

Structure and chemistry of a zwitterionic amine–aldehyde adduct

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The zwitterionic tetrahedral addition product **1** is the preferred form of the amino-aldehyde **4** in polar solvents and in the crystal, where a molecule of water controls the structure.

We describe the preparation and full structural characterisation of the stable zwitterionic addition product **1** of a tertiary amine to an aldehyde, with the tetrahedral N⁺–C–O[−] fragment built into a 1-azaadamantane cage.

The synthesis of the 1,3,5,7-tetramethyl-1-azaadamantane derivative **1** (Scheme 1) started from the known anhydride of Kemp's triacid.¹ Oxidation of the amino-alcohol **2** with Jones reagent followed by alkaline work-up gave **1** as a volatile but thermally stable crystalline compound, mp 63 °C, which was purified by vacuum sublimation. Remarkably, compound **1** was also obtained, as the sole product by reduction of (the anion of!) the amino acid **3** under basic conditions.[†]

A number of examples of comparable intramolecular N...C=O interactions have been reported in the literature.² Careful examination of the crystal structures of a selection of such systems led to the definition of the Bürgi–Dunitz angle,³ which identifies the preferred trajectory for the addition of an amine nitrogen to a carbonyl group. These structures all involve ketone C=O groups, the additional constraint being necessary to hold the C=O and amino groups together in productive conformations and orientations. In the case of **1**, this interaction is particularly efficient in the conformation **4a** of the aminoaldehyde shown in Scheme 2: more important, C–N bond formation produces the adamantane structure, thermodynamically highly stable compared with any alternative conformation, such as **4b** (Scheme 2).

We can find only one published (though neglected) example involving such a covalent tertiary amine–aldehyde interaction. 3,3-Dimethyl-4-dimethylaminobutanal **5** is clearly an aldehyde

in solution in CDCl₃, showing the expected low field proton signal, at δ 9.62: but in D₂O the corresponding signal is at δ 5.43, consistent with a predominant cyclic structure **6**.⁴

These reactions (**4** \rightleftharpoons **1**, **5** \rightleftharpoons **6**) involve aminoaldehydes, with normal CH=O and tertiary amino groups but limited conformational flexibility, in equilibrium with cyclic forms in which the new N–C bond of the N⁺–C–O[−] system will be lengthened, and the C–O[−] bond shortened by a strong $n_{\text{O}} \rightarrow \sigma^*_{\text{C-N}^+}$ interaction (the generalised anomeric effect.^{5,6} The degree of C–N bond formation is of special interest, and will be determined by the intrinsic structural preferences of the N⁺–C–O[−] group and of the ring system which holds it together, as well as the properties of the medium. The crystal structure (Fig. 1)[‡] shows a molecule with C–N bond formation well-advanced, and holds clues to some remarkable properties of compound **1**.

The former aldehyde carbon centre is tetrahedral in **1**, with only the internal NCC angle (104.9°) differing by more than 1° from 109°28': the N–C–O angle (109.2°) is the closest to the tetrahedral value. The interatomic N–C distance is 1.624(2) Å, and the C–O bond length 1.312(2) Å, substantially longer and shorter, respectively, than typical C–N and C–O single bonds,

