An Electron Spin Resonance Spectroscopic Study of Aminocarbonyl Nitroxides. Long-Range Hyperfine Splitting of Amino Substituents and Conformational Preferences around the C_α–N(O) Bond in Aminocarbonyl Tosylmethyl Nitroxides

Rense M. Tel and Jan B. F. N. Engberts*

Department of Organic Chemistry, The University, Zernikelaan, Groningen, The Netherlands

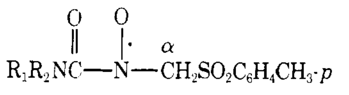
Received April 11, 1977

A series of aminocarbonyl tosylmethyl nitroxides **2a–f** was generated from the corresponding *N*-hydroxyurea derivatives. Their ESR spectral features are discussed and compared with those of some simple aminocarbonyl nitroxides (**4a–e**). Usually coupling with only one nitrogen atom is observed despite noticeable hyperfine interaction with the amino substituents (H, alkyl) across the carbonyl group. The ESR spectra of **2a–f** show pronounced line-width alternation effects which are rationalized in terms of slow rotation around the C_α–N(O) bond. For **2c**, the two energetically equivalent conformations could be frozen out at −45 °C ($\Delta G^{\ddagger}$ = 6.2 kcal mol^{-1}). In these conformations, the S–C_α bond is nearly eclipsed with the half-filled $2p_z$ orbital on the nitroxide nitrogen atom.

Recent NMR studies have shown that in the preferred solution conformation of *N,N′*-[bis(α-tosylbenzyl)]urea (**1**) the tosyl methyl protons are positioned above (or below) the most remote benzyl aromatic ring.[1] A subsequent x-ray investigation of **1** revealed that a similar folded conformation is present in the crystal.[2] Unfortunately, the instability and low solubility of **1** precluded NMR investigation of the conformational flexibility over a range of temperatures. We therefore resorted to a faster spectroscopic technique, i.e., electron spin resonance spectroscopy (ESR), to assess the conformational mobility around the C_α–N bond in some structurally related ureas. Here we report the preparation (in situ) of a series of aminocarbonyl tosylmethyl nitroxides **2** and

$[p\text{-}CH_3C_6H_4SO_2CH(C_6H_5)NH]_2C{=}O$

1



$R_1R_2NC(=O)\text{—}N(O^\cdot)\text{—}\overset{\alpha}{C}H_2SO_2C_6H_4CH_3\text{-}p$

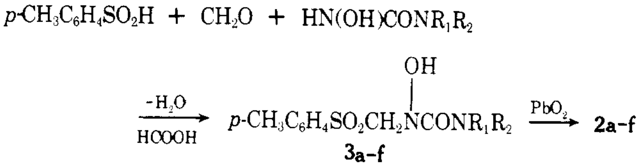
2

an analysis of their ESR spectral features as a function of temperature. We find that the ESR spectra exhibit pronounced line width alternation (LWA) effects even at ambient temperatures which we have rationalized in terms of slow rotation around the C_α–N(O) bond on the ESR time scale. In one case, definite conclusions could be drawn about the favored conformation as well as about the barrier to rotation.

Results and Discussion

ESR Spectra of Aminocarbonyl Nitroxides. The aminocarbonyl tosylmethyl nitroxides[3] **2a–f** were prepared via the route shown in Scheme I. The one-step synthesis of the *N*-hydroxy-*N′*-(tosylmethyl)ureas **3a–f** from the corresponding *N*-hydroxyureas constitutes a further extension of the versatile Mannich-type condensation reaction of sulfinic acids with aldehydes and amino compounds to afford N-substituted α-aminosulfones.[4,5] Unfortunately, no N,N′-disubstituted *N*-hydroxyureas could be prepared by this method.[6]

Scheme I



$$p\text{-}CH_3C_6H_4SO_2H + CH_2O + HN(OH)CONR_1R_2 \xrightarrow[HCOOH]{-H_2O} p\text{-}CH_3C_6H_4SO_2CH_2\overset{OH}{\overset{|}{N}}CONR_1R_2 \xrightarrow{PbO_2} \mathbf{2a\text{–}f}$$

