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1-Alkoxyamino-4-dimethylaminopyridinium derivatives as new representatives of O–N–N$^+$ geminal systems and their structure[†]

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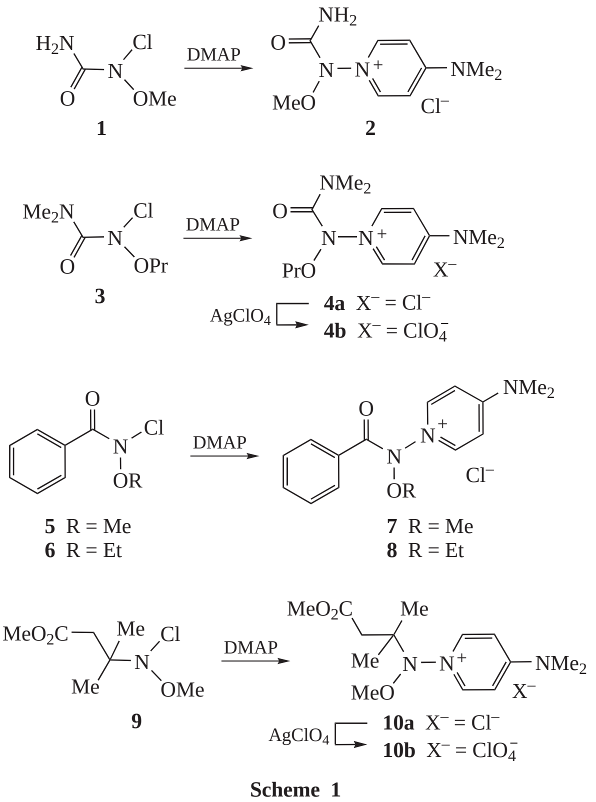
_N_-Alkoxy-_N_-(4-dimethylaminopyridin-1-ium-1-yl)-substituted ureas, benzamides and _N_-_tert_-alkylamines were prepared by the reaction of the corresponding (_N_-chloro-_N_-alkoxy)amino compounds with 4-dimethylaminopyridine. The XRD study of _N_-alkoxy-_N_-(4-dimethylaminopyridin-1-ium-1-yl)ureas has revealed the high pyramidality of the central nitrogen atom in O–N–N$^+$ geminal system.

As shown by Glover and co-workers,[2] *N*-acyloxy-*N*-alkoxybenzamides are the first example of 'anomeric' amides with strong pyramidal amide nitrogen. In *N*-acyloxy-*N*-alkoxybenzamides, N–OC(O)R bond is to some some extent longer and is destabilized due to anomeric effect $n_{\mathrm{O(Alk)}} \rightarrow \sigma^*_{\mathrm{N–OC(O)R}}$.[2(*a*)–(*e*)] Recently we reported on new types of anomeric amides, such as *N*-acyloxy-*N*-alkoxyureas,[3(*a*)–(*c*)] *N*-acyloxy-*N*-alkoxycarbamates,[3(*a*)] *N*-chloro-*N*-alkoxyureas,[3(*c*),(*d*)] *N*,*N*-dialkoxyureas[3(*b*)] and *N*-alkoxy-*N*-(1-pyridin-1-ium-1-yl)urea salts.[3(*b*)] XRD study of all these 'anomeric' ureas and carbamates revealed some elongation of N–X [X = Cl, OC(O)R, OAlk, $N^+C_5H_5$] bonds and some shortening of N–OAlk bonds caused by the anomeric effect $n_{\mathrm{O(Alk)}} \rightarrow \sigma^*_{\mathrm{N–X}}$.[3] In all kinds of such O–N–X geminal systems, the amide nitrogen atom possesses strongly pyramidal configuration.[3] The biological activity of *N*-acyloxy-*N*-alkoxyamides[2(*c*),4–6] is based on the susceptibility of acyloxy group to substitution by N-nucleophiles. In anomeric *N*–X–*N*-alkoxyureas (X = Cl, OAc, $N^+C_5H_5$) similar nucleophilic substitution at the nitrogen proceeds also readily.[3(*b*),(*d*),7] However, most of *N*–X–*N*-alkoxyureas is water-insoluble, or sometimes their hydrolysis took place. *N*-Methoxy-*N*-(1-pyridin-1-ium-1-yl)urea salts[3(*b*)] are soluble in water, however, these compounds are unstable and would decompose quickly even at room temperature. We investigated reaction of *N*-chloro-*N*-alkoxyureas **1**, **3**,[3(*d*),7] *N*-chloro-*N*-alkoxybenzamides **5**, **6**[2(*c*)] and *N*-chloro-*N*-methoxy-*N*-*tert*-alkylamine **9**[8] with 4-dimethylaminopyridine (DMAP) aiming to obtain the stable *N*-alkoxy-*N*-(pyridin-1-ium-1-yl)urea salts and related compounds (Scheme 1).



