mechanisms operative in these moderately complex bichromophoric molecules.

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Registry No. **1a**, 6510-63-0; **1a**·$C(NO_2)_4$, 124854-89-3; **1b**, 136954-47-7; **2a**, 25557-82-8; **2a**·$C(NO_2)_4$, 124822-76-0; **2b**, 136954-48-8; **3a**, 25837-66-5; **3a**·$C(NO_2)_4$, 124822-77-1; **3b**, 136954-49-9; **4a**, 22335-46-2; **4a**·$C(NO_2)_4$, 124822-78-2; **4b**, 136954-50-2; **5a**, 60834-40-4; **5a**·$C(NO_2)_4$, 124822-79-3; **5b**, 136954-51-3; **6a**, 86-28-2; **6a**·$C(NO_2)_4$, 124822-80-6; **6b**, 86-20-4; **7a**, 86-74-8; **7a**·$C(NO_2)_4$, 136954-52-4; **7b**, 3077-85-8; 4-$MeC_6H_4SO_2O(CH_2)_2OSO_2C_6H_4Me$-4, 6315-52-2; carbazole, 86-74-8.

Supplementary Material Available: NMR data and spectra for compounds **1a–6a** and spectra for **1b–6b** (24 pages). Ordering information is given on any current masthead page.

Origin of "Hetero Effect" on Nitrogen Inversion. Comparison of Hydroxylamines and Aminoxide Anions

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Rate constants for nitrogen inversion in *N*-benzyl-*N*-methylhydroxylamine, *N*,*N*-diethylhydroxylamine, 1-hydroxy-2,2,4,4-tetramethylpyrrolidine, their conjugate bases, and their *O*-acetyl derivatives in dimethylformamide-d_7 were determined based on the ^1H NMR coalescence temperatures. Relative to –OH, the $-O^-$ substituent ought to either raise the barrier to inversion owing to stronger lone-pair repulsions or lower the barrier owing to weaker σ-inductive effects. Yet nearly identical barriers to inversion, $\Delta G^\ddagger$ = 12.0–13.3 kcal/mol, are observed for both the hydroxylamine and its conjugate base. Since the observed barrier is little changed upon deprotonation, it is concluded that the π-repulsive and σ-inductive contributions must be nearly equal.

Introduction

Substituent Effects in Nitrogen Inversion. A nitrogen atom with three substituents and a nonbonding lone pair of electrons has a pyramidal geometry capable of inverting its configuration. The ground state has a nominally sp^3-hybridized nitrogen atom with the lone pair occupying an orbital that is approximately sp^3. The transition state has an sp^2-hybridized nitrogen with the lone pair in a pure p orbital.

The rate at which the nitrogen inverts is subject to steric, conjugative, inductive, and angle-constraint effects of substituents.[1-4] Electronegative heteroatoms such as oxygen, nitrogen, or halogen increase the barriers to nitrogen inversion. Thus, the barriers increase across the first row from R_2N–CH_3 (7.4 kcal/mol) to R_2N–NH_2 (8.5 kcal/mol) to R_2N–OH (13.1 kcal/mol) to R_2N–F (20 kcal/mol). Extreme cases are *N*-chlorooxaziridine and dioxaziridine (which also include a contribution from a three-membered ring) as well as NF_3, for which calculated barriers are 44.2,[5] 55.6,[6] and 78.2 kcal/mol,[7] respectively.

These substituents have both a σ-inductive electron-withdrawing character and a π-repulsive character due to the lone pairs. According to simple rules for hybridization,[8] atomic p character concentrates in orbitals directed toward electronegative substituents. This results in more s character in the nitrogen lone pair, which in the transition state must occupy a pure p orbital. The σ-inductive effect of electronegative substituents therefore increases the barrier to inversion. (An equivalent approach to this effect is in terms of HOMO–LUMO mixing.[9]) There is also a π-repulsive effect, associated with overlap of the lone pair with π orbitals on adjacent atoms. Lone-pair repulsions create a destabilization which is greatest in the transition state, since overlap with a pure p orbital is maximum. This too increases the barrier to inversion.

Both of these effects must be operative. In the absence of lone pairs, barriers to phosphorus inversion in RP(Ph)M$(CH_3)_3$ increase with the electronegativity of M.[10] The conjugative effect of electron-withdrawing acyl groups to reduce the barrier to nitrogen inversion in aziridines is well-known.[11]

The relative contribution of these two effects of adjacent heteroatoms is a long-standing question, which most researchers have explicitly despaired of answering.[1-4,9,12] Does the increased barrier arise primarily because of the inductive effect of electronegative substituents or because of the repulsion of their lone pairs? The latter seems more likely, since repulsions in the π system are generally stronger than σ-inductive effects. It has not been possible to distinguish these, because they usually operate in the same direction. Molecular-orbital calculations[13] can re-