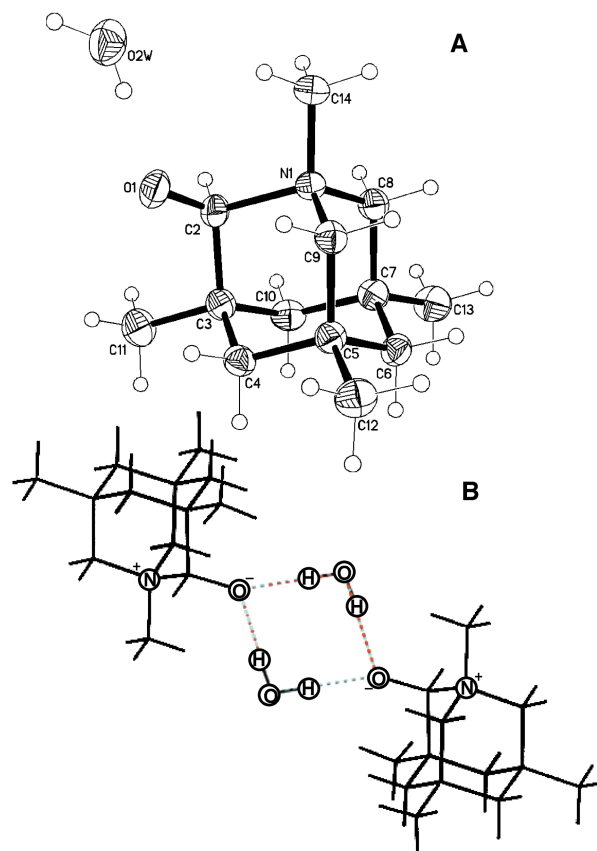
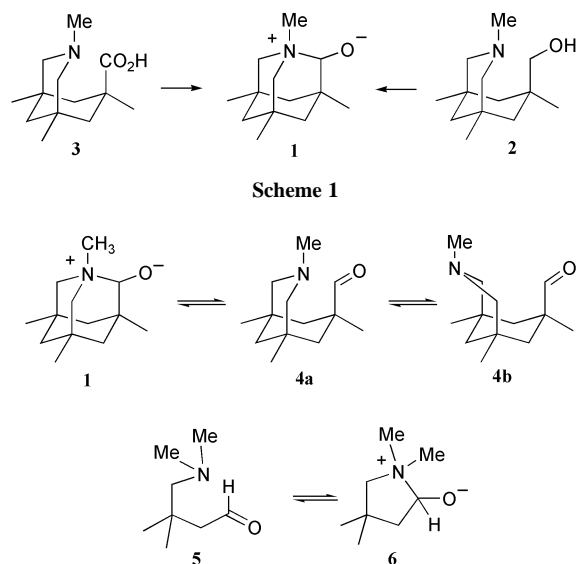
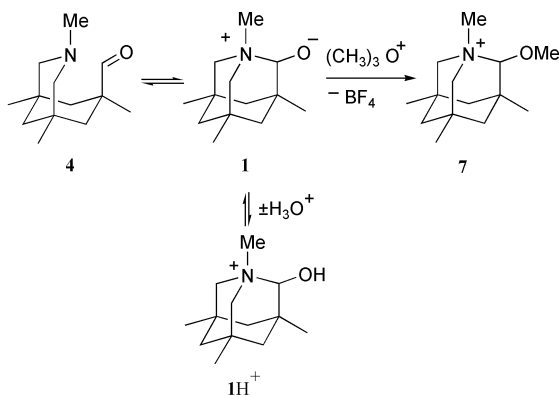


Fig. 1 (A) Molecular structure of **1**, showing displacement ellipsoids at the 30% probability level. (B) The dimer structure, showing the central H-bonding motif.[‡]

and consistent with the expected interactions of the generalised anomeric effect.

Of special interest is the way the system accommodates the developing charges, particularly the exposed O[−], of the zwitterionic structure **1**. The crystal structure shows the most stable arrangement under one particular set of conditions, in the crystal in the presence of one molecule of water of crystallisation. The zwitterion crystallises as a hydrogen-bonded dimer, centred on a planar rhombus (HOH angle 103.5°) of four linear (180 ± 3°) O–H...O hydrogen bonds of length 2.821(2) Å (Fig. 1(B)). This solvation motif is unprecedented for an alkoxide (we find no example in the Cambridge Structural Database), though not uncommon for sp²-hybridised oxygen: it is tempting to see this as a ‘memory’ of the mode of formation of **1** from **4**, and the torsion angle C–C–O–HOH is indeed close to *antiperiplanar*, at 164.5°; though this could also have a steric explanation. Remarkably this ‘hydrate’ is produced by sublimation (we tried to prepare anhydrous **1** by sublimation under dynamic vacuum in pre-dried glassware, but the monohydrate was still the only isolable product): which raises the interesting possibility that it actually sublimates as a molecular hydrate (rather than as neutral **4**). It is significant that under the conditions of FABS mass spectroscopy, the closest we have to an insight into a gas phase structure, the [M + H]⁺ signal is accompanied by a strong [2M + H]⁺ ion peak, indicative of molecular association in the gas phase. Semiempirical theoretical calculations on **1** (MNDO/PM3 wavefunction) in the gas phase optimised to form **4**, with C=O and C...N bond orders of 1.949 and 0.003, respectively. In contrast the same calculations employing solvation effects showed **1** to be the more stable geometry in water with C...O and C–N bond orders of 1.38 and 0.56, respectively.