Scheme 1

In the reaction of compounds **1**, **3** with DMAP the stable *N*-alkoxy-*N*-(4-dimethylaminopyridin-1-ium-1-yl)urea chlorides **2**, **4a**[‡] were selectively formed. As chloride **4a** is hygroscopic, it was converted into perchlorate **4b**. The structures of the urea salts **2** and **4b** have been investigated by XRD analysis (Figures 1 and 2).[§] Compounds **5**, **6** yield *N*-alkoxy-*N*-(4-dimethylamino-pyridin-1-ium-1-yl)benzamide chlorides **7**, **8** [characterized by ^{1}H NMR spectra (and MS for **8**)][‡] which are the first examples of

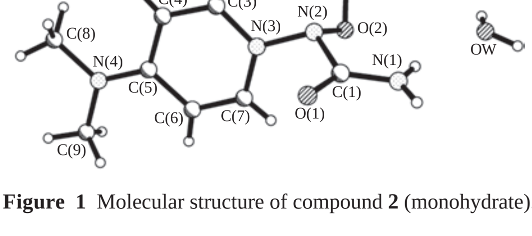


Figure 1 Molecular structure of compound **2** (monohydrate).

[†] Geminal systems. Part 61; for the previous communication, see ref. 1.

[‡] For synthetic procedures and characteristics of compounds **2**, **4a**,**b**, **5**, **7**, **8**, **10a**,**b** and **13**, see Online Supplementary Materials.

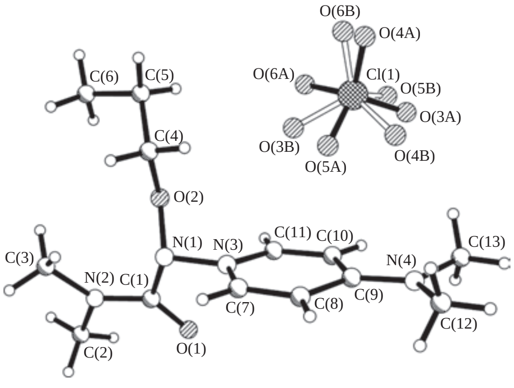


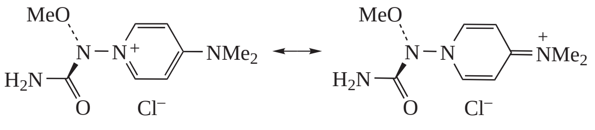
Figure 2 Molecular structure of compound **4b**.

relatively stable primary products of nucleophilic substitution at nitrogen by N-nucleophiles in *N*-chloro-*N*-alkoxybenzamides.[2(*a*),9] Compounds **7** and **8** are stable for some time at –27 °C but decompose significantly on storing for 1 month at –5 °C. By the action of DMAP, *N*-chloro-*N*-methoxy-*N*-*tert*-alkylamine **9** selectively affords hygroscopic *N*-methoxy-*N*-(4-dimethylaminopyridin-1-ium-1-yl)-*N*-*tert*-alkylamine chloride **10a**, which was then converted into more stable perchlorate **10b**.[‡]

XRD studies of compound **2** (Figure 1) revealed that amide N(2) nitrogen is pyramidal. The sum of bond angles centered at this atom (Σß) is 332.7°, the deviation of N(2) atom from the plane bonded with N(2) atoms (h_N) is 0.440 Å. The nitrogen pyramidality degree in salt **2** is more comparable to that for *N*-methoxy-*N*-(pyridin-1-ium-1-yl)urea perchlorate (MPUP)[3(*b*)] (Σß = 333.9°, h_N = 0.429 Å). The electron lone pair (Lp) of N(2) atom is oriented in the plane of pyridine ring [the torsion angle LpN2–N(2)–N(3)–C(3) is 6°] as in the cases of *N*-methoxy-*N*-(pyridin-1-ium-1-yl)-*N*-*tert*-alkylamine perchlorate (MPAP)[10] and MPUP[3(*b*)] (27.3° and 0.2°, respectively). The conjugation between LpN2 and π-system of pyridine is impossible. The other nitrogen atoms in compound **2** have planar configuration: for N(3), N(1) and N(4) atoms Σß is equal 359.9, 360.0 and 360.0°, respectively.