(1) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 219.
(2) Rauk, A.; Allen, L. C.; Mislow, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 400.
(3) Lambert, J. B. *Top. Stereochem.* **1971**, *6*, 19.
(4) Lehn, J. M. *Fortschr. Chem. Forsch.* **1971**, *15*, 311.
(5) Shustov, G. V.; Varlamov, S. V.; Shibaev, A. Yu.; Puzanov, Yu. V.; Kostyanovskii, R. G. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1989**, 1663.
(6) Alcami, M.; de Paz, J. L. G.; Yáñez, M. *J. Comput. Chem.* **1989**, *10*, 468.
(7) Mack, H.-G.; Christen, D.; Oberhammer, H. *J. Mol. Struct.* **1988**, *190*, 215.
(8) Walsh, A. D. *Discuss. Faraday Soc.* **1947**, *2*, 18. Bent, H. A. *Chem. Rev.* **1961**, *61*, 275.
(9) Levin, C. C. *J. Am. Chem. Soc.* **1975**, *97*, 5649. Cherry, W.; Epiotis, N. *Ibid.* **1976**, *98*, 1135.
(10) Baechler, R. D.; Mislow, K. *J. Am. Chem. Soc.* **1971**, *93*, 773.
(11) Anet, F. A. L.; Osyany, J. M. *J. Am. Chem. Soc.* **1967**, *89*, 352.
(12) Bach, R. D.; Evans, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 1374.

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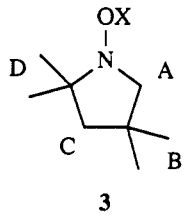
produce the trends, but they do not distinguish the origin. In this paper, we attempt to separate these two effects through comparison of substituents where they operate in opposite directions.

Method and Objective. σ-Inductive and π-repulsive effects on nitrogen inversion might have been distinguished by comparison of the trimethylammonio substituent, $-N^+(CH_3)_3$, with the dimethylamino substituent, $-N(CH_3)_2$. The $-N^+(CH_3)_3$ group has no lone pairs to destabilize the transition state yet is substantially more electron-withdrawing than $-N(CH_3)_2$. Unfortunately, this comparison could not be made experimentally, since nitrogen inversion in $PhCH_2NX(CH_3)$, with X = either $-N(CH_3)_2$ or $-N^+(CH_3)_3$, is too fast.[14] Besides, analysis would suffer from complications due to steric bulk of the $-N^+(CH_3)_3$.

It is possible to distinguish σ-inductive and π-repulsive effects on nitrogen inversion by comparing –OH and $-O^-$ substituents, along with OAc as control. Deprotonation of a hydroxyl group results in a full negative charge at oxygen and larger, more diffuse lone-pair orbitals. Moreover, the lone-pair repulsions can no longer be minimized by rotating about the N–O bond.[15] Destabilizing interactions between nonbonding lone pairs on oxygen and those on a neighboring nitrogen atom are thereby increased with $-O^-$. Therefore, this effect is expected to *raise* the barrier to inversion. Yet deprotonation also leads to a decrease in the electronegativity of the oxygen. Upon deprotonation, the adjacent nitrogen places less p character in the bond to oxygen, leaving more p character for the lone pair. Therefore, this effect is expected to *lower* the barrier to inversion.

Thus the two effects now operate in opposite directions. If σ-inductive effects are small compared to lone-pair repulsions, then deprotonation should decrease the rate of nitrogen inversion, whereas if lone-pair repulsions are small compared to σ-inductive effects, then deprotonation should increase the rate of nitrogen inversion. Moreover, the steric demands of –OH and $-O^-$ are low and quite similar.

In this study, we report the barriers to nitrogen inversion for *N*-benzyl-*N*-methylhydroxylamine ($PhCH_2N(OH)CH_3$, **1a**), *N*,*N*-diethylhydroxylamine (**2a**), 1-hydroxy-2,2,4,4-tetramethylpyrrolidine (**3a**), their conjugate bases **1b**, **2b**, **3b**, and two corresponding *N*-acetoxyamines **2c**, **3c**. These have diastereotopic hydrogens or methyls that become equivalent when the nitrogen becomes planar in the transition state for nitrogen inversion, and each of **3a–c** has four different sites (A–D) by which to gauge the inversion barrier.



3

a, X=H
b, X=-
c, X=$COCH_3$

It is necessary to convert the hydroxylamine entirely into its conjugate base. Surprisingly, there are no reports of hydroxylamine pK_as to guide in finding suitable conditions. It is expected that the pK_a will be intermediate between those of CH_3OH (pK_a = 15.2) and alkyl peroxides[16] ($pK_a \approx 12$), reflecting the intermediate electronegativity of nitrogen. Indeed, the gas-phase acidity of Et_2NOH is 0.4 kcal/mol greater than that of $PhCH_2OH$,[17] and that of H_2NOH is calculated to be 0.2 or 16.4 kcal/mol greater than that of CH_3OH or H_2O, respectively.[18] Since the pK_a of *tert*-butyl alcohol is near 19, a slight excess (15%) of potassium *tert*-butoxide was deemed sufficient to completely deprotonate a hydroxylamine.

