z-**13b**	$CDCl_3$	5.27 (8.8)	6.17 (3.9 and 7.3)	**13a**	$CDCl_3$	3.84 (2.9 and 11.2), 3.38 (9.8)
E-**13b**		5.79 (6.8)	5.58 (5.4)			
Z-**13b**	CD_3OD	5.16 (8.3)	6.12 (6.4 and 7.3)			
E-**13b**		5.67 (6.8)	5.52 (6.3)			
14b	$CDCl_3$	4.89 (10.7)	5.53 (9.3)	**14a**	$CDCl_3$	3.87 (10.5)
	CD_3OD	4.74 (10.7)	5.41 (10.2)			
15b	$CDCl_3$	4.96 (10.7)	5.79 (2.9)	**15a**	$CDCl_3$	3.44 (9.9)
	CD_3OD	4.89 (10.2)	5.73 (4.4)			
16b[d]	$CDCl_3$	5.88 (5.4)	5.18 (6.4)	**16a**[d]	$CDCl_3$	4.41 (2.7)
17b[d]	$CDCl_3$	5.70 (6.4)	4.95 (6.9)	**17a**[d]	$CDCl_3$	4.35 (2.5)

[a] Chemical shifts in ppm, coupling constants in hertz. [b] The signal located by a COSY experiment. [c] The coupling constant cannot be measured because of the severe line broadening. [d] From ref 21.

this purely electronic effect remains beyond the MM2 method.[13] Similarly solvation effects, proved to influence conformations of some compounds, are neglected by the method.

^{1}H and ^{13}C NMR Spectra. The ^{1}H NMR data of nitrosamines **3b–15b** and their parent amines are summarized in Table 3. The piperidinones **3a–10a** and piperidines **11a–15a** prefer in solution a chair conformation with the phenyl groups occupying the equatorial positions as indicated by the ^3J vicinal coupling constants of the H-2 and H-6 benzylic protons, larger axial–axial and smaller axial–equatorial ones (ca. 10 and 3–4 Hz, respectively).

The conformational behavior of the corresponding nitrosamines is more complex, especially in the case of unsymmetrically substituted compounds, where *Z* and *E* stereoisomers, usually in two or more conformations, are present in the equilibrium. This is reflected by the solvent and temperature dependence of some spectra (e.g., **7b**). In contrast, a majority of compounds derived from the symmetrically substituted amines seems to be nearly conformationally homogeneous as predicted by the MM2 calculations and confirmed by a weak variation of their spectra with solvent and temperature changes (e.g., **3b**, **11b**, **14b** and **15b**).

Due to its partial double bond character, the N–N rotation in *N*-nitroso compounds is slow on the NMR time scale, which gives rise to different chemical shifts of the protons oriented *syn* and *anti* to the nitroso oxygen. The assignment of the *syn* and *anti* benzylic hydrogens was based on their chemical shifts and the aromatic solvent induced shifts (ASIS).[4b,23] It has been shown that the $\Delta\delta = \delta(CDCl_3) - \delta(C_6D_6)$ is more positive for *anti* than for *syn* protons (see supporting information). A strong shielding anisotropy of the NNO group facilitates conformational analysis of nitrosamines. According to the proposed shielding zones, the α-equatorial hydrogens in the piperidine ring are further downfield from the corresponding axial ones, which lie deeper in the shielding zone.[24] It is known that the hydrogens that are coplanar with the NNO group show comparable chemical shifts. However, the proton *syn* to the nitroso oxygen resonates at a slightly lower frequency than the one *anti* to the oxygen. On the other hand, the out-of-plane *syn* protons are strongly shielded relatively to *anti* ones.

(23) Karabatsos, G. J.; Taller, R. A. *J. Am. Chem. Soc.* **1964**, *86*, 4373.

(24) (a) Harris, R. K.; Spragg, R. A. *J. Mol. Spectrosc.* **1967**, *23*, 158. (b) Chow, Y. L.; Colon, C. J. *Can. J. Chem.* **1968**, *46*, 2827. (c) ApSimon, J. W.; Cooney, J. D. *Can. J. Chem.* **1971**, *49*, 2377.

