J|A|C|S
COMMUNICATIONS

Published on Web 09/01/2006

Hydroxylamine as an Oxygen Nucleophile. Structure and Reactivity of Ammonia Oxide

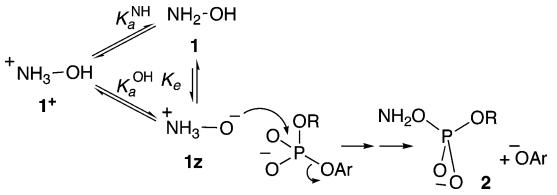
Anthony J. Kirby,*,† John E. Davies,† Tiago A. S. Brandão,‡ Pedro F. da Silva,‡ Willian R. Rocha,§ and Faruk Nome*,‡

University Chemical Laboratory, Cambridge CB2 1EW, U.K., Departamento de Química, Universidade Federal de Santa Catarina, Florianópolis, SC, 88040-900, Brazil. Departamento de Química, ICEX, Universidade Federal de Minas Gerais, Belo Horizonte, MG, 31270-901, Brazil

Received July 28, 2006; E-mail: ajk1@cam.ac.uk; faruk@qmc.ufsc.br

Ammonia oxide $^{+}NH_3O^{-}$, the zwitterionic tautomer **1z** of hydroxylamine, is one of the last very simple molecules to be characterized, and has been discussed since the 19th century.[1] More recently it has attracted the interest of theoreticians,[2,3] and the absence of direct evidence for its existence is considered "a major challenge to experimentalists working in the field of elusive molecules".[2] We report firm evidence for its existence in the condensed phase, in the shape of a crystal structure containing equal amounts of **1z** and $\mathbf{1}^{+}$ (Scheme 1). This structure provides the missing experimental benchmark for calculational work and important new evidence relevant to the exceptional reactivity of hydroxylamine.

Scheme 1. Suggested Mechanism of Attack by Hydroxylamine Oxygen on a Phosphate Diester



Hydroxylamine itself is a unique, ambident α-effect nucleophile. It is alkylated on nitrogen but often acylated[4,5] and generally phosphorylated [6] on oxygen, indicating that reaction through oxygen is favored for harder electrophiles. N-alkylated hydroxylamines show similar enhanced reactivity, but NH_2OMe, which cannot react through oxygen, is significantly less reactive toward phosphorus than NH_2OH.[7−9] The α-effect, the enhancement of reactivity observed for nucleophiles with lone pair electrons on the atom adjacent to the nucleophilic center, is also favored for reactions with harder electrophiles. α-Effect nucleophiles are of special interest because their high reactivity toward phosphorus makes them reagents of choice for the destruction of nerve gases and other organophosphorus poisons.[10,11]

The mechanism of nucleophilic attack by hydroxylamine oxygen has been discussed for many years. Jencks in his authoritative text concluded that "this extraordinary reactivity must almost certainly mean that it is ... the oxygen anion of the dipolar form ... that is the reactive nucleophilic species."[12] (Scheme 1).

This mechanism has been discussed a number of times, but always inconclusively. There is no evidence—or obvious experimental way of obtaining it—for the presence of the zwitterionic tautomer **1z** in aqueous solution, and a small amount would in any case have to be highly reactive to support the observed enhanced rates of reaction.

† University Chemical Laboratory.
‡ Universidade Federal de Santa Catarina, Florianópolis.
§ Universidade Federal de Minas Gerais.

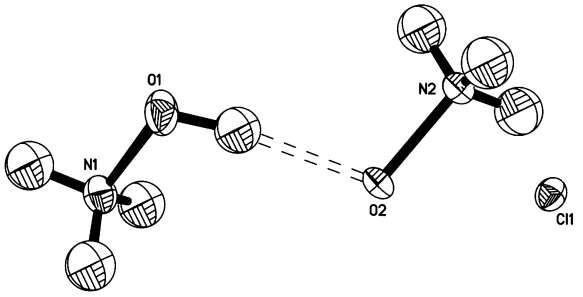


Figure 1. Molecular structure of hydroxylamine half-hydrochloride (**1z** + $\mathbf{1}^{+}$ Cl^{-}) at 120 K, showing ellipsoids at the 40% probability level.