Near completion of this work a similar study[19] was discovered. STO-3G//MNDO calculations on $(CH_3)_2NOH$ and $(CH_3)_2NO^-$ indicate that the barrier to inversion of the anion ought to be 3.3 kcal/mol greater than that of the hydroxylamine. This result strongly suggests that the π-repulsive effect is dominant. Nevertheless, the experimental $\Delta G^{\ddagger}$s for nitrogen inversion of **1a** and **1b** in CD_3OD were reported as 12.8 ± 0.7 and 13.5 ± 2.4 kcal/mol, respectively. Although the barrier is slightly higher in the anion, the difference is not statistically significant. Besides, there is no guarantee that methanolic sodium methoxide converts a hydroxylamine completely into its conjugate base. We therefore avoid protic solvents, and we seek accurate rate constants for nitrogen inversion in hydroxylamines and their corresponding anions.

Experimental Section

Materials. Mesityl oxide, nitromethane, benzyltrimethylammonium hydroxide (Triton B, 40% in methanol), methylmagnesium bromide (3.0 M in ether), potassium *tert*-butoxide, *N*,*N*-diethylhydroxylamine (**2a**), *N*-methylhydroxylamine hydrochloride, 3-ethylpyridine, acetone-d_6, and dimethylformamide-d_7 (DMF-d_7) (ampoules) were purchased from Aldrich. Zinc dust, sodium bicarbonate, acetic anhydride, and ammonium chloride were purchased from Mallinckrodt. Benzaldehyde, sodium hydroxide, magnesium sulfate, and sodium sulfate were purchased from Fisher. Sodium dithionite and *p*-nitrophenol were purchased from Matheson Coleman and Bell. These compounds were used without further purification. The hydroxylamines, potassium *tert*-butoxide, and DMF-d_7 were stored in a drybox to exclude moisture.

Initial studies on *N*-benzyl-*N*-methylhydroxylamine were performed in 3-ethylpyridine or acetone-d_6, but these were not optimum. Subsequently, dimethylformamide was chosen as solvent because it is aprotic, available deuterated, low-melting, and sufficiently polar to solvate the anions. Samples were prepared in a drybox under a nitrogen atmosphere to prevent oxidation of the hydroxylamines or their anions and absorption of water by the DMF.

^{1}H NMR Spectroscopy. NMR identification was done on either a Varian EM390 90-MHz spectrometer or a GE QE300 300-MHz spectrometer. All variable-temperature experiments were done on the QE300, after at least 15 min of temperature equilibration. The probe thermocouple was calibrated at the end of each experiment with a methanol sample.[20] Chemical shifts and coupling constants were measured at –57 °C, where nitrogen inversion is slow. To facilitate spectral analysis in the Et_2NOH series, the methylene peaks were simplified by homonuclear decoupling of the methyl peaks.

Rate constants were evaluated by measuring coalescence temperatures T_c of ^{1}H NMR signals. The spectrum was scanned at 5° intervals, and then at smaller intervals to locate T_c within 2 °C. For diastereotopic methyl groups the rate constant at T_c is given by eq 1[21] where $\Delta\nu$ is the chemical-shift separation, in Hz,

(13) Rauk, A.; Andose, J. D.; Frick, W. G.; Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1971**, *93*, 6507. Wolfe, S.; Mitchell, D. J.; Schlegel, H. B. *Can. J. Chem.* **1982**, *60*, 1291. Nelsen, S. F.; Petillo, P. A.; Rumack, D. T. *J. Am. Chem. Soc.* **1990**, *112*, 7144.
(14) Griffith, D. L.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 4089.
(15) Ohkubo, K.; Azuma, Y.; Okada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1397. Jennings, W. B.; Worley, S. D. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1512. Pople, J. A.; Raghavachari, K.; Frisch, M. J.; Binkley, J. S.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1983**, *105*, 6389. Yabushita, S.; Gordon, M. S. *Chem. Phys. Lett.* **1985**, *117*, 321.
(16) Everett, A. J.; Minkoff, G. J. *Trans. Faraday Soc.* **1953**, *49*, 410.
(17) Bartmess, J. E.; Basso, T.; Georgiadis, R. *J. Phys. Chem.* **1983**, *87*, 912.
(18) Hinde, A. L.; Pross, A.; Radom, L. *J. Comput. Chem.* **1980**, *1*, 118.
(19) Lobo, A. M.; Prabhakar, S.; Santos, M. A.; Rzepa, H. S. *Rev. Port. Quim.* **1985**, *27*, 492.
(20) Raiford, D. S.; Fisk, C. L.; Becker, E. D. *Anal. Chem.* **1979**, *51*, 2050.

$$k = \pi\Delta\nu/\sqrt{2} \quad (1)$$

measured at low temperature. For diastereotopic methylene protons of an AB system with coupling constant J the rate constant was determined according to eq 2[22] where the chemical-shift

$$k = [(\Delta\nu^2 + 6J^2)/2]^{1/2} \quad (2)$$

separation $\Delta\nu = (\Delta^2 - J^2)^{1/2}$, with Δ the distance in Hz between the centers of the doublets. Although $\Delta\nu$ varies with temperature, the variation is quite small (generally less than 10%) across the relevant range, and the extrapolation of $\Delta\nu$ to the coalescence temperature is uncertain. Therefore, taking $\Delta\nu$ as constant introduces only a small error. Finally, free energies of activation were determined from the Eyring equation.