Table 4. ^{13}C Chemical Shifts (in ppm) in $CDCl_3$

compd	*syn*-C_α	*anti*-C_α	C_β	compd	C_α	C_β
1b[a]	40.0	51.0	24.9, 26.6	**1a**[a]	47.6	27.4
2b[b]	43.8	54.5	29.8, 30.7	**2a**[c]	52.7	34.7
3b	53.7	60.3	43.0, 43.3	**3a**	61.1	50.3
4b	61.8	66.0	44.5, 45.5	**4a**	68.8	52.0
5b	59.3	66.0	57.5, 58.0	**5a**	68.1	65.3
Z-**6b**	62.1	59.5	42.1, 45.9	**6a**	68.3, 61.4	50.8, 51.5
E-**6b**	53.1	66.7	41.2, 46.1			
Z-**7b**	60.1	59.6	41.5, 58.1	**7a**	68.0, 65.0	50.8, 65.2
E-**7b**	53.2	66.4	42.3, 57.1			
Z-**8b**	58.4	61.3	41.8, 52.4	**8a**	64.7, 61.1	51.9, 61.0
E-**8b**	57.9	62.7	42.2, 53.3			
9b	66.3	70.8	45.9, 48.0	**9a**	70.5	49.9
Z-**10b**	61.4	61.1	42.0, 47.5	**10a**	69.5, 61.6	47.2, 49.8
E-**10b**	55.8	71.3	43.0, 48.1			
11b	52.0	60.5	26.9, 27.0	**11a**	62.6	34.7
Z-**12b**	60.8	58.9	29.0, 33.5	**12a**	71.2, 63.3	31.9, 33.5
E-**12b**	49.9	73.3	29.2, 34.1			
Z-**13b**	60.2	62.0	24.2, 31.8	**13a**	69.9, 62.5	34.8, 37.3
E-**13b**	54.2	68.1	25.7, 31.3			
14b	60.9	66.1	40.0, 41.2	**14a**	61.8	42.9
15b	63.1	67.7	39.4, 39.4	**15a**	67.3	45.4
16b[d]	64.8	69.1	50.6, 51.8	**16a**[d]	64.7	35.1
17b[d]	64.1	68.8	33.7, 34.4	**17a**[d]	65.3	35.1

[a] From ref 29d. [b] From ref 29a. [c] Neat, from Jones, A. J.; Hassan, M. M. A. *J. Org. Chem.* **1972**, *37*, 2332. [d] From ref 21.

In the 500 MHz ^1H NMR spectrum of **11b** in $CDCl_3$, the *syn* benzylic proton is observed at a slightly lower field than the *anti* one. Their separation is less than 0.03 ppm, and both show very similar couplings to the vicinal protons. In C_6D_6 solution, the *anti* benzylic hydrogen is shifted upfield by 0.29 ppm from the *syn* one. According to the above considerations, these hydrogens must be equatorially oriented and thus the nitrosamine **11b** exists in solution in the **CA** conformation, similarly to the solid state. An analogous conformational preference was predicted for **3b** and **5b**. However, small differences in the chemical shifts and coupling constants of the H-2 and H-6 resonances suggest a small contribution from the **B1** conformer to the equilibrium. In the case of **5b** this contribution increases appreciably in polar solvents, as shown by the corresponding ^3J values. In the **B1** conformer, which apparently dominates in solutions of **4b** and **15b**, the axial–axial orientation of H-2 and H-3 and equatorial–equatorial orientations of H-5 and H-6 lead to two different ^3J values, ca. 10 and 3 Hz, respectively. Also the chemical shifts of the *syn* and *anti* benzylic protons differ considerably. According to the NMR data, nitrosamine **14b** is the only monocyclic compound favoring the **CE** conformation. The equatorial location of the phenyl and methyl substituents in **14b** gives rise to two strong axial–axial couplings of the corresponding hydrogens, and the axial H-2 and H-6 protons placed far from the NNO plane resonate at relatively high field.