3a–f

R_1, R_2: see Table I

ESR parameters for the nitroxides **2a–f** are collected in Table I. The magnitudes of the nitrogen hyperfine splitting constants (hfsc's) and of the g values are consistent with those reported previously for some aminocarbonyl nitroxides.[7-10] Further support for the structural assignment is found in the internal consistency of the A_N and A_H values within the series and in comparison of the hfsc's of **2a–f** with those of the simple aminocarbonyl nitroxides **4a–e** (Table I) which were obtained from the reaction of authentic *N*-hydroxyurea derivatives with PbO_2. Since the structural features of aminocarbonyl nitroxides have received little attention thus far, the hfsc's of **2a–f** and of **4a–e** will be discussed in some detail. First, we note that the A_N values are somewhat higher than those of acyl alkyl nitroxides, reflecting cross-conjugation of the lone pairs of both nitrogen atoms with the carbonyl moiety. Second, and more interestingly, the ESR spectra clearly reveal hyperfine interaction with the amino substituents (R_1, R_2) across the carbonyl function.[11] Furthermore, in all cases only the ESR spectrum of one of the several possible rotamers, originating from hindered rotation around the N–C(O) bond is observed. We have assigned the A_{R1}^{H} and A_{R2}^{H} splittings (Table I) on the basis of the following assumptions. (1) The favored conformation of *N*-hydroxyurea in which the oxygen atoms adopt a trans position (in view of steric reasons and confirmed by the crystal structure of *N*-hydroxyurea[12,13]) is retained in the aminocarbonyl nitroxides. (2) If one of the amino substituents is hydrogen, we propose that the second more bulky substituent will preferentially reside in trans position to the nitroxide oxygen. (3) In view of the small A_H values observed for **2b**, **2d**, **2f**, **4b**, **4d**, and **4e**, we suggest that the amino substituents of **2a**, **2e**, and **4a** which exhibit the highest splittings will occupy a trans position with respect to the nitroxide oxygen atom.

The ESR spectra of **2b**, **2c**, **4b**, and **4c** do not show hfs by the phenyl protons. Since the line width is smaller than 0.2 G, hyperfine interaction with the second nitrogen atom can also be excluded. The same situation holds for **2a**, **2d**, **2f**, **4a**, **4d**, and **4e** and can be quite adequately explained in terms of the small magnetic moment of nitrogen relative to that of hydrogen. Only for **2e** a small hfsc of the second nitrogen atom ($A_{N}2$ = 0.30 G) could be resolved (Figure 1). This may well be a consequence of the electron-releasing ability of the dimethylamino substituent which will tend to increase the spin density at the amino nitrogen atom.[14] The significance of this factor is illustrated by the relatively large magnitude of the N^1 hfsc of **2e** as compared with that of **2c**.

Line Width Alternation (LWA). At room temperature,

Table I. Hyperfine Splitting Constants [a] and *g* Values for the Aminocarbonyl Nitroxides $R_1R_2NCON(O)R_3$ (2 and 4)

Nitroxide	Registry no.	R_1	R_2	R_3	A_N	$A^H_{CH_2}$	A^H_{NH}	$A^H_{R_1}$	$A^H_{R_2}$	g^b
2a	63216-22-8	H	H	p-$CH_3C_6H_4$-SO_2CH_2	8.8 (8.6)	5.4 (5.4)		0.75 (0.70)	0.32 (0.17)	2.0066
2b	63216-23-9	H	C_6H_5	p-$CH_3C_6H_4$-SO_2CH_2	8.9 (9.0)	5.4 (5.4)		0.4 (0.4)		
2c	63216-24-0	C_6H_5	C_6H_5	p-$CH_3C_6H_4$-SO_2CH_2	8.1 (8.1)	5.0 (5.0)				
2d	63216-25-1	H	CH_3	p-$CH_3C_6H_4$-SO_2CH_2	9.0 (9.0)	5.5 (5.5)		0.80 (0.80)[c]	0.40 (0.40)	2.0064
2e	63216-26-2	CH_3	CH_3	p-$CH_3C_6H_4$-SO_2CH_2	9.2 (9.1)[d]	5.4 (5.3)		0.9 (0.96)	0.3 (0.32)	
2f	63216-27-3	H	$C_6H_5CH_2$	p-$CH_3C_6H_4$-SO_2CH_2	8.9 (9.0)	5.5 (5.5)		0.4 (0.37)[e]	0.5 (0.57)	
4a	19224-51-2	H	H	H	8.0		11.7	0.73	0.32	2.0066
4b	63216-28-4	H	C_6H_5	H	8.0 (8.0)		11.5 (11.6)	0.45		
4c	63216-29-5	C_6H_5	C_6H_5	H	7.1		10.8			
4d	63216-30-8	H	CH_3	H	8.2		11.7	0.8[c]	*f*	2.0068
4e	63216-31-9	H	$C_6H_5CH_2$	H	8.2		11.7	0.5	0.5	