Synthesis. *N*-Benzyl-*N*-methylhydroxylamine (1a). *N*-Methylbenzaldimine *N*-oxide (88% yield) was prepared from benzaldehyde and *N*-methylhydroxylamine and was recrystallized from petroleum ether/benzene: mp 83–84 °C (lit.[23] 84 °C); ^{1}H NMR (300 MHz, CD_3CN) δ 3.76 (s, 3 H), 7.42 and 8.21 (m, 5 H), 7.53 (s, 1 H). This was reduced with $LiAlH_4$ in ether. After aqueous washings, evaporation of the ether gave white, crystalline *N*-benzyl-*N*-methylhydroxylamine (75% yield): mp 40–41 °C (lit.[24] 40 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (s, 3 H), 3.75 (s, 2 H), 7.32 (m, 5 H), 6.1 (bs).

1-Hydroxy-2,2,4,4-tetramethylpyrrolidine (3a) was synthesized according to standard procedure.[25] First, 5-nitro-4,4-dimethyl-2-pentanone (93% yield) was prepared from mesityl oxide and nitromethane, with benzyltrimethylammonium hydroxide as catalyst: bp 83–85 °C (2.5 Torr) (lit.[26] bp 112–113.5 °C (14 Torr); ^{1}H NMR (60 MHz, neat) δ 1.13 (s, 6 H), 2.12 (s, 3 H), 2.62 (s, 2 H), 4.58 (s, 2 H). Reduction and cyclization of this nitro ketone was accomplished with Zn dust in aqueous ammonium chloride to give 2,4,4-trimethylpyrroline *N*-oxide (49% yield): bp 90–95 °C (1 Torr) (lit.[25] bp 72 °C (0.4 Torr)); ^{1}H NMR (60 MHz, neat) δ 1.15 (s, 6 H), 1.85 (s, 3 H), 2.52 (s, 2 H), 3.58 (s, 2 H). This was reacted with methylmagnesium bromide in ether. After aqueous washes the ether was evaporated at reduced pressure. The resulting yellow crystals were purified by sublimation at 30–35 °C (1 Torr) to give white crystals of 1-hydroxy-2,2,4,4-tetramethylpyrrolidine (15% yield, mp 58–60 °C (lit.[25] mp 62 °C)), which were stored under N_2: ^{1}H NMR (300 MHz, acetone-d_6) δ 1.06 (s, 6 H), 1.09 (s, 6 H), 1.49 (s, 2 H), 2.86 (s, 2 H), 7.84 (bs, 1 H).

1-Hydroxy-2,2,5,5-tetramethylpyrrolidine could be successfully prepared exactly analogous to **3a**, starting with condensation of methyl vinyl ketone and 2-nitropropane, followed by reduction and cyclization with Zn dust and addition of methyl Grignard to the nitrone. The resulting orange oil showed exceedingly broad peaks in the ^{1}H NMR spectrum, and it was concluded that a stable tetramethylpyrrolidinoxy ("TEMPO") free radical had formed. To reduce this,[27] the oily oxidized hydroxylamine was added to sodium dithionite in 50% (v/v) aqueous acetone. Upon swirling, the dark orange solution turned into an opaque light yellow solution. Acetone was removed at reduced pressure, and the hydroxylamine taken up in ether, dried over $MgSO_4$, filtered, and concentrated at reduced pressure to give bright yellow crystals which were further purified by sublimation (4 Torr, 40 °C) to give white crystals (mp 48–52 °C). This hydroxylamine must be stored under N_2 since any trace of oxygen results in immediate oxidation to the free radical: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (s, 12 H), 1.19 (s, 4 H), 6.14 (bs, 1 H).

Aminoxide Anions 2b and 3b. The conjugate bases of the hydroxylamines were generated in situ by adding, e.g., Et_2NOH (40 μL, 0.39 mmol) to a solution of potassium *tert*-butoxide (52 mg, 0.46 mmol) in DMF-d_7 (1.0 mL). At lower concentrations (0.07 M) a homogeneous solution could be obtained, but at these high concentrations the potassium salts are not completely soluble in DMF. Nevertheless, solubilities are high enough to obtain good spectra.