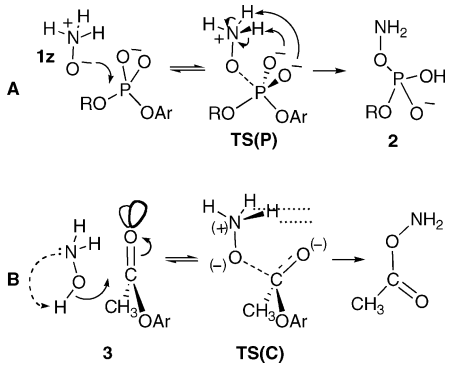
We find that NH_2OH exists in crystals of the half-hydrochloride $(NH_2OH)_2{\cdot}HCl$ exclusively as the zwitterionic tautomer **1z**. Stable, well-formed colorless crystals are obtained, simply and reproducibly, from a solution containing equal quantities of NH_2OH and its hydrochloride (and thus nominally at a pH equal to its pK_a).[13] The unit cell contains well-defined molecules of **1z** and $\mathbf{1}^{+}$ hydrogen-bonded to each other (Figure 1) and embedded in an extensive hydrogen-bonding network. The rather strong H-bond between **1z** and $\mathbf{1}^{+}$ has an O(1)···O(2) distance of 2.583(1) Å and an angle at H of 172.7(12)°. The proton in the hydrogen bond is located unambiguously (see Supporting Information (SI)), with interatomic distances O1−H1···O2 of 0.877(12)) and 1.711(13) Å, respectively. N−O bond lengths are closely similar, at 1.4170(15) and 1.4151-(17) Å for the $^{+}N-O^{-}$ and $^{+}N-OH$ systems of **1z** and $\mathbf{1}^{+}$. These bond lengths match the interatomic distances calculated for the two species in the gas phase, given a full complement of hydrogen-bonds to water molecules as a first solvation shell.

Is it possible for **1z**, *not* an α-effect nucleophile as usually defined because the lone pair on nitrogen is protonated, to support the observed rates of reaction of hydroxylamine as an oxygen nucleophile? We take attack at phosphorus (in water) as a specific example: NH_2OH reacts with bis(2,4-dinitrophenyl) phosphate, through oxygen, 100 times more slowly than NH_2O^{-} and about as fast as hydroxide ion; but 150 times more rapidly[7] than the α-effect nucleophile NH_2OMe (which is 1 p*K* unit less basic under the conditions, and reacts, necessarily, through nitrogen). Other things being equal, oxyanions react more slowly than nitrogen nucleophiles with phosphodiesters by some 2 orders of magnitude (an effect ascribed to electrostatic repulsion),[14] but **1z** is not a typical oxyanion nucleophile. As a zwitterion it is ideally suited to perform substitutions at the P centers of phosphate esters, because an enabling proton transfer from the H_3N^{+} group becomes thermodynamically favorable during the course of the reaction (**TS(P)**, Scheme 2A).

We have no way of estimating accurately the magnitudes of this and other effects on the reactivity of **1z**, but estimate that there

10.1021/ja065147q CCC: $33.50

Scheme 2. Suggested Rate Determining Transition States for (A) the Attack of Ammonia Oxide on a Phosphodiester and (B) of the OH Group of NH_2OH on 4-Nitrophenyl Acetate[15] [a]



[a] The dashed arrow in Scheme **2**B illustrates the stereoelectronic problem involved in direct deprotonation of the OH group by the adjacent general base. No such problem arises for direct attack on C═O by **1z** (see the text).

must be at least 1% at equilibrium with NH_2OH in aqueous solution to support the mechanism of Scheme 2 for attack on phosphate ester anions. The geometry of the H-bonding interaction of **TS(P)** is clearly not available for an S_N2 reaction at saturated carbon, which could explain why O-alkylation is not observed.

The stereoelectronic requirements for O-acylation are different again. H-bonding stabilization is unavailable during the initial stages of attack on C═O from the Bürgi−Dunitz angle (**3**, Scheme 2B). However, the (late) **TS(C)**, suggested for the O-acylation of hydroxylamine by 4-nitrophenyl acetate (**3)** on the basis of a careful examination of kinetic isotope effects,[15] offers similar features to **TS(P)**, and looks to be considerably more readily accessible from **1z**. Isotope effects are consistent with either transition state (**TS**) of Scheme 2.

The key parameter for significant reaction through ammonia oxide is the equilibrium constant K_e for **1** ⇌ **1z** (Scheme 1) in aqueous solution; insofar as this is unfavorable, **1z** must react, through oxygen, faster than **1** by a factor large enough to compensate. K_e is simply the ratio, K_a^{OH}/K_a^{NH} of the ionization constants for the OH and $^+NH_3$ groups of $\mathbf{1}^+$. The measured pK_a of $\mathbf{1}^+$, which reflects the ionizations of both groups, is close to 6 at 25 °C, while that of Me_3N^+OH, the closest analogue of $\mathbf{1}^+$, is 4.65.[16] Me_3N^+ is more strongly electron-withdrawing than H_3N^+,[17] no doubt because of H-bonding solvation, but these figures clearly suggest that **1z** could be present in significant amounts.