[a] Hfsc's (in G) in 1,4-dioxane as the solvent; the hfsc's between parentheses are for CH_2Cl_2 as the solvent. [b] Estimated accuracy: ±0.0002. [c] A_{CH_3}. [d] The hfsc for the second nitrogen is 0.30 G. [e] A_{CH_2}. [f] Not resolved.

the ESR spectra of **2a–f** show alternating line width effects. For example, the ESR spectrum of **2c** at 35 °C exhibits broadening of the $m_I = \pm 0.5$ lines, while the outside lines of the triplets are sharp (Figure 2). Upon lowering of the temperature, the central lines further broaden, and at −10 °C these lines are so broad that they cannot be detected. At still lower temperatures, new lines appear, and at −45 °C the spectrum is consistent with two nonequivalent hydrogen hyperfine splittings of 3.0 and 6.9 G, respectively. Such LWA is indicative for a slow interconversion process between two conformations in which the methylene protons are nonequivalent. Since the two forms are equally populated, the equation $A_{H_\beta} = 0.5(A_{H_{\beta 1}} + A_{H_{\beta 2}})$ should hold, a condition which is very well fulfilled (Table I).

We propose that the exchange process finds its origin in slow rotation around the C_α–N(O) bond in **2a–f.** Similar LWA effects have been observed for some structurally related radicals, including arylsulfonylmethyl benzoyl nitroxides[6] and phenyloxycarbonyl tosylmethyl nitroxide.[15] Assuming planar geometry around the nitroxide nitrogen and employing the Heller–McConnell relation (eq 1 in which ρ_N is the spin density in the $2p_z$ orbital on nitrogen, θ the dihedral angle between the axis of the nitrogen $2p_z$ orbital and the C–H_β bond, and B_0 and B_1 parameters related to spin polarization and hyperconjugation, respectively) with $B_0 = 0$ and $\rho_N B_1 = 16$ G,[16] we can calculate the dihedral angles θ for the preferred conformations around the C_α–N(O) bond.

$$A_{H_\beta} = \rho_N(B_0 + B_1 \langle \cos^2 \theta \rangle) \qquad (1)$$

The results are depicted in Figure 3. Apparently, the nitroxide radical favors conformations in which the S–C_α bond is nearly eclipsed with the half-filled $2p_z$ orbital on the nitroxide nitrogen atom. A similar eclipsing phenomenon has been proposed for a series of arylsulfonylmethyl alkoxy nitroxides[17] mainly on basis of substituent effects on A_N. At present we cannot decide between the several factors which may contribute to the conformational preferences for **2a–f,** but only note that the phenomenon is quite frequently observed for radicals of the type X-C-Y· (X = heteroatom, Y = radical site).[18] Interestingly, a comparable conformational preference has been found for 1 in the solid state.[2] For this molecule empirical potential-energy calculations strongly suggest that both nonbonded repulsive and attractive interactions significantly contribute to the conformational preferences,[2] but more detailed interpretations must await further investigation.