The conjugate base (**1b**) of *N*-benzyl-*N*-methylhydroxylamine was prepared in a slightly different manner. Potassium hydride was washed with hexanes under a flow of N_2 to remove mineral oil and then weighed (5.1 mg, 0.13 mmol). The hydroxylamine (5.3 mg, 0.038 mmol in 0.5 mL 3-ethylpyridine) was added to this KH, suspended in 3-ethylpyridine (0.5 mL). The deprotonation proceeds with evolution of H_2. Again, even though not all of the salt went into solution, the solubility is sufficient to obtain good spectra. This procedure is also adaptable to preparation of solutions in acetone-d_6.

N-Acetoxyamines were prepared by stirring the hydroxylamine with acetic anhydride according to Huisgen.[28] *N*-Acetoxydiethylamine (**2c**) (22% yield): bp 69–73 °C (23 Torr) (lit.[28] bp 48–49 °C (12 Torr); ^{1}H NMR (300 MHz, DMF-d_7) δ 1.03 (t, 6 H), 2.06 (s, 3 H), 2.85 (q, 4 H). 1-Acetoxy-2,2,4,4-tetramethylpyrrolidine (**3c**) (55% yield): bp 60–65 °C (10 Torr); ^{1}H NMR (300 MHz, DMF-d_7) δ 1.12 (s, 6 H), 1.13 (s, 6 H), 1.56 (s, 2 H), 2.04 (s, 3 H), 3.00 (s, 2 H).

Table I. Kinetics of Nitrogen Inversion in Hydroxylamine Derivatives in DMF-d_7

deriv	peak	δ, ppm	J,[a] Hz	$\Delta\nu$,[b] Hz	T_c,[c] °C	k, s^{-1}	$\Delta G^{\ddagger}$,[d] kcal/mol
1a[e]	CH_2	3.72	12.6	62.2	−14	154	12.5[f]
1b[e]	CH_2	3.73	11.2	83.5	−6	195	12.8[f]
2a	CH_2	2.52	12.9	38.1	−2	110	13.3
2b	CH_2	2.48	12.0	48.6	0	126	13.3
2c	CH_2	2.85	13.4	58.5	−17	149	12.4
3a	A	2.75	8.7	14.4	−34	57	12.0
	B	1.00		5.4	−47	12	12.0
	C	1.38	12.5	43.8	−25	119	12.0
	D	1.00		27.6	[g]	[g]	[g]
3b	A	2.75	8.4	43.9	−24	108	12.2
	B	1.02		13.2	−36	29	12.2
	C	1.39	12.3	14.4	−32	74	11.9
	D	1.03		45.9	[g]	[g]	[g]
3c	A	2.99	9.2	84.2	−29	194	11.6
	C	1.52	12.6	36.8	−37	107	11.5

[a] ±0.1 Hz. [b] ±0.5 Hz. [c] ±2 °C. [d] ±0.1 kcal/mol. [e] In acetone-d_6. [f] ±0.2 kcal/mol. [g] Not determined owing to signal overlap.

Results

Kinetics of Nitrogen Inversion in Hydroxylamines and Aminoxides. Initial results on *N*-benzyl-*N*-methylhydroxylamine (**1a, 1b**) were ambiguous. In 3-ethylpyridine the aminoxide has the same spectral characteristics as the hydroxylamine, so there is no guarantee of conversion to the conjugate base. The coalescence temperatures of both the hydroxylamine and the potassium salt of its conjugate base are very similar in either acetone-d_6 (−14 or −6 °C) or 3-ethylpyridine (−54 or −55 °C). Additionally, a large extra peak at δ 3.7 ppm indicated that substantial decomposition had occurred, perhaps due to elimination of H_2O. In order to avoid these complications, studies were undertaken on hydroxylamines lacking acidic α hydrogens. Also acetone was abandoned, since the oxyanion might add to the carbonyl.

Nitrogen inversion of 1-hydroxy-2,2,5,5-tetramethylpyrrolidine in methanol could not be frozen out at −95 °C. The exceptionally low barrier to inversion is probably due to steric interactions between the hydroxy and methyl groups, which raise the ground-state energy and result in more nearly sp^2 (planar) hybridization at nitrogen. Further work on this system was abandoned.

N,N-Diethylhydroxylamine (**2a**) and 1-hydroxy-2,2,4,4-tetramethylpyrrolidine (**3a**) proved to be more tractable

(21) Sandström, J. *Dynamic NMR Spectroscopy*; Academic: New York, 1982, Chapter 6, p 79.
(22) Reference 21, p 84.
(23) Brady, O. L.; Dunn, F. P.; Goldstein, R. F. *J. Chem. Soc.* **1926**, 2386.
(24) Exner, O. *Collect. Czech. Chem. Commun.* **1955**, *20*, 202.
(25) Bonnett, R.; Brown, R. F. C.; Clark, V. M.; Sutherland, I.; Todd, A. *J. Chem. Soc.* **1959**, 2094.
(26) Kloetzel, M. C. *J. Am. Chem. Soc.* **1947**, *69*, 2271.
(27) Ozinskas, A. J.; Bobst, A. M. *Helv. Chim. Acta* **1980**, *63*, 1407.
(28) Huisgen, R.; Bayerlein, F. *Liebigs Ann. Chem.* **1960**, *630*, 138.

systems because they have higher coalescence temperatures, even though signal overlap made it difficult to determine all four of them in the latter. Additionally, a milder (and bulkier) base, potassium *tert*-butoxide, was used. Although there was some indication in the NMR spectrum of decomposition products, these were always minor components.