Since the equilibrium **1**⇌**1z** has so far proved impossible to quantify experimentally, we turned to theoretical calculations in an attempt to evaluate the energetics associated with this process. Our results are summarized in Tables S1-S4 of the SI. Consistent with previous calculations, **1z** is higher in energy than neutral **1** by some 25 kcal·mol^{-1} in the gas phase. Including solvent effects without specific interactions does not change the picture, and the calculated process remains unfavorable in solution. However, the inclusion of specific interactions, using small hydrogen-bonded clusters, and long-range interactions by means of the polarizable continuum model (PCM),[18] makes **1z** about 4 kcal·mol^{-1} more stable than **1**. The bond lengths calculated for **1z** (Tables S2 and S3) are consistent with the experimental values. We also evaluated the equilibrium by including solvent effects implicitly, through Monte Carlo statistical mechanical simulations,[19] in NpT ensemble at T = 298 K and 1 atm, using the free energy perturbation method.[20] Again the equilibrium **1**⇌**1z** was initially calculated to be strongly unfavorable, but inclusion of solvent polarization effects on the gas phase charges using PCM reversed this result (Table S4). These conflicting results seem to be occasioned mainly by solvent polarization effects, which affect drastically and unevenly the charge distribution of the tautomers. Work is in progress to describe the solvent polarization effects in a self-consistent way.

It remains to be proven whether the mechanism of Scheme 1 can deliver the rate enhancement needed to account for the observed rates of the reactions of hydroxylamine as an oxygen nucleophile. However, the evidence that **1z** can be the *preferred* form of hydroxylamine in the condensed phase shows that ammonia oxide is a serious—we would say likely—candidate for the active nucleophile in these reactions.

Acknowledgment. We are grateful to Capes, PRONEX, and CNPq, and to Prof. Sylvio Canuto and Dr. Kaline Coutinho for providing their Monte Carlo simulation program DICE. We are grateful to EPSRC for financial assistance toward the purchase of the Nonius CCD diffractometer.

Supporting Information Available: Full details of the crystallography, plus calculational methods and results. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Haber, F. *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 2444−2445.
(2) Bronstrup, M.; Schroder, D.; Kretzschmar, I.; Schalley, C. A.; Schwarz, H. *Eur. J. Inorg. Chem.* **1998**, 1529−1534.
(3) Trindle, C. D.; Shillady, D. *J. Am. Chem. Soc.* **1973**, *95*, 703−707. Bach, R. D.; Owensby, A. L.; Gonzalez, C.; Schlegel, H. B.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1991**, *113*, 6001−6011.
(4) Jencks, W. P. *J. Am. Chem. Soc.* **1958**, *80*, 4581−4585.
(5) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1960**, 82, 1778−1786.
(6) Domingos, J. B.; Longhinotti, Bunton, C. A.; Nome, F. *J. Org. Chem.* **2003**, *68*, 7051−7058.
(7) Domingos, J. B.; Longhinotti, E.; Brandao, T. A. S.; Bunton, C. A.; Santos, L. S.; Eberlin, M. N.; Nome, F.; *J. Org. Chem.* **2004**, *69*, 6024−6033.
(8) Kirby, A. J.; da Silva, D.; Lima, M. F.; Roussev, C. D.; Nome, F. Unpublished work.
(9) Kirby, A. J.; da Silva, D.; Lima, M. F.; Roussev, C. D.; Nome, F. *J. Am. Chem. Soc.* **2005**, *127*, 7033−7040.
(10) Simanenko, Y. S.; Popov A. F.; Prokop'eva T. M.; Karpichev E. A.; Savelova V. A.; Suprun I. P.; Bunton C. A. *Russ. J. Org. Chem.* **2002**, *38*, 1286−1298.
(11) Yang, Y.-C.; *Acc. Chem. Res.* **1999**, *32*, 109−115.
(12) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969, p 106.
(13) Full crystallographic details appear in the Supporting Information.
(14) Kirby, A. J.; Younas, M. *J. Chem. Soc., Sect. B* **1970**, 1165−1172.
(15) Hess, R. A.; Hengge, A. C.; Cleland, W. W. *J. Am. Chem. Soc.* **1997**, *119*, 6980−6983.
(16) Tykarska, E.; Dega-Szafran, Z.; Szafran, M. *J. Mol. Struct.* **1999**, *477*, 49−60.
(17) For example, the pK_a of $Me_3N^+CH_2COOH$ is 1.82, compared with 2.35 for the carboxyl group of the glycine cation: Kresge, A. J.; Chiang, Y. *J. Am. Chem. Soc.* **1973**, *95*, 803−806.
(18) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327.
(19) Allen, M. P.; Diltesley, D. J. *Computer Simulation of Liquids*; Claredon: New York, 1987.
(20) (a) Bash, P. A.; Singh, U. C.; Langridge, R.; Kollman, P. A. *Science* **1987**, *236*, 564. (b) Jorgensen, W. L.; Buckner, J. K.; Boudon, S.; Tirado-Rives, J. *J. Chem. Phys.* **1988**, *89*, 3742.

JA065147Q