LpN2 is oriented perpendicular in respect to the N(1)–C(1)–O(1)–N(2) plane (angle 94°), which is favorable condition for *n*–π conjugation. Note that the N(2)–C(1) bond [1.450(2) Å] is much longer than N(1)–C(1) bond [1.310(2) Å]. The same difference in the amide N–C bond lengths takes place in MPUP.[3(*b*)] It results from different degrees of C(1)=O(1) conjugation with sp^2 hybridized N(1) and sp^3 hybridized N(2) atoms.

In compound **2**, the N(2)–N(3)$^+$ bond is somewhat shorter [1.413(2) Å] than N–N$^+$ bond in MPUP (1.4254 Å).[3(*b*)] On the other hand, the N(2)–O(2)(Me) bond is somewhat longer [1.411(2) Å] than N–OMe bond in MPUP (1.3999 Å).[3(*b*)] Probably, it is a sequence of the diminishing action of the $n_{O(Me)} \rightarrow \sigma^*_{N-N^+}$ anomeric effect caused by 4-Me$_2$N substituent in pyridine moiety. The observed altering of the pyridine bonds conforms to this assumption. In the pyridine ring, the bonds C(5)–C(4) [1.425(2) Å], C(5)–C(6) [1.426(2) Å], N(3)–C(7) [1.361(2) Å] and N(3)–C(3) [1.345(2) Å] are elongated, whereas C(4)–C(3) [1.353(3) Å] and C(6)–C(7) [1.341(2) Å] bonds are shortened in comparison with average bond lengths of pyridine (1.379, 1.337 and 1.380 Å, respectively[11]). The N(4)–C(5) bond (1.324 Å) is shorter than the C_{arom}–N bond (1.371 Å), whereas the length of N(4)–C(5) bond is close to that of N=C bond (1.316 Å). All this data may be regarded as the evidence of certain contribution of quinonoid structure **2A** (Scheme 2).



2 **2A**

Scheme 2

The methoxy substituent is turned relatively to the amide group plane [the torsion angle C(1)–N(2)–C(2)–O(2) is –140.2(2)°]. Such orientation of MeO group is stabilized by attractive intermolecular shortened contact H···O 2.28 Å (the sum of the van der Waals radii is 2.46 Å[12]).

XRD study of perchlorate **4b** (Figure 2) demonstrated that amide nitrogen N(1) is strongly pyramidal: Σß is 324.22°, h_N is 0.509(2) Å. This degree of pyramidality is somewhat similar to that of amine nitrogen in *N*-alkoxy-*N*-(pyridin-1-ium-1-yl)-*N*-*tert*-alkylamine perchlorate[10] (Σß is 322.8°, h_N is 0.531 Å). On the other hand, N(1) pyramidality degree in compound **4b** is close to the nitrogen pyramidality degree in *N*-acyloxy-*N*-alkoxybenzamides (Σß are 323.51°, 324.14°)[2(*b*)] and *N*-(4-chlorobenzoyloxy)-*N*-butoxyurea (Σß = 323.8° and h_N = 0.511 Å).[3(*b*)] Probably this increase in amide nitrogen pyramidality degree in urea **4b** in comparison with urea **2** and MPUP[3(*b*)] is caused by the lower electronegativity of *N*,*N*-dimethylcarbamoyl substituent in comparison with the carbamoyl one.[2(*a*)]

The Lp of N(1) lies in the plane of pyridine ring [the torsion angle C(7)–N(3)–N(1)–LpN1 is 10.6°]. This orientation of LpN1 is favourable for anomeric effect $n_{N(1)} \rightarrow \sigma^*_{C(7)-C(8)}$ which causes the certain elongation of C(7)–C(8) bond [1.349(3) Å] in comparison with C(10)–C(11) bond [1.334(3) Å].