Conformational nonhomogeneity and an uncertain shielding effect of the substituents at C-3 complicate the interpretation of the spectra of the unsymmetrically substituted nitrosamines. A simple comparison of their NMR data with those of the above symmetric compounds in most cases indicates contributions from the **CA** and **B1** or **B2** forms to the equilibrium. Often conformational preferences of the *Z* and *E* stereoisomers are different, e.g., *Z*-**6b** favors the **B2** and *E*-**6b** the **CA** conformation. As already mentioned, the conformational equilibria for some compounds appeared to be solvent and temperature dependent, e.g., the solvent- and temperature-induced changes in the spectra of **7b** suggest that the population of the boat form increases in polar media for both *Z* and *E* stereoisomers and an analogous effect was observed upon temperature lowering. In contrast, the spectrum of **8b** is not appreciably affected by solvent polarity. The calculations predicted the triaxial form **CA** to be the most stable one for this compound, in accordance with the X-ray structure. Similarly the **CA** form seems to be favored by *Z*-**8b** and *E*-**8b** in solution, as proved by the H-2 and H-3 resonances located at very low field and by the long-range couplings between the H-3 and H-5 protons (^4J = 0.8 Hz for *E*-**8b** and 1.0 Hz for *Z*-**8b**). This type of coupling across the carbonyl carbon, observed frequently in substituted cyclohexanones,[25] requires a **W** path between corresponding hydrogens, and thus it is possible only in the **CA** conformation. Surprisingly, the vicinal ^3J coupling shown by H-2 in *Z*-**8b** and *E*-**8b** (2.9 Hz in CD_3OD) is much smaller than that observed in other nitrosamines adopting this conformation.[26] The most plausible explanation of this anomaly is a molecular deformation imposed by the bulky isopropyl substituent. Decreased coupling constants of hydrogens near the *tert*-butyl function have been reported on many occasions.[28]

The ^{13}C NMR spectra (Table 4) afford additional information on the stereochemistry of the title compounds. In particular, they confirm a significance of the **CA** form in the conformational equilibria. It is known that the introduction of the NO group at the amino nitrogen causes a strong upfield shift of the *syn*-C_α and a weaker downfield shift of the *anti*-C_α (cf. **1a** and **1b**).[29] The chemical shifts of the β- and γ-carbons are very little

(25) (a) Cuvelier, C.; Ottinger, R.; Reisse, J. *Tetrahedron Lett.* **1972**, 277. (b) Atta-ur-Rahman. *Nuclear Magnetic Resonance. Basic Principles*; Springer: New York, 1986; p 86.

(26) Attempts to calculate the vicinal ^3J coupling constants using relations of Altona[27a] or Gandour and co-workers[27b,c] and the corresponding dihedral angles obtained from the MM2 method gave a reasonable agreement with the observed ^3J values for axial–axial coupling only, whereas for the axial–equatorial and equatorial–equatorial interactions the calculated values were too low. A comparison of the ^3J values for **16a** and **17a** with those for **16b** and **17b**—compounds with rigid skeletons—show unusually strong influence of the *N*-nitroso group on the vicinal coupling constants of the protons located close to the NNO system plane.

(27) (a) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783. (b) Colucci, W. J.; Jungk, S. J.; Gandour, R. D. *Magn. Reson. Chem.* **1985**, *23*, 335. (c) Colucci, W. J.; Gandour, R. D.; Mooberry, E. A. *J. Am. Chem. Soc.* **1986**, *108*, 7141.

