N,*N*-Dimethoxy-*N*-*tert*-alkylamines: new synthesis methods and the crystal structure of the precursor†

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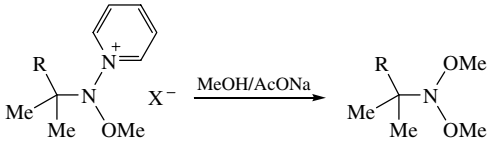
Under the methanolysis of *N*-methoxy-*N*-(1-pyridinium)amines salts **1a–c**, nucleophilic substitution occurs at the nitrogen atom to form *N*,*N*-dimethoxyamines **2a**,**b**; the crystal structure of precursor **1c** has been studied.

Nucleophilic substitution at the nitrogen atom is known for different *N*-chloro-*N*-alkoxy- and *N*-acyloxy-*N*-alkoxy geminal systems. *N*,*N*-Dialkoxyamines are formed under the alcoholysis of *N*-chloro-*N*-alkoxy-*N*-*tert*-alkylamines[2] and *N*-acyloxy-*N*-alkoxy-*N*-*tert*-alkylamines.[3] The corresponding *N*,*N*-dialkoxyamides were obtained by the alcoholysis of *N*-chloro-*N*-alkoxyureas,[4] *N*-chloro-*N*-alkoxybenzamides,[5] *N*-chloro-*N*-alkoxycarbamates,[6] *N*-acyloxy-*N*-alkoxyureas[3] and *N*-acyloxy-*N*-alkoxycarbamates.[3,6] Nucleophilic substitution at the nitrogen atom takes place in the reactions of *N*-acyloxy-*N*-alkoxybenzamides with amines[7,8] and NaN_3,[9,10] under their alkaline hydrolysis;[11] in reactions of *N*-acyloxy-*N*-alkoxyamides with K and Na carboxylates.[12] However, nucleophilic substitution at the central nitrogen atom in the RO-*N*-N^+ geminal system was unknown. Prepared from *N*-chloro-*N*-alkoxy-amines,[13] *N*-methoxy-*N*-(pyridinium)amine salts **1** are stable in the methanol solution at room temperature and nucleophilic substitution at the central N atom in this geminal system was not studied.[13]

We found presently that salts **1a–c** under methanolysis in the presence of AcONa at 100 °C (in a sealed glass tube) are converted into corresponding *N*,*N*-dimethoxyamines[2] **2a** (74% yield from **1a**) and **2b** (67% and 70% yields from **1b** and **1c**, respectively) (Scheme 1).‡



1a–c **2a**,**b**

a X = Cl, R = MeO_2CCH_2
b X = Cl, R = MeO_2C
c X = ClO_4, R = MeO_2C

a R = MeO_2CCH_2
b R = MeO_2C

Scheme 1 *Reagents and conditions*: ~100 equiv. of MeOH, ~10 equiv. of AcONa, 100 °C, 2.5 h.

Pyridine was liberated in the form of acetate. Thus, the first example of nucleophilic substitution at the nitrogen atom for this kind of geminal systems was developed. The *N*-pyridinium substituent in salts **1a–c** can be considered as a protective group that substantially stabilises these geminal systems in comparison with *N*-chloro-*N*-alkoxyamines. Based on this new method of synthesis, the first optically active compounds with asymmetric nitrogen in open chains have been obtained.[2] Obviously, the above method might be extended to the synthesis of cyclic *N*,*N*-dialkoxyamines[14,15] and trialkoxyamines (orthonitrites).[16]

The configurational stability of salts **1a**,**c** ($\Delta G^{\#}_{inv}$ = 14.3–15.3 kcal mol^{-1} at 2–27 °C)[13] is noticeably lower than that of dialkoxyamines ($\Delta G^{\#}_{inv}$ = 21.9–24.6 kcal mol^{-1} at 20 °C).[2] To understand the nature of this decrease, an XRD study of salt **1c** was performed (crystals were grown from MeOH).§