Owing to the presence of the dimethylcarbamoyl substituent in urea **4b** the N(1)–N(3)$^+$ bond is elongated to 1.425(3) Å compared to N–N$^+$ bond in MPUP.[3(*b*)] Probably the decrease of electronegativity of the third substituent at the pyramidal nitrogen [Me$_2$NC(O) group] favours to anomeric effect[2(*a*)] $n_{O(2)} \rightarrow \sigma^*_{N(1)-N(3)^+}$ in spite of donor action of NMe$_2$ group in pyridine ring. As in urea **2**, the bonds of the pyridine ring in urea **4b** are substantially deformed. The C(8)–C(9), C(9)–C(10), N(3)–C(11) and N(3)–C(7) bonds are elongated to 1.430(3), 1.413(3), 1.366(3) and 1.346(3) Å, respectively. The C(7)–C(8) and C(10)–C(11) bonds are shortened to 1.349(3) and 1.334(3) Å, respectively. Me$_2$N(4)–C(9) bond is shortened to 1.333(3) Å. It is the evidence of the positive charge partial localization on N(4). The quinonoid structure of ureas **2**, **4** and amide **7** is confirmed by the presence of the absorption bands of C=N$^+$(Me$_2$) group in their IR spectra [1628 (**2**), 1645 (**4a**) and 1643 cm^{-1} (**7**)]. In these compounds, the infrared carbonyl absorption is 'ester-like' and is typical of anomeric amides.[2(*a*)]

The N–C amide bonds of urea **4b** are very different. The length of N(1)–C(1) bond is 1.465(3) Å, the N(2)–C(1) bond is shorter [1.324(3) Å]. Like in urea **2**, this results from different

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[§] *Crystal data for* **2**. Crystals were grown from MeCN–CHCl$_3$–Pr^{i}OH at –20 °C, [C$_9$H$_{15}$N$_4$O$_2$]$^+$Cl$^-$·H$_2$O, M = 264.72, monoclinic, space group $P2_1/n$, a = 7.7239(3), b = 19.9349(9) and c = 9.5096(3) Å, β = 113.96°, V = 1338.1(1) Å^3, F(000) = 560, d_{calc} = 1.314 g cm^{-1}, Z = 4, μ = 0.289 mm^{-1}.

Crystal data for **4b**: crystals were grown from CH$_2$Cl$_2$–hexane at – 20 °C, [C$_{13}$H$_{23}$N$_4$O$_2$]$^+$[ClO$_4$]$^-$, M = 366.80, triclinic, space group $P\bar{1}$, a = 7.9504(6), b = 10.5513(9) and c = 12.4015(8) Å, V = 936.11(13) Å^3, F(000) = 388, d_{calc} = 1.301 g cm^{-1}, Z = 2, μ = 0.238 mm^{-1}.

Crystal data for **10b**: crystals were grown from CH$_2$Cl$_2$ at –20 °C, [C$_{14}$H$_{24}$N$_3$O$_3$]$^+$[ClO$_4$]$^-$, M = 382.81, monoclinic, space group $P2_1/c$, a = = 8.0747(15), b = 22.202(3) and c = 10.3732(16) Å, β = 98.780(19)°, V = 1837.9(5) Å^3, F(000) = 808, d_{calc} = 1.38 g cm^{-1}, Z = 4, μ = 0.25 mm^{-1}.

For details of X-ray experimental procedure, see Online Supplementary Materials.

CCDC 756713, 756714 and 849018 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2012.

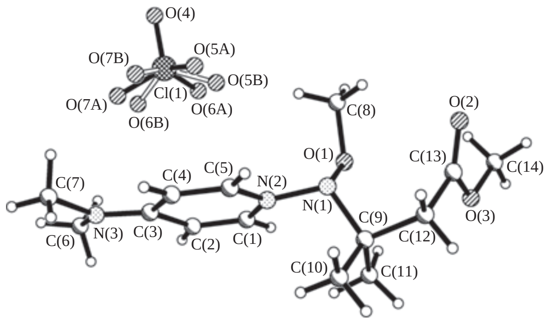
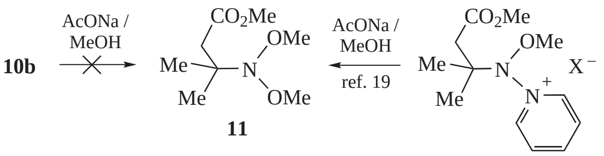


Figure 3 Molecular structure of compound **10b**.

degrees of carbonyl C(1)=O(1) conjugation with sp^3 hybridized N(1) and sp^2 hybridized N(2) nitrogen atoms.