affected. Due to the $A^{(1,3)}$ strain, the N-nitrosation of **2a** changes the position of the methyl groups from diequatorial into diaxial; on the other hand the deshielding α-effect of the axial methyl is considerably weaker than that of the equatorial one, with the result that the signal of *anti*-C_α in **2b** is observed at almost the same field as that of C_α in the parent amine **2a**. Similarly, it is known that a deshielding α-effect of the axial phenyl group is much smaller than that of the equatorial one ($\Delta\delta = 17.4$ and 9.2 ppm, respectively).[30] Thus, the N-nitrosation of **11a** results in the upfield shift of the *syn*-C_α and *anti*-C_α by 10 and 2 ppm, respectively, unequivocally indicating diaxial orientation of the phenyl groups in **11b**. Also the β and γ carbons experience shielding by ca. 7 and 8 ppm, respectively, as a consequence of the β and γ effects imposed by the axial phenyls. The analogous behavior of **3b**, ***E*-6b**, **7b**, ***Z*-8b**, ***Z*-10b**, **12b**, and **13b** points to significant participation of the **CA** form in the conformational equilibria. In contrast, bicyclic compounds **16b** and **17b** with the phenyls forced to the equatorial positions show the *anti*-C_α peaks downfield and the *syn*-C_α resonances at almost the same field as the C_α signals in their precursors **16a** and **17a**, whereas the β-carbons remain almost unaffected. The monocyclic nitrosamine **14b**, preferring the **CA** conformation according to the ^1H data, behaves exactly in the same way. A differentiation between the **CA** and **B1** or **B2** conformers on the basis of ^{13}C NMR is more problematic, although an upfield shift of the *syn*-C_α in **9b** and **15b** (but not in **4b**), the nitrosamines existing in the **B1** form, appears to be somewhat smaller than that in the compounds adopting the **CA** conformation.

In conclusion, our MM2 calculations, X-ray crystallographic analysis, and ^1H and ^{13}C NMR spectra consistently showed that the *N*-nitroso group changes the geometry of the piperidine ring due to the powerful pseudoallylic $A^{(1,3)}$ strain. To avoid this strain, brought about by a nearly coplanar location of the NNO group and the α-substituents, the molecule may (i) force the α-substituents into the axial positions of the chair ring conformer, (ii) convert a chair into a boat-like conformation, or (iii) drive the *N*-nitroso group out of the plane of the N-1 atom and α-equatorial substituents increasing the pyramidal character of the amino nitrogen. Contrary to the earlier literature suggestions that exclude the diaxial conformation, we found several examples of the *N*-nitroso-2,6-diphenylpiperidines and *N*-nitroso-2,6-diphenylpiperidin-4-ones that favor a diaxial orientation of the phenyl groups, which makes them a stereochemically important class of compounds.

Experimental Section

^1H and ^{13}C NMR spectra were measured at 500 and 50 MHz, respectively. The deuteriated solvents were used as an internal lock. The amines **3a**, **5a**–**11a**, and **13a**–**15a** and *N*-nitrosamines **3b**, **5b**–**8b**, **10b**, **11b**, and **13b** were obtained according to the literature methods.[9,11]

3,3,5,5-Tetramethyl-*cis*-2,6-diphenylpiperidin-4-one (9a). A solution of ammonium acetate (7.7 g, 100 mmol), benzaldehyde (21.1 mL, 200 mmol), and diisopropyl ketone (14.3 mL, 100 mmol) was refluxed in ethanol (20 mL) for 24 h. After the mixture was cooled, the precipitated crystals were filtered and recrystallized from toluene–heptane: yield 5.8 g (19%); mp 197–198 °C; ^1H NMR ($CDCl_3$) δ 7.50–7.26 (complex m, 10 H), 3.92 (s, 2 H), 1.96 (br s, 1 H), 1.12 (s, 6 H), 1.06 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 217.9, 139.9, 128.7, 127.7, 127.6, 70.5, 49.9, 22.8, 22.4.

Anal. Calcd for $C_{21}H_{25}NO$ (307): C, 82.04; H, 8.20; N, 4.56. Found: C, 81.74; H, 8.36; N, 4.51.

3,3-Dimethyl-*cis*-2,6-diphenylpiperidin-4-one (10a). A solution of ammonium acetate (3.85 g, 50 mmol), benzaldehyde (10.5 mL, 100 mmol), and isopropyl methyl ketone (5.2 mL, 50 mmol) in methanol (20 mL) was refluxed for 5 h. The precipitated crystals were filtered and recrystallized from toluene: yield 5.6 g (40%); mp 116–117 °C (lit.[11a] mp 114–115 °C); ^1H NMR ($CDCl_3$) δ 7.52–7.26 (complex m, 10 H), 4.06 (dd, J = 3.2 and 12.0 Hz, 1 H), 3.82 (s, 1 H), 2.93 (dd, J = 12.0 and 13.7 Hz, 1 H), 2.48 (dd, J = 3.2 and 13.7 Hz), 1.99 (br s, 1 H), 1.21 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 212.8, 143.1, 139.3, 128.8, 128.7, 127.8, 126.5, 69.5, 61.6, 49.9, 47.3, 20.4, 20.0.