Compound **1c** crystallises as a racemate (space group $P\bar{1}$). The N(2) atom is characterised by pronounced pyramidality with the deviation of N(2) from the plane of O(1), C(7) and N(1) atoms equal to 0.531(2) Å; the sum of bond angles at the N(2) atom is 322.8°. The latter value is noticeably higher than those of $(MeO)_2NH$ (311.6°),[16(a)] $(MeO)_2NN(OMe)_2$ (311.5°),[16(b)] 2-metoxy-3,3-dicarbamoyl-1,2-oxazolidine (312.1°)[14(a)] and *N*-substituted perhydro-1.3.2-dioxazine (317.5°).[15(b)] Alhough it was reasonable to propose that the configuration stability of **1c** is the consequence of conjugation between the electron lone pair (Lp) of N(2) with the pyridine π system, the pseudotorsion angle Lp–N(2)–N(1)–C(1) (ϕ) is equal to 27.3°. On the other hand, the observed conformation can be stabilised by stereoelectronic interaction between the Lp and the σ* orbital of the N(1)–C(5) bond. However, the lengths of the N(1)–C(5) and N(1)–C(1) bonds are almost equal. Finally, cation conformation can be influenced by crystal packing effects. Nevertheless, the

† Asymmetric Nitrogen. Part 95. Geminal Systems. Part 54. Previous communications see ref. 1.

‡ *Methanolysis of* N-*methoxy*-N-*(1-pyridinium)*-N-tert-*alkylamines salts*. A solution of **1a**[13] (0.55 g, 2 mmol) (9 ml) and AcONa (1.5 g, 9 mmol) in methanol was heated at 100 °C in a sealed glass tube for 2.5 h. Then, the solid was filtered off and washed with CH_2Cl_2; the filtrate was concentrated *in vacuo*. The residue was extracted by hexane (10 ml). The extract was evaporated *in vacuo* and after distilling *in vacuo* 0.284 g (74%) **2a** was obtained as a colourless liquid and identified by ^{1}H NMR spectroscopy with an authentic sample.[2] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 6H, Me_2C), 2.55 (s, 2H, CH_2), 3.66 (s, 3H, CO_2Me), 3.74 [s, 6H, $N(OMe)_2$].

In a similar manner, **2b**[2] was obtained from **1b** and **1c** in 67 and 70% yields, respectively.

§ *Crystallographic data for* **1c**: at 120 K crystals of $C_{11}H_{17}ClN_2O_7$ are triclinic, space group $P\bar{1}$, a = 5.9922(7), b = 8.216(1), c = 15.162(2) Å, α = 90.534(5)°, β = 92.939(5)°, γ = 91.281(5)°, V = 745.3(2) Å^3, Z = 2, M = 324.72, d_{calc} = 1.447 g cm^{-3}, μ(MoKα) = 2.90 cm^{-1}, F(000) = 340. Intensities of 7719 reflections were measured with a Smart 1000 CCD diffractometer at 120K [λ(MoKα) = 0.71072 Å, ω-scans with a 0.3° step in ω and 8 s per frame exposure, $2\theta < 56°$], and 3569 independent reflections (R_{int} = 0.0290) were used in the further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The positions of hydrogen atoms were calculated and refined in an isotropic approximation in a riding model. The analysis of the Fourier electron density synthesis revealed that ClO_4^- anions are disordered by two positions with relative oxygen atom occupancies of 7:3. The refinement converged to wR_2 = 0.1106 and GOF = 0.997 for all independent reflections [R_1 = 0.0459 was calculated against F for 2748 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 299193. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2006.