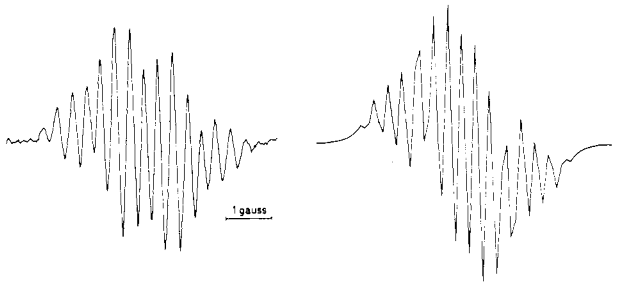


Figure 1. Low-field nitrogen line of **2e:** observed (left), computer simulated (right).

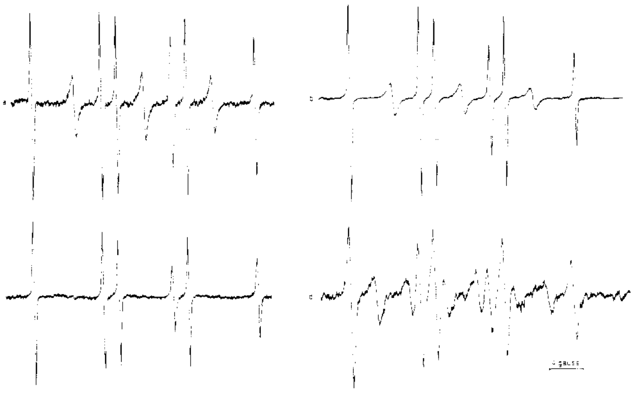


Figure 2. ESR spectra of **2c:** (a) at +35 °C, (b) at +20 °C, (c) at −10 °C, (d) at −45 °C.

From the line widths of the lines in the ESR spectrum of **2c** at −45 °C, the lifetime τ of the preferred conformations could be evaluated by using eq 2.[19] Herein Γ = line width at −45 °C, Γ_0 = line width in the absence of exchange, γ_e = magnetogyric ratio of the electron, and τ = lifetime of the conformation.

$$\Gamma = \Gamma_0 + 1/2\tau\gamma_e \qquad (2)$$

We find $\tau = 9.47 \times 10^{-8}$ s and, since $k = (2\tau)^{-1}$ (k = rate constant for exchange), the barrier to rotation[20] is $\Delta G^{\ddagger} = 6.2$ kcal mol^{-1}.

Experimental Section

Elemental analyses were carried out in the Analytical Department of this laboratory under the supervision of Mr. A. F. Hamminga. Melting points were determined using a Mettler FP2 melting-point

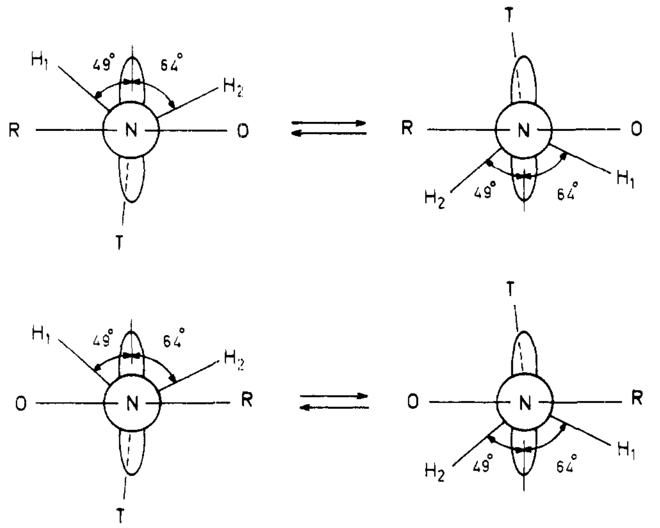


Figure 3. Newman projections of the two sets of equilibrium conformations of **2c** at −45 °C. T = tosyl.

apparatus with a Mettler FP21 microscope attachment. NMR spectra were recorded on a Varian Model A-60 spectrometer using Me_2SO-d_6 as the solvent and Me_4Si ($\delta = 0$) as an internal standard. IR spectra were measured on a Perkin-Elmer grating spectrophotometer, Model 125. The ESR spectra were recorded on a Varian E-4 apparatus fitted with a Varian A-1268 variable temperature controller. All solutions used for ESR experiments were purged with nitrogen for 30 min in order to remove dissolved oxygen. The g values (±0.0002) were measured using α,α'-diphenyl-β-picrylhydrazyl as a reference compound ($g = 2.0037$). The ESR spectrum of nitroxide **2e** was satisfactorily simulated by using the hfsc's listed in Table I.