***cis*-2,6-Diphenylpiperidine (11a).** The amine **11a** was obtained by Wolff–Kishner reduction of piperidinone **3a** according to the literature procedure:[9] mp 74 °C (MeOH) (lit.[11b] mp 73–74 °C); ^1H NMR ($CDCl_3$) δ 7.52–7.26 (complex m, 10 H), 3.86 (dd, J = 2.0 and 10.7 Hz, 2 H), 2.02 (m, 1 H), 1.86 (m, 2H), 1.83 (br s, 1 H), 1.76–1.54 (complex m, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.8, 128.3, 126.9, 126.7, 62.6, 34.7, 25.8.

3,3-Dimethyl-*cis*-2,6-diphenylpiperidine (12a). The amine **12a** was obtained by Wolff–Kishner reduction of piperidinone **10a** according to the literature procedure:[9] mp 95–96 °C (ethanol); ^1H NMR ($CDCl_3$) δ 7.58–7.29 (complex m, 10 H), 3.87 (dd, J = 2.9 and 11.2 Hz, 1 H), 3.71 (s, 1 H), 1.95–1.85 (m, 1 H), 1.77–1.62 (complex m, 4 H), 1.06 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.0, 142.2, 128.7, 128.3, 127.4, 127.0, 126.9, 126.7, 71.2, 63.3, 41.1, 33.5, 31.9, 28.8, 19.5.

Anal. Calcd for $C_{19}H_{23}N$ (265): C, 85.99; H, 8.74; N, 5.28. Found: C, 86.11; H, 8.77; N, 5.12.

***t*-3,*t*-5-Dimethyl-*r*-2,*c*-6-diphenylpiperidin-*c*-4-ol (14a)** was obtained by Meerwein–Ponndorf–Verley reduction of piperidinone **4a**[9] according to the literature procedure:[31] mp 110–112 °C (toluene–hexane) (lit.[31] mp 111–112 °C); ^1H NMR ($CDCl_3$) δ 7.45–7.20 (complex m, 10 H), 3.87 (d, J = 10.5 Hz, 2 H), 3.85 (t, J = 1.8 Hz, 1 H), 1.97 (m, 2 H), 1.65 (br s, 2 H), 0.79 (d, J = 7.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 143.6, 128.4, 128.0, 127.3, 75.3, 61.8, 42.9, 14.9.

***t*-3,*t*-5-Dimethyl-*r*-2,*c*-6-diphenylpiperidin-*t*-4-ol (15a)** was obtained by $LiAlH_4$ reduction of piperidinone **4a**[9] in Et_2O according to the literature procedure:[31] mp 130–131 °C (toluene–hexane) (lit.[31] mp 133–134 °C); ^1H NMR ($CDCl_3$) δ 7.45–7.20 (complex m, 10 H), 3.45 (d, J = 9.9 Hz, 2 H), 3.08 (t, J = 9.9 Hz, 1 H), 1.78 (m, 2 H), 1.63 (br s, 2 H), 0.83 (d, J = 6.5 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 143.0, 128.2, 128.0, 127.4, 81.0, 67.3, 45.8, 45.4, 14.4.

***N*-Nitroso-3,3,5,5-tetramethyl-*cis*-2,6-diphenylpiperidin-4-one (9b).** To a solution of piperidinone **9a** (1.52 g, 5 mmol) in chloroform (10 mL) were added concd hydrochloric acid (1.5 mL) and water (1.5 mL), and while stirring, solid $NaNO_2$ (0.84 g, 12 mmol) was added in portions during 0.5 h. The stirring was continued for another 0.5 h. The organic layer was washed with water and saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. After removal of the chloroform, the residue was crystallized from ethanol: yield 1.26 g (75%); mp 167–168 °C; ^1H NMR ($CDCl_3$) δ 7.38 (m, 5 H), 7.12 (m, 3 H), 6.66 (m, 2 H), 6.30 (s, 1 H), 5.52 (s, 1H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.31 (s, 3 H), 0.73 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 216.0, 136.7, 136.3, 129.5, 128.6, 128.5, 128.1, 127.2, 70.8, 66.3, 48.0, 45.9, 30.0, 27.0, 26.6, 22.8.