Average chemical shifts ($\bar{\delta}$), coupling constants (J), chemical-shift differences between diastereotopic groups ($\Delta\nu$), coalescence temperatures (T_c), rate constants, and free energies of activation ($\Delta G^{\ddagger}$) are reported in Table I. The $\Delta G^{\ddagger}$s reported here are similar to barriers for nitrogen inversion in other dialkyl hydroxylamines[29] and in excellent agreement with previously reported barriers (12.8 kcal/mol in methanol-d_4,[18] 12.4 kcal/mol in acetone-d_6[30]) for *N*-benzyl-*N*-methylhydroxylamine.

The major contributions to the error in $\Delta G^{\ddagger}$ are the uncertainties in finding the exact coalescence temperature and in not knowing $\Delta\nu$ at that temperature, but even these are small. These would lead to systematic errors in the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, but $\Delta G^{\ddagger}$ can usually be determined with an acceptably low error of ±0.1 kcal/mol. Also, for both **3a** and **3b**, there are three separate peaks that provide independent measures of $\Delta G^{\ddagger}$ that are in admirable agreement with each other.

Evidence for Aminoxide Anions. Since the energies of activation are so similar in both the hydroxylamine and the aminoxide anion, it is necessary to verify that conversion to the conjugate base occurs and is complete. Even though the pK_as suggest that *tert*-butoxide ought to be sufficiently basic to produce the aminoxide, there is no assurance that relative acidities might not reverse in aprotic solvents. Besides, trace water or impurity might protonate the aminoxide. The values in Table I show that deprotonation leads to little change in either the average chemical shifts ($\bar{\delta}$) or the coupling constants (J). Nor is significant change (>1 ppm) observed in ^{13}C chemical shifts upon deprotonation. The primary evidence for the formation of the aminoxide anion is the large changes in ^1H chemical-shift differences between diastereotopic groups ($\Delta\nu$), observed upon deprotonation.

To verify that the hydroxylamine is converted completely to its conjugate base, deprotonation of **3a** was repeated with a 12-fold excess of base (0.46 mmol tBuOK, 0.036 mmoles hydroxylamine in 0.5 mL DMF-d_7). The chemical-shift differences and rate constants are observed to be unchanged, showing that the aminoxide anions had been successfully and completely generated. Additionally, reprotonation of the aminoxide anion with *p*-nitrophenol results in values for $\Delta\nu$ and T_c that are the same as those of the original hydroxylamine, showing that the deprotonation is reversible. Therefore, we conclude that the aminoxide is indeed formed and that the hydroxylamine can be converted entirely to its conjugate base.

Discussion

The remarkable result is that within an acceptably small experimental error identical barriers to inversion are observed for both the hydroxylamine and its conjugate base. This result holds for at least two and perhaps all three hydroxylamines studied. The rates may differ slightly, but it would be futile to try to reduce the experimental error further in order to distinguish them. The identity of barriers is not some artifact of this system or of the NMR method, since the corresponding acetoxyamines have measurably different barriers, 0.5–0.9 kcal/mol lower. This reduction may be due to the greater effective electronegativity of the acetoxy oxygen or to its reduced lone-pair repulsions, but it is not readily separated from a steric effect.

This result raises the question of whether –OH and –O$^-$ substituents really do differ in their σ-inductive powers or lone-pair repulsions. Perhaps the barriers are so similar because these two substituents are very similar. Nevertheless, several pieces of evidence indicate that both the inductive and repulsive differences should be substantial.

The MO calculations[17] on $(CH_3)_2NOH$ indicate that the barrier to inversion of the conjugate base ought to be 3.3 kcal/mol greater than that of the parent hydroxylamine. This calculation does not distinguish σ-inductive from π-repulsive origins, but whatever the origin, the difference between –OH and –O$^-$ is large. Admittedly, MO calculations on anions require large basis sets[31] and may still be at variance with experiment,[32] but even a small fraction of so large a difference would have been detectable by NMR methods.

The difference in inductive effects between –OH and –O$^-$ is certainly large, as judged by the estimated ΔpK_a of 4.8 between $ArCMe(OH)NH_2^+OMe$ and $ArCMe(O^-)NH_2^+$-OMe (Ar = triazolyl).[33] The difference in hydroxylamines ought to be even larger, since the nitrogen and oxygen are in direct proximity, rather than separated by a carbon atom. It is not possible to convert pK_a values into a quantitative measure of rehybridization, but –OH and –O$^-$ certainly differ markedly in their inductive abilities.