The Pr–ON bond has *sc*-orientation relative to the LpN1 [the torsion angle C(7)–O(2)–N(1)–LpN1 is 37.4°], the PrO substituent has *ap-sc*-conformation [N(1)–O(2)–C(4)–C(5), –176.5(2)° and O(2)–C(4)–C(5)–C(6), 66.4(4)°]. The carbonyl group C(1)=O(1) is coplanar to N(1)–N(3)$^+$ bond [N(3)–N(1)–C(1)–O(1) is –4.6(3)°].

XRD study of compound **10b** (Figure 3)[§] revealed that nitrogen N(1) pyramidality degree [Σß = 325.7°, h_N = 0.507(2) Å] is lower than that in MPAP.[10] The N(1)–N(2)$^+$ bond is shorter [1.4454(19) Å] than N–N$^+$ bond in MPAP (1.466 Å).[10] And *vise versa*, the N(1)–O(1)Me bond is somewhat longer [1.4253(17) Å] than N–O(Me) bond in MPAP (1.414 Å).[10] As in the previous cases, these structure variations are probably caused by the diminished $n_{O(Me)}\rightarrow\sigma^*_{N-N^+}$ anomeric effect due to the donor action of 4-Me$_2$N group in the pyridine moiety. This lowering of N–N$^+$ bond destabilization due to $n_{O(Me)}\rightarrow\sigma^*_{N-N^+}$ anomeric effect makes the nucleophilic substitution at N(1) atom impossible. *N*-Methoxy-*N*-(pyridin-1-ium-1-yl)-*N*-*tert*-alkylamine salts may be easily converted into *N*,*N*-dimethoxy-*N*-*tert*-alkylamines **11** by the action of AcONa/MeOH.[10] However, perchlorate **10b** remained unchanged on keeping in AcONa/MeOH solution (Scheme 3). This is the first example of the nitrogen pyramidality degree substantial influence on chemical properties in 1-(*N*-alkoxy-*N*-*tert*-alkylamino)pyridinium salts.



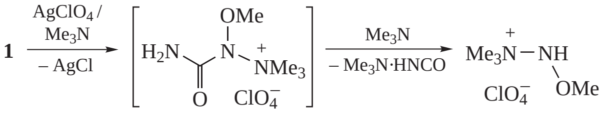
Scheme 3

As in previous cases, in salt **10b**, the pyridine bond deformation takes place. The C(1)–C(2) and C(4)–C(5) bonds are shortened to 1.344(2) and 1.341(2) Å, whereas the C(2)–C(3) and C(3)–C(4) bonds are elongated to 1.421(2) and 1.419(2) Å, respectively. The N(2)–C(1) and N(2)–C(5) bonds are also elongated to 1.356(2) and 1.348(2) Å, respectively. The length of N(3)–C(3) [1.327(2) Å] is close to that of N=C bond.

Analogously to salts **2** and **4**, in salt **10b** the Lp of N(1) lies in the plane of the pyridine ring [C(5)–N(2)–N(1)–LpN1 is 18°]. Probably, this orientation of Lp of pyramidal nitrogen is typical of all known salts of *N*-alkoxy-*N*-(pyridin-1-ium-1-yl)amino compounds.[3(*b*),10] *N*-Methoxy group in **10b** has *sc*-orientation relatively to the LpN1 [C(8)–O(1)–N(1)–LpN1 is –29°]. Compounds **10a**,**b** are stable and soluble in water.

Thus, the presence of 4-dimethylamino group in the pyridine moiety has important influence on the structure, stability and chemical properties of salts of *N*-alkoxy-*N*-(pyridin-1-ium-1-yl) derivatives of ureas, amides and amines.

Unlike the reaction with pyridines, compound **1** reacts with excess of trimethylamine in the presence of AgClO$_4$ yielding 1,1,1-trimethyl-2-methoxyhydrazinium perchlorate **13** (Scheme 4). Perhaps, the firstly formed labile *N*-trimethylammonio-*N*-methoxyurea perchlorate **12** eliminates HNCO by the action of excess trimethylamine giving the stable product **13**.



Scheme 4

In summary, the reaction of *N*-chloro-*N*-alkoxy derivatives of ureas, benzamides and *N*-*tert*-alkylamines with 4-dimethylaminopyridine is a simple route to the corresponding *N*-(4-dimethylaminopyridin-1-ium-1-yl) derivatives. In these compounds, the central nitrogen atom of the O–N–N$^+$ geminal system has high pyramidality degree, to this the presence of 4-dimethylamino group causes the substantial deformation of the pyridine ring.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.03.014.

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