Hydroxylamine,[21] *N*-hydroxyurea,[22] *N*-hydroxy-*N'*-phenylurea,[23] benzyl carbamate,[24] benzyl isocyanate,[25] *N*-benzyl-*N'*-hydroxyurea,[26] and *N,N*,-dimethyl-*N'*-hydroxyurea[27] were prepared by known procedures. *N*-Hydroxy-*N'*-methylurea was obtained by a procedure analogous to that for *N*-benzyl-*N'*-hydroxyurea.[26] *N,N*-Diphenyl-*N'*-hydroxyurea was synthesized by a method analogous to that described for *N,N*-diethyl-*N'*-hydroxyurea.[27] Commercially available sodium *p*-toluenesulfinate and formaldehyde (36% aqueous solution) were employed. The new compounds **3** were purified by crystallization from 70% ethanol at temperatures below 50 °C.

N-Hydroxy-N-(tosylmethyl)urea (3a). Formaldehyde (0.022 mol) and 2 mL of formic acid were added to a solution of sodium *p*-toluenesulfinate (3.56 g, 0.02 mol) and *N*-hydroxyurea (1.52 g, 0.02 mol) in 3 mL of water (pH ~3). After 5 min the first crystals separated and after 1 h the yield of **3a** was 94%: mp 134–135 °C; NMR δ 2.39 (s, 3 H), 4.90 (s, 2 H), 6.51 (s, 2 H), 7.61 (m, 4 H), 9.81 (s, 1 H) ppm; IR (KBr) 3495, 3380, 3180, 1675, 1560, 1315, 1145 cm^{-1}. Anal. Calcd for $C_9H_{12}N_2O_4S$: C, 44.26; H, 4.95; N, 11.46; S, 13.12. Found: C, 44.20; H, 4.84; N, 11.49; S, 13.01.

N-Hydroxy-N-(tosylmethyl)-N'-phenylurea (3b). Formaldehyde (0.022 mol) and formic acid (2 mL) were added to a suspension of sodium *p*-toluenesulfinate (3.56 g, 0.02 mol) and *N*-hydroxy-*N'*-phenylurea (3.04 g, 0.02 mol) in 35 mL of water and 15 mL of ethanol (pH ~3). The suspension was stirred for 10 min. After 1 h the yield of crystalline **3b** was 75%. A sample had mp 134–135 °C (dec); NMR δ 2.37 (s, 3 H), 5.03 (s, 2 H), 7.3 (m, 6 H), 7.62 (m, 4 H), 9.06 (s, 1 H) ppm; IR (KBr) 3365, 3200, 1670, 1550, 1320, 1145 cm^{-1}. Anal. Calcd for $C_{15}H_{16}N_2O_4S$: C, 56.23; H, 5.03; N, 8.75; S, 10.01. Found: C, 56.16; H, 5.04; N, 9.28; S, 9.42.

N,N-Diphenyl-N'-hydroxy-N'-(tosylmethyl)urea (3c). Prepared by a procedure analogous to that for **3b**. After stirring for 30 min, the yield was 57%: mp 143–144.5 °C (dec); NMR δ 2.39 (s, 3 H), 5.00 (s, 2 H), 7.2 (m, 10 H), 7.62 (m, 4 H), 9.45 (s, 1 H) ppm; IR (KBr) 3200, 1635, 1585, 1320, 1145 cm^{-1}. Anal. Calcd for $C_{21}H_{20}N_2O_4S$: C, 63.61; H, 5.09; N, 7.07; S, 8.09. Found: C, 63.48; H, 5.10; N, 7.02; S, 8.04.

