Structural Correlations for Nucleophilic Addition to the C=O Group: The Solvation Angle

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Dedicated to Professor *Jack D. Dunitz* on the occasion of his 80th birthday

We report some new observations in *Bürgi–Dunitz* territory – structure–structure correlations for the addition of N nucleophiles to the C=O group. The amino aldehyde **1** exists predominantly in polar solvents, and exclusively in the crystal, as the carbonyl-addition structure **2**, but appears to demand hydrogen-bonding solvation as part of the process. In terms of C–O bond lengthening, the new system lies somewhere nearly halfway between an amino aldehyde and a stable quaternary ammonium aminal: we present the structure **2**·**Me** of the N^+–C–OMe derivative of **2** as an example. We have investigated the effects on the cyclisation equilibrium in this system of hydration, which is important, and of the degree of methylation of the azaadamantane skeleton, which – unexpectedly – is not. In terms of the reverse process, *i.e.*, breaking the C–N^+ bond: in each case, the bond is lengthened by ($n_{(O)}$–$\sigma^*_{(C-N)}$) electron-pair donation from the O-atom (the generalised anomeric effect, as in **2**·**Me** ↔ **3**, below) [4]. This effect is strongest when the O-atom is negatively charged, reduced by hydrogen-bonding, and minimised by alkylation.

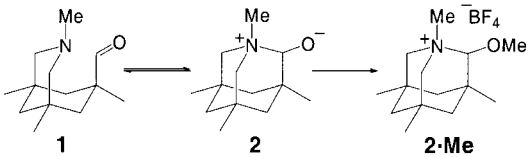
Introduction. – The work of the *Dunitz* school has had a major and lasting impact on the way we think about – and teach – some very fundamental chemistry. The idea that crystal structures – to a first approximation static representations of stable molecules – can provide important insights into reactivity is by now so familiar, and supported by so much evidence, that it no longer seems counterintuitive. We accept, for example, that the *Bürgi–Dunitz* angle defines the preferred trajectory of approach of a nucleophile as it adds to a C=O group, and, thus, contains fundamental information about the geometry of the orbital interactions involved in bond formation [1].

We have learned also that crystal structure correlations can illustrate, or even reveal, quite subtle conformational and basic stereoelectronic preferences in suitable systems [2]. If the relevant data set is large enough, it is generally a reasonable assumption that intramolecular and packing forces specific to individual structures will 'average out', so that small molecules at least adopt the same conformation in the crystal and in solution. For example, the conformational preferences determined by the anomeric effect are observed in detail in series of crystal structures [2]; making the leaving group XO^- better drives the conformations of benzylic systems ArCH(Me)–OX towards the conformation required for optimal π–σ^* overlap and subsequent cleavage [3], and the directionality of H-bonding to a C=O group can be related to the shape of the electron density in the nonbonding orbitals of sp^2-hybridised O-atom [4].

Bond lengths are the geometric parameters least susceptible to perturbation [5], and, so, the most likely to yield sensible correlations from a small data set. Thus, the

simple, linear correlation between the length of a bond C–OX and the rate at which it is cleaved, first observed for acetals containing the structural unit RO–C–OX, appears to be general for bonds Z–OX; where Z can be C, N or P (at least where conformations, and, thus, through-bond stereoelectronic interactions, do not change significantly across the series) [2]. We have called these relationships 'real' structure–reactivity correlations [6]: in contrast to the structure–reactivity correlations familiar to the physical organic chemist, which are typically linear free energy relationships, and correlate rate and equilibrium constants. We report here some new observations in this general area, involving – like the original observations of *Bürgi* and *Dunitz* – structure–structure correlations relevant to the addition of N nucleophiles to the C=O group.

We reported recently that the amino aldehyde **1** exists predominantly in polar solvents, and exclusively in the crystal, as the C=O addition structure **2** [7]. The thermodynamically stable adamantane unit provides an energy sink deep enough to accommodate the high-energy tetrahedral zwitterion. The crystal structure is unique in that it illustrates the addition of tertiary amine N-atom to an aldehyde group. (The structures studied in the classic investigations of *Bürgi* and *Dunitz* were all derived from ketones, the second C–C=O bond providing the additional constraint necessary to hold the two groups together productively.) We report here further details of our investigation, define more clearly the factors driving cyclisation, and show that compound **2**, and its methylated derivative **2** · **Me**, fit a structure correlation defined by the *Bürgi–Dunitz* series of amino ketones.



1 **2** **2·Me**

Results and Discussion. – *Crystal-Structure Correlations.* We first compare the structure of our amine–aldehyde adduct **2** with the series of amino ketones studied in the classic work of *Bürgi* and *Dunitz* [1]. We are not unmindful of an important caveat that we have articulated as follows: '*for most purposes evidence based on a single structure is basically anecdotal*' [2]. Not only is **2** a single compound, it is observed in the crystal '*under one particular set of conditions, in the crystal in the presence of one molecule of water of crystallization*' [7]. Calculations suggest that it would exist in the ring-opened form in the gas phase, and NMR evidence is consistent with increasing amounts of N–C bond-formation in more polar solvents [7]. So the detailed structure is expected to depend on the environment – in solution on the polarity of the solvent, and in the crystal on the presence or absence of water of crystallisation. This is what is observed.

The most convenient correlation for comparison, because our new system lacks the second C–C=O bond, is between the C–N and C–O bond lengths at C(2). *Fig. 1* shows the smooth curve, which correlates these bond lengths for the original data set of *Bürgi* and *Dunitz* (six – partially or fully – open circles) [1]. The point for compound **2** (filled circle) falls nicely on the same curve, and effectively fills a gap between amino

ketones with close N···C=O approach distances ($d_{(C-N)}$ greater than *ca.* 2 Å) and the two compounds with single N–C bonds slightly lengthened by the generalised anomeric effect. Points *A* and *B* of *Fig. 1* refer, respectively, to retusamine, with a fully protonated N^+–C–OH group (partial structure **A**; *c.f. Fig. 3*) [8], and the quaternary ammonium aminal group N^+–C–OMe of the mitomycin system [9]. Compound **2** is present in our crystal structure as the monohydrate, with the developing alkoxide O-atom stabilised by H-bonding to H_2O (part structure **2a**) [7]. For a further comparison, we have obtained the crystal structure (*Fig. 2*) of the quaternary ammonium aminal **2**·**Me** (obtained by alkylation of **2** – but only by using *Meerwein*'s reagent [7]).