The difference in lone-pair repulsions ought also to be substantial. According to simple HMO theory, including overlap, the π-repulsion energy of four electrons in atomic orbitals on oxygen and nitrogen is given by eq 3[34] where

$$E_{rep} = 2S[S(\alpha_N + \alpha_O) - 2\beta]/(1 - S^2) \quad (3)$$

S, α, and β are, respectively, overlap, Coulomb, and resonance integrals. In the transition state the nitrogen orbital is a p orbital. For simplicity we take the nitrogen orbital in the ground state as an sp^3 hybrid, for which the overlap with an adjacent p orbital on oxygen can readily be shown to be reduced by a factor $(^2/_3)^{1/2}$. We also take β proportional to S. This leads to a difference in repulsion energies between ground state and transition state given by eq 4. With reasonable values of $S = 0.2$ for p–p overlap

$$\Delta E_{rep} = 2S[S(\alpha_N + \alpha_O) - 2\beta_{pp}]/(1 - S^2)(3 - S^2) \quad (4)$$

and a difference of 3 eV between Coulomb integrals of –OH and –O$^-$, this corresponds to a repulsion contribution of 2 kcal/mol to the activation barrier. So large a contribution would have been detected.

Given that both the σ-inductive and the π-repulsive effects are large, the absence of any net change of the inversion barrier means that these two must have cancelled nearly equally. It is likely that this is purely a coincidence, peculiar to hydroxylamines. In other systems either effect may be stronger or weaker, and the cancellation need not hold.

(29) Lehn, J. M.; Wagner, J. *Tetrahedron* **1970**, *26*, 4227.
(30) Griffith, D. L.; Olson, B. L.; Roberts, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 1648.
(31) Radom, L. *Application of Electronic Structure Theory*; Schaefer, H. F., III, Ed.; Plenum: New York, 1977; p 333. Spitznagel, G. W.; Clark, T.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Comput. Chem.* **1982**, *3*, 363. Simons, J.; Jordan, K. D. *Chem. Rev.* **1987**, *87*, 535. Siggel, M. R. F.; Thomas, T. D.; Saethre, L. J. *J. Am. Chem. Soc.* **1988**, *110*, 91.
(32) Perrin, C. L.; Thoburn, J. D. *J. Org. Chem.* **1989**, *54*, 764.
(33) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436.
(34) Müller, K. *Helv. Chim. Acta* **1970**, *53*, 1112. Baird, N. C.; West, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 4427.

Conclusions

Since the rates of nitrogen inversion in hydroxylamines and their conjugate bases are the same, we conclude that the effect of increased lone-pair repulsion of $-O^-$ is equal to the σ-inductive effect of its reduced electronegativity. These two effects happen to cancel nearly exactly, so that there is no net effect. This cancellation represents a challenge to MO calculations. It is no surprise that these two effects had not previously been separated, since both do contribute and neither can be ignored.

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Improved Methods for the N-Nitration of Amides

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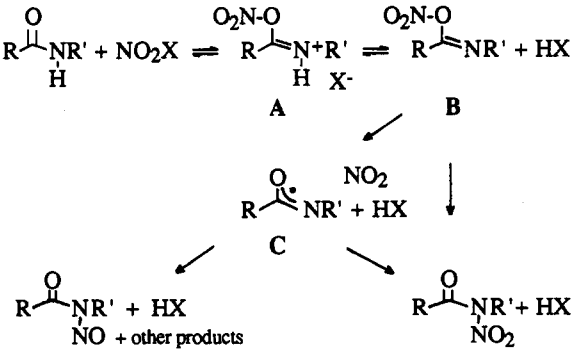
The reactivity of several nitrating mixtures with amides has been compared. Ammonium nitrate/trifluoroacetic anhydride, morpholinium nitrate/trifluoroacetic anhydride, and morpholinium nitrate/heptafluorobutyric anhydride are the reagents of choice since, in CH_2Cl_2 at 0 °C, they give *N*-alkyl-*N*-nitrocarboxamides and *N*-nitrolactams in excellent yields. Mechanistic details of these nitrations have been elucidated. Trifluoroacetyl nitrate, which arises from the reaction $R_2NH_2^+NO_3^- + 2(CF_3CO)_2O \rightarrow CF_3COONO_2 + CF_3CONR_2 + 2CF_3COOH$, appears to cause the direct N-nitration of carboxamides.