N-Hydroxy-N-(tosylmethyl)-N'-methylurea (3d) was obtained using a procedure analogous to that for **3a**, but using 50 mL of 1:1 (v/v) EtOH–H_2O as the solvent. The yield was 85% and a sample had mp 129–130 °C (dec); NMR δ 2.39 (s, 3 H), 2.57 (d, J = 5 Hz, 3 H), 4.91 (s, 2 H), 7.00 (q, 1 H), 7.60 (m, 4 H), 9.77 (s, 1 H) ppm; IR (KBr) 3465, 3165, 1660, 1525, 1320, 1145 cm^{-1}. Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 5.46; N, 10.85; S, 12.41. Found: C, 46.32; H, 5.32; N, 11.15; S, 12.05.

N,N-Dimethyl-N'-hydroxy-N'-(tosylmethyl)urea (3e). A solution of sodium *p*-toluenesulfinate (3.56 g, 0.02 mol) in 25 mL of water was mixed with a solution of *N,N*-dimethyl-*N'*-hydroxyurea (2.1 g, 0.02 mol) in 20 mL of dioxane. Then formaldehyde (0.022 mol) and formic acid (3 mL) were added. After 2 h the first crystals of **3e** separated and after one night the yield was 53%. A sample of **3e** showed mp 132–133 °C (dec); NMR δ 2.40 (s, 3 H), 2.80 (s, 6 H), 4.86 (s, 2 H), 7.60 (m, 4 H), 9.75 (s, 1 H) ppm; IR (KBr) 3360, 1650, 1500, 1320, 1140 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29; S, 11.78. Found: C, 48.50; H, 5.96; N, 10.29; S, 11.78.

N-Benzyl-N'-hydroxy-N'-(tosylmethyl)urea (3f) was prepared using a procedure analogous to that for **3a** using 70 mL of 1:1 (v/v) EtOH–H_2O as the solvent. The yield was 91%: mp 127–128 °C (dec); NMR δ 2.39 (s, 3 H), 4.20 (d, J = 6 Hz, 2 H), 4.93 (s, 2 H), 7.24 (s, 5 H), 7.59 (m, 4 H), 9.86 (s, 1 H) ppm; IR (KBr) 3400, 3195, 1645, 1525, 1320, 1145 cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38; S, 9.59. Found: C, 57.57; H, 5.46; N, 8.97; S, 9.02.

Registry No.—**3a,** 63216-32-0; **3b,** 63216-33-1; **3c,** 63216-34-2; **3d,** 63216-35-3; **3e,** 63216-36-4; **3f,** 63216-37-5; formaldehyde, 50-00-0; sodium *p*-toluenesulfinate, 824-79-3; *N*-hydroxyurea, 127-07-1; *N*-hydroxy-*N'*-phenylurea, 7335-35-5; *N,N*-diphenyl-*N'*-hydroxyurea, 53731-89-8; *N*-hydroxy-*N'*-methylurea, 7433-46-7; *N,N*-dimethyl-*N'*-hydroxyurea, 52253-32-4; *N*-benzyl-*N'*-hydroxyurea, 24966-37-8.