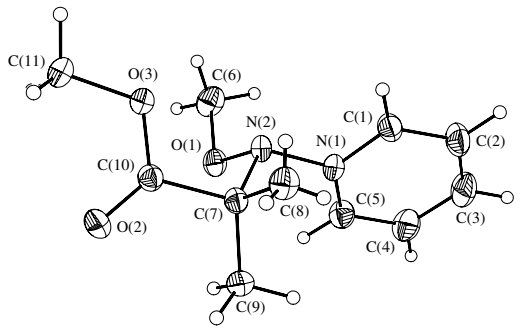


Figure 1 General view of the cation of **1c**. The selected bond lengths (Å): N(1)–C(5) 1.345(2), N(1)–C(1) 1.348(2), N(1)–N(2) 1.466(2), N(2)–O(1) 1.4142(16), N(2)–C(7) 1.505(2), O(1)–C(6) 1.440(2), C(7)–C(8) 1.524(2), C(7)–C(9) 1.526(2), C(7)–C(10) 1.540(2), C(10)–O(2) 1.199(2), C(10)–O(3) 1.331(2); bond angles (°): N(2)–O(1)–C(6) 107.86(12), C(5)–N(1)–C(1) 122.79(14), C(5)–N(1)–N(2) 122.35(13), C(1)–N(1)–N(2) 114.7(1), O(1)–N(2)–N(1) 106.6(1), O(1)–N(2)–C(7) 105.3(1), N(1)–N(2)–C(7) 110.9(1).

B3PW91/6-31G* calculation¶ has revealed that the above conformation is also preserved in the isolated cation (ϕ is 33.8°). In addition, note that the potential energy scan along the ϕ coordinate for the cation has revealed that the difference in energy between the minimum and a conformer with $\phi = 90°$ is 11.49 kcal mol^{-1}.

In order to estimate the inversion barrier, we have carried out the additional optimization of the transition state (TS) with the planar N(2) atom. The additional verifications of transition state localization have been obtained within the frequency calculation: one imaginary frequency (146i cm^{-1}) corresponding to the out-of-plane bending of the N(2) atom was found. The energy difference between the minimum and transition state with the ZPE correction according to B3PW91/6-31G* optimization is 6.81 kcal mol^{-1}, which is about two times lower than the experimental estimation.

Surprisingly, the analysis of TS geometry has revealed that, in spite of a lower barrier of inversion, the mutual disposition of the Lp of the N(2) atom and the pyridine π system found in the isolated cation retains in the transition state ($\phi = 33.8°$). Such a conformation in the TS is *a fortiori* unexpected assuming the Lp is totally *p* in nature according to NBO analysis [for comparison in the isolated cation the Lp of N(2) has 30% *s*-contribution]. Thus, the significant shortening of the N(1)–N(2) bond from 1.451 Å [1.466(2) Å in crystal] in an energy minimum down to 1.380 Å in TS resulted from the *s*-orbital contribution decrease rather than conjugation. In addition, the role of stereoelectronic interactions, namely, between oxygen of the methoxy group and the N–N bond, can be mentioned. Indeed, according to NBO analysis, the energy of LpO(1) → σ*[N(1)–N(2)] orbital is equal to 11.32 or 10.18 kcal mol^{-1} for isolated cation or TS, respectively. Such a value of stereoelectronic interaction in part explains that the torsion angles C(1)–N(1)–N(2)–O(1) in a crystal (148.8°) and an isolated molecule (145.6°) are almost equal.

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References

1 (*a*) D. A. Lenev, K. A. Lyssenko, D. G. Golovanov, V. Buss and R. G. Kostyanovsky, *Chem. Eur. J.*, 2006, DOI: 10.1002/chem.200501532; (*b*) R. G. Kostyanovsky, O. R. Malyshev, K. A. Lyssenko, Yu. A. Strelenko, G. K. Kadorkina, V. R. Kostyanovsky, O. G. Nabiev and I. V. Fedyanin, *Mendeleev Commun.*, 2004, 315.

2 R. G. Kostyanovsky, V. F. Rudchenko, V. G. Shtamburg, I. I. Chervin, and S. S. Nasibov, *Tetrahedron*, 1981, **37**, 4245.