Anal. Calcd for $C_{21}H_{24}N_2O_2$ (336): C, 74.97; H, 7.19; N, 8.33. Found: C, 74.91; H, 7.24; N, 8.35.

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(31) Balasubramanian, M.; Padma, N. *Tetrahedron* **1963**, *19*, 2135.

***N*-Nitroso-3,3-dimethyl-*cis*-2,6-diphenylpiperidin-4-one (10b)** was obtained from **10a** in a manner similar to that of compound **9b** and had mp 122 °C (MeOH): ^{1}H NMR (C_6D_6) δ 7.12–6.46 (complex m, 10 H), 6.35 (s, 0.27 H), 5.94 (s, 0.73 H), 5.90 (t, J = 6.9 Hz, 0.27 H), 5.43 (dd, J = 7.3 and 9.8 Hz, 0.73 H), 2.98 (dd, J = 6.9 and 17.1 Hz, 0.27 H), 2.71 (dd, J = 9.8 and 18.6 Hz, 0.73 H), 2.69 (dd, J = 6.8 and 17.1 Hz, 0.27 H), 2.50 (dd, J = 7.3 and 18.6 Hz, 0.73 H), 1.39 (s, 0.81 H), 1.14 (s, 2.19 H), 0.81 (s, 2.19 H), 0.79 (s, 0.81 H); ^{13}C NMR ($CDCl_3$) δ 209.8, 209.3, 138.7, 135.8, 135.4, 129.1, 128.9, 128.6, 128.4, 128.2, 127.7, 127.1, 126.3, 125.4, 71.3, 61.4, 61.1, 55.8, 48.1, 47.3, 43.0, 42.0, 27.0, 26.1, 21.2.

Anal. Calcd for $C_{19}H_{20}N_2O_2$ (308): C, 74.00; H, 6.54; N, 9.08. Found: C, 74.01; H, 6.53; N, 9.06.

***N*-Nitroso-*cis*-2,6-diphenylpiperidine (11b)** was obtained from **11a** in a manner similar to that of compound **9b** and had mp 66–67 °C (hexane) (lit.[32] mp 66.5–67.5 °C): ^{1}H NMR (C_6D_6) δ 7.04–6.81 (complex m, 10 H), 6.10 (dd, J = 4.0 and 5.9 Hz, 1 H), 5.81 (dd, J = 4.3 and 5.9 Hz, 1 H), 1.97 (m, 1 H), 1.75 (m, 1 H), 1.63 (m, 1 H), 1.54 (m, 1 H), 1.27 (m, 1 H), 1.12 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 139.1, 138.5, 128.1, 127.9, 127.3, 126.8, 60.5, 52.0, 27.0, 26.9, 17.4; UV (cyclohexane) λ_{max} 368 (ϵ 70).

***N*-Nitroso-3,3-dimethyl-*cis*-2,6-diphenylpiperidine (12b)** was obtained from **12a** in a manner similar to that of compound **9b** and had mp 55–57 °C (toluene–hexane): ^{1}H NMR ($CDCl_3$) δ 7.20–6.76 (complex m, 10 H), 6.24 (br m, 0.45 H), 6.17 (br d, J = 5.3 Hz, 0.55 H), 5.87 (s, 0.55 H), 5.57 (s, 0.45 H), 2.80 (m, 0.55 H), 2.56–2.31 (complex m, 2 H), 2.12 (m, 0.55 H), 1.64 (m, 1 H), 1.24 (s, 1.35 H), 1.11 (s, 1.65 H), 1.02 (s, 1.35 H), 0.84 (s, 1.65 H); ^{13}C NMR ($CDCl_3$) δ 138.6, 137.9, 137.5, 136.1, 130.0, 129.5, 128.2, 127.6, 127.3, 126.7, 126.3, 73.3, 60.8, 59.0, 49.9, 34.1, 33.5, 31.5, 31.3, 29.6, 29.2, 29.0, 28.0, 27.7, 22.6, 22.1; UV (cyclohexane) λ_{max} 368 nm (ϵ 67).