Introduction

During the past recent years, our group has been taking advantage of the enhanced reactivity of *N*-alkyl-*N*-nitrosoamides and *N*-alkyl-*N*-nitroamides (henceforward called nitrosoamides and nitroamides) with different nucleophiles, to convert RCONHR′ into RCONHR″, RCOSR″, $RCON_3$, etc. under mild conditions.[1] The amide activation by means of the NO_2 group seemed preferable since nitroamides react much more rapidly with nucleophiles than nitrosoamides and, in general, turn out to be more stable thermally.[2] However, nitroamides show an important shortcoming: their preparation usually requires acidic media and long reaction times and proceeds in variable yields. In fact, under classical nitration conditions (HNO_3/Ac_2O),[3] many simple aliphatic amides and lactams are nitrated only in 40–80% yields. When the substrates contain hindered amide groups, their nitration cannot be carried out successfully; in addition, attempts to nitrate these substrates under either more vigorous or different reaction conditions have been reported to give variable amounts of nitrosoamides[4] besides poor yields of nitroamides. In other words, N-nitration of most amides is an unsolved problem that deserves further attention.

Scheme I



The appearance of three interesting communications[5-7] related to the subject has prompted us to summarize results which we have obtained during the past recent years. Suri and Chapman[5] have reported that 2-pyrrolidinone can be N-nitrated in 30% yield[8] in nitromethane with a mixture of NH_4NO_3 and TFAA, a procedure developed by Crivello to nitrate aromatic compounds at rt.[9] Carvalho et al. have shown that imidoyl nitrates, prepared from imidoyl chlorides and silver nitrate, rearrange to nitroamides by an intramolecular mechanism involving likely the homolytic cleavage of the O–NO_2 bond,[6] and more recently that a mixture of $Bu_4N^+NO_3^-$ and TFAA in

(1) (a) Garcia, J.; Vilarrasa, J. *Tetrahedron Lett.* **1982**, *23*, 1127. (b) Garcia, J.; González, J.; Segura, R.; Urpí, F.; Vilarrasa, J. *J. Org. Chem.* **1984**, *49*, 3322. (c) Garcia, J.; González, J.; Segura, R.; Vilarrasa, J. *Tetrahedron* **1984**, *16*, 3121. (d) Torra, N.; Urpí, F.; Vilarrasa, J. *Tetrahedron* **1989**, *45*, 863. (e) Berenguer, R.; Garcia, J.; Vilarrasa, J. *Synthesis* **1989**, 305. (f) For a related work, see: Romea, P., Urpí, F.; Vilarrasa, J. *J. Org. Chem.* **1989**, *54*, 3209.

(2) White, E. H.; Grisley, D. W. *J. Am. Chem. Soc.* **1961**, *83*, 1191.

(3) Campbell, R.; Peterson, C. J. *J. Org. Chem.* **1963**, *28*, 2294 and references cited therein.

(4) (a) In some cases, this may be attributed to the decomposition of the nitrating agent in the reaction medium to give lower nitrogen oxides (see refs 2 and 1b), which may mainly occur when the nitration is too slow. In other cases, the cause may be the presence of impurities in the reagent; for example, it has been proved that some commercial samples of NO_2BF_4 contain significant percentages of $NOBF_4$: Elsenbaumer, R. L. *J. Org. Chem.* **1988**, *53*, 437. (b) Nitration of ureas by different reagents also leads to nitrosoureas as major products (and to the cleavage of the CO–N bond). See: White, E. H.; Ryan, T. J.; Hahn, B. S., Erickson, R. H. *J. Org. Chem.* **1984**, *49*, 4860 and refs 14–16 therein. (c) Imidoyl nitrates may give nitrosoamides as well. See: Carvalho, E.; Norberto, F.; Rosa, E.; Iley, J.; Patel, P. *J. Chem. Res., Synop.* **1985**, 132. According to these authors, the most appropriate conditions to avoid nitrosoamides as byproducts are the use of dilute solutions, low temperatures, and exclusion of light.

(5) Suri, S. C.; Chapman, R. D. *Synthesis* **1988**, 743. (The nitration of 2-pyrrolidinone with HNO_3/Ac_2O had been earlier reported: Coburn, M. D.; Ungnade, H. E. *J. Heterocycl. Chem.* **1965**, *2*, 308.)

(6) Carvalho, E.; Iley, J.; Rosa, E. *J. Chem. Soc., Chem. Commun.* **1988**, 1249.

(7) (a) Carvalho, E.; Iley, J.; Norberto, F.; Rosa, E. *J. Chem. Res., Synop.* **1989**, 260. (b) We have obtained a similar yield of *N*-nitro-2-pyrrolidinone under their conditions, but also substantial amounts of *N*-(trifluoroacetyl)-2-pyrrolidinone as byproduct.

(8) We have confirmed this result of Suri and Chapman (ref 5); the final mixture also contains starting amide and *N*-trifluoroacetyl-2-pyrrolidinone. If the reagents are mixed at room temperature, 18% of *N*-nitro-2-pyrrolidinone and 12% of *N*-nitroso-2-pyrrolidinone are obtained.

(9) Crivello, J. V. *J. Org. Chem.* **1981**, *46*, 3056. For the nitration of enol acetates with this reagent mixture, see Dampawan, P.; Zajac, W. W. *Synthesis* **1983**, 545. For a very recent, comprehensive review on nitration reagents, see: Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration, Methods and Mechanisms*; VCH: New York, 1989.

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