In solution at ambient temperature the two forms are in rapid equilibrium. The ¹H NMR spectra of **1** in different solvents show sharp signals at chemical shifts presumably averaged over the two structures (**4** ⇌ **1**), with the apparent position of equilibrium depending on both medium and temperature. (The extent of C–N bond formation will also depend on the medium, with the more polar, more fully developed zwitterionic structure favoured by more polar media.) Most informative is the chemical shift of the aldehyde CHO ⇌ C(2)H proton. This is the lowest-field signal in the ¹H NMR spectrum, appearing as a singlet at δ 7.12 at 25 °C in CD₂Cl₂, closer to the expected shift of the CHO proton. The equilibrium shifts markedly in the direction of the more polar **1** in more polar solvents, the lowest-field signal moving to δ 5.12 in CD₃OD and δ 4.89 in (CD₃)₂SO. Protonation of **1** gives the conjugate acid **1**·H⁺ (Scheme 3; obtained as the tetrafluoroborate), which shows the C(2)H signal at δ 4.62 in CDCl₃. Potentiometric titration of the **1**·HBF₄ salt by base in water gives the a single pK_a = 10.093 ± 0.005 at 25 °C. This value falls in the region expected for such zwitterionic species, and can be compared with the value of 9.33 obtained by Hine and Kokesh⁷ for the parent compound Me₃N⁺CH₂OH.



Scheme 3

The lowest-field signal shifts upfield at lower temperatures, consistent with a significant dependence of the equilibrium constant on the temperature. At temperatures lower than about −60 °C equilibration becomes slow on the NMR time scale, and at −80 °C two separate signals are observed in the low field region, at δ 5.18 and 8.46; assigned to the C(2)H and CHO protons of **4** and **1**, respectively (the aliphatic region also shows two sets of signals corresponding to **1** and **4**). Analysis of the spectra gives approximate thermodynamic parameters for the equilibrium (**4** ⇌ **1**): ΔH° ~ −3.5 kcal (15 kJ) mol^{−1}, ΔS° ~ −12 cal (50 J) K^{−1} mol^{−1} (K = 0.79 at 25 °C in weakly polar CD₂Cl₂). For comparison, the equilibrium constant for the addition of diazabicyclooctane to 1,1,1-trifluoroacetophenone is also close to unity (in *d*₆-acetone),⁸ also because the (more favourable) enthalpy term is largely compensated by the (larger, negative) entropy of the addition reaction. The rate constant for the equilibration of **1** and **4**, based on the coalescence temperature of −60 °C for the CHO and C(2)H signals, is ~ 840 s^{−1}.

The chemical behaviour of the system confirms that that the equilibrium **1** ⇌ **4** (Scheme 2) lies well to the left in more polar solvents, and that the cyclic form **1** is not a fully developed zwitterion. On the one hand **1** is highly resistant to further oxidation or reduction: on the other, the nucleophilicity of the oxygen in **1** is very low in benzene: it does not react with methyl iodide or dimethyl sulfate, and we obtain the O-methylated product **7** only after treatment of **1** with (CH₃)₃O⁺BF₄[−] (Scheme 3).

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Notes and references

† The reduction used LiAlH₄ in diethyl ether. The tricyclic structure is confirmed by spectroscopic methods, and by the crystal structure (Fig. 1). The IR spectrum (KBr disc) shows no C=O stretching absorption; the 2-CH (‘aldehyde’) proton appears as a singlet at 6.61 ppm in the ¹H NMR spectrum (in CDCl₃), the ¹³C NMR shift of the 2-C is 130.0 ppm in (CD₃)₂SO; and the 2D HMBC spectrum (in (CD₃)₂SO) reveals a correlation through three bonds between the 2-CH and the N-CH₃ protons, unequivocal evidence for covalent bonding between N and C(2).

‡ Crystal data for **1**: C₁₃H₂₅NO₂, M = 227.34, monoclinic, space group C2/c (no. 15), a = 23.5697(18), b = 8.2191(4), c = 13.2975(11) Å, β = 95.489(3)°, U = 2564.2(3) Å³, Z = 8, λ(Mo-Kα) = 0.71073 Å, μ(Mo-Kα) = 0.078 mm^{−1}, 7716 reflections measured at 180(2) K using an Oxford Cryosystems Cryostream cooling apparatus, 2895 unique (R_{int} = 0.049); R₁ = 0.053, wR₂ = 0.129. The structure was solved with SHELXS-97 and refined with SHELXL-97 (G. M. Sheldrick University of Göttingen, 1997. CCDC 189673. See <http://www.rsc.org/suppdata/cc/b2/b206639d/> for crystallographic data in CIF or other electronic format).

§ Semi-empirical calculations were carried out using MOPAC implemented through Quantum Cache (Fujitsu Co.). Calculations started from the crystal structure of **1**, and were allowed to converge freely to an optimised (energy-minimised) structure.

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