Anal. Calcd for $C_{19}H_{22}N_2O$ (294): C, 77.52; H, 7.53; N, 9.52. Found: C, 77.31; H, 7.55; N, 9.41.

***N*-Nitroso-*t*-3,*t*-5-dimethyl-*r*-2,*c*-6-diphenylpiperidin-*c*-4-ol (14b)** was obtained from **14a** in a manner similar to that of compound **9b** and had mp 208–210 °C (toluene): ^{1}H NMR ($CDCl_3$) δ 7.50–7.20 (complex m, 10 H), 5.53 (d, J = 9.3 Hz, 1 H), 4.89 (d, J = 10.7 Hz, 1 H), 3.90 (t, J = 2.2 Hz, 1 H), 2.64 (m, 1 H), 2.21 (m, 1 H), 1.72 (br s, 1 H), 1.22 (d, J = 6.3 Hz, 3 H), 1.07 (d, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 140.8, 140.1, 128.6, 128.2, 128.1, 127.9, 127.5, 126.8, 72.0, 66.1, 60.9, 41.2, 40.0, 16.4, 15.7; UV (cyclohexane–dioxane, 9:1) λ_{max} 381 nm (ϵ 55).

Anal. Calcd for $C_{19}H_{22}N_2O_2$ (310): C, 73.52; H, 7.14; N, 9.02. Found: C, 73.60; H, 7.24; N, 9.02.

***N*-Nitroso-*t*-3,*t*-5-dimethyl-*r*-2,*c*-6-diphenylpiperidin-*t*-4-ol (15b)** was obtained from **15a** in a manner similar to that of compound **9b** and had mp 158–159 °C (MeOH): ^{1}H NMR ($CDCl_3$) δ 7.51 (m, 2 H), 7.40 (m, 3 H), 7.12 (m, 3 H), 6.77 (m, 2 H), 5.78 (d, J = 2.9 Hz, 1 H), 4.96 (d, 1 H), 3.18 (t, J = 8.3 Hz, 1 H), 2.91 (m, 1 H), 2.41 (m, 1 H), 2.20 (br s, 1 H), 1.30 (d, J = 6.8 H z, 3 H), 0.91 (d, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 139.3, 137.4, 128.6, 128.4, 128.2, 128.0, 127.3, 76.4, 67.7, 63.0, 39.4, 19.6, 15.8; UV (cyclohexane–dioxane, 9:1) λ_{max} 369 nm (ϵ 52).

Anal. Calcd for $C_{19}H_{22}N_2O_2$ (310): C, 73.52; H, 7.14; N, 9.02. Found: C, 73.43; H, 7.33; N, 9.24.

Computational Methods. The molecular mechanics calculations were performed using the MM2 program of Allinger and Yuh[33] with some additional parameters necessary to deal with the NNO group. Several other parameters involving the phenyl sp^2-hybridized carbon atoms were taken from the MMX program.[34] The new van der Waals parameters for the *N*-nitroso oxygen and the NO nitrogen electron lone pair were introduced to enhance a steric interaction of the NNO group with the neighboring substituents. The following values were used: VDW radii r = 2.3 and 1.6 Å and ϵ = 0.05 and 0.016 kcal/mol for the oxygen atom and the nitrogen lone pair, respectively. Bond dipole moments of the NNO function do not significantly influence the resulting geometries and were omitted from the calculations. The set of parameters involving the NNO group are given in the supporting information.

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Supporting Information Available: Table comparing ^{1}H NMR spectra in $CDCl_3$ and C_6D_6 and table with force field parameters used in the MM2 calculations and 500 MHz ^{1}H NMR spectra of **11b** in $CDCl_3$ and C_6D_6 (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS. Ordering information is given on any current masthead page.

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