3 V. G. Shtamburg, E. A. Klots, A. P. Pleshkova, V. I. Avramenko, S. P. Ivonin, A. V. Tsygankov and R. G. Kostyanovsky, *Izv. Akad. Nauk, Ser. Khim.*, 2003, 2132 (*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 2251).

4 V. F. Rudchenko, V. I. Shevchenko and R. G. Kostyanovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1986, 598 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1986, **35**, 543).

5 (*a*) M. Buccigross, S. A. Glover, J. P. Hammond and C. A. Rowbottom, *Aust. J. Chem.*, 1995, **48**, 353; (*b*) S. A. Glover, *Tetrahedron*, 1998, **54**, 7229.

6 V. G. Shtamburg, A. P. Pleshkova, V. N. Serdiuk and S. P. Ivonin, *Zh. Org. Khim.*, 1999, **35**, 1120 (*Russ. J. Org. Chem.*, 1999, **35**, 1096).

7 J. J. Campbell and S. A. Glover, *J. Chem. Soc., Perkin Trans. 2*, 1992, 1661.

8 (*a*) J. J. Campbell and S. A. Glover, *Chem. Res. (S)*, 1999, **8**, 474; (*b*) J. J. Campbell and S. A. Glover, *Chem. Res. (M)*, 1999, **8**, 2075.

9 S. A. Glover and G. Mo, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1729.

10 S. A. Glover and A. Rauk, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1740.

11 A. M. Bonin, S. A. Glover and G. P. Hammond, *J. Org. Chem.*, 1998, **63**, 9684.

12 V. G. Shtamburg, A. V. Tsygankov, E. A. Klots and R. G. Kostyanovsky, *Mendeleev Commun.*, 2004, 208.

13 (*a*) V. G. Shtamburg, V. F. Rudchenko, S. S. Nasibov, I. I. Chervin and R. G. Kostyanovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1981, 2327 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1981, **30**, 1914); (*b*) V. F. Rudchenko, S. M. Ignatov, V. S. Nosova, I. I. Chervin and R. G. Kostyanovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1986, 2272 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1986, **35**, 2076).

14 (*a*) R. G. Kostyanovsky, V. Schurig, K. A. Lyssenko, O. Trapp, G. K. Kadorkina, V. R. Kostyanovsky and B. B. Averkiev, *Mendeleev Commun.*, 2004, 306; (*b*) R. G. Kostyanovsky, V. F. Rudchenko, O. A. D'yachenko, I. I. Chervin, A. B. Zolotoi and L. O. Atovmyan, *Tetrahedron*, 1979, **35**, 213.

15 (*a*) G. V. Shustov, A. B. Zolotoi and R. G. Kostyanovsky, *Tetrahedron*, 1982, **38**, 2319; (*b*) A. B. Zolotoi, O. A. D'yachenko, I. I. Chervin, V. F. Rudchenko, L. O. Atovmyan and R. G. Kostyanovsky, *Khim. Geterotsikl. Soedin.*, 1985, 1341 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1985, **21**, 1098].

16 (*a*) M. Yu. Antipin, Yu. T. Struchkov, I. F. Shishkov, A. V. Golubinsky, T. L. Elfimova, L. V. Vilkov, A. A. Bredikhin, A. N. Vereshchagin, S. M. Ignatov, V. F. Rudchenko and R. G. Kostyanovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1986, 2235 (*Chem. Abstr.*, 1987, **107**, 175223e); (*b*) M. Yu. Antipin, Yu. T. Struchkov, V. F. Rudchenko, S. M. Ignatov and R. G. Kostyanovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 1825 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 1672).

17 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, *Gaussian 98, Revision A.9*, Gaussian, Inc., Pittsburgh PA, 1998.

¶ DFT calculations of **1c** and its transition state were performed with the Gaussian 98 program package[17] at the B3PW91/6-31G* level of theory. As convergence criteria, the normal threshold limits of 2×10^{-6} and 6×10^{-6} were applied for the maximum force and displacement, respectively. To enhance the B3LYP calculation accuracy, the pruned (99590) grid was used.

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