References and Notes

(1) R. M. Tel and J. B. F. N. Engberts, *Recl. Trav. Chim. Pays-Bas,* **93,** 37 (1974).
(2) R. M. Tel and J. B. F. N. Engberts, *J. Chem. Soc., Perkin Trans. 2,* 483 (1976).
(3) The nitroxides **2a–f** are relatively unstable due to the presence of two β-hydrogen atoms which can participate in a bimolecular decay process to give the corresponding *N*-hydroxyurea and nitrone. See: K. Adamic, D. F. Bower, and K. U. Ingold, *J. Am. Chem. Soc.,* **92,** 1093 (1970).
(4) J. B. F. N. Engberts and J. Strating, *Recl. Trav. Chim. Pays-Bas,* **83,** 733 (1964).
(5) H. Meijer, R. M. Tel, J. Strating, and J. B. F. N. Engberts, *Recl. Trav. Chim. Pays-Bas,* **92,** 72 (1973) and references cited therein.
(6) The condensation products derived from ureas are often rather unstable. See: G. Rawson and J. B. F. N. Engberts, *Tetrahedron,* **26,** 5653 (1970).
(7) J. V. Ramsbottom and W. A. Waters, *J. Chem. Soc. B,* 132 (1966).
(8) H. G. Aurich, H. G. Scharpenberg, and K. Kabs, *Tetrahedron Lett.,* 3559 (1970).
(9) V. S. Griffiths and G. R. Parlett, *J. Chem. Soc. B,* 997 (1969).
(10) An A_N value as high as 11.75 G has been reported for *tert*-butyl *N,N*-dimethylaminocarbonyl nitroxide: (a) R. J. Holman and M. J. Perkins, *J. Chem. Soc., Chem. Commun.,* 244 (1971); (b) C. M. Camaggi, R. J. Holman, and M. J. Perkins, *J. Chem. Soc., Perkin Trans. 2,* 501 (1972). This high A_N as well as the observation of hfs due to only one methyl group are not easily reconciled with our ESR spectral data.
(11) Such hfs across the carbonyl group has only rarely been observed. See ref 10 and B. L. Booth, D. J. Edge, R. N. Haszeldine, and R. G. G. Holmes, *J. Chem. Soc., Perkin Trans. 2,* 7 (1977).
(12) I. K. Larsen and B. Jerslew, *Acta Chem. Scand.,* **20,** 983 (1966).
(13) N. Amargan, J. P. S. Richards, and A. A. Uraz, *Acta Crystallogr., Sect. B,* **32,** 1042 (1976).
(14) R. A. Kaba and K. U. Ingold, *J. Am. Chem. Soc.,* **98,** 7375 (1976).
(15) R. van Est-Stammer and J. B. F. N. Engberts, *Recl. Trav. Chim. Pays-Bas,* **91,** 1298 (1972).
(16) Methyl phenylaminocarbonyl nitroxide (ref 8; $A_N = A_H = 10.0$ G, $\langle\theta\rangle = 120°$) was taken as a reference compound. Accordingly, $\rho_N B_1 = 20$ G, and for **2c** this value is lowered to 16 G in view of the lower A_N. We note that the conformational preferences are not critically sensitive to the exact choice of $\rho_N B_1$.
(17) J. J. Zeilstra and J. B. F. N. Engberts, *J. Am. Chem. Soc.,* **97,** 7091 (1975).
(18) See, for example, K. S. Chen and J. K. Kochi, *J. Am. Chem. Soc.,* **96,** 1383 (1974).
(19) J. E. Wertz and J. R. Bolton, "Electron Spin Resonance, Elementary Theory and Practical Applications", McGraw-Hill, New York, N.Y., 1972, Chapter 9.
(20) This barrier to rotation is definitely higher than that found for the bis(methylthiomethyl)nitroxide radical: G. Brunton and K. U. Ingold, *J. Chem. Soc., Perkin Trans. 2,* 1659 (1976).
(21) G. Brauer, "Handbuch der Präparativen Anorganischen Chemie", F. Enke Verlag, Stuttgart, 1960, p 450.
(22) R. Deghenghi, *Org. Synth.,* **40,** 60 (1960).
(23) E. E. Gilbert and E. J. Rumanowski, French Patent 1,320,068 (Mar. 8, 1963); *Chem. Abstr.,* **59,** 9886h (1963).
(24) Prepared according to the procedure given for isobutyl carbamate: J. W. Cook, R. A. Raphael, and A. I. Scott, *J. Chem. Soc.* 695 (1951).
(25) H. Ulrich, U.S. Patent 3,404,170 (Oct. 1, 1968); *Chem. Abstr.,* **70,** 11114m (1969).
(26) G. Zinner and R. Stoffel, *Arch. Pharm.* (*Weinheim, Ger.*), **302,** 838 (1969).
(27) G. Zinner and G. Isensee, *Arch. Pharm.* (*Weinheim, Ger.*), **307,** 7 (1974). The compound was prepared in situ in dioxane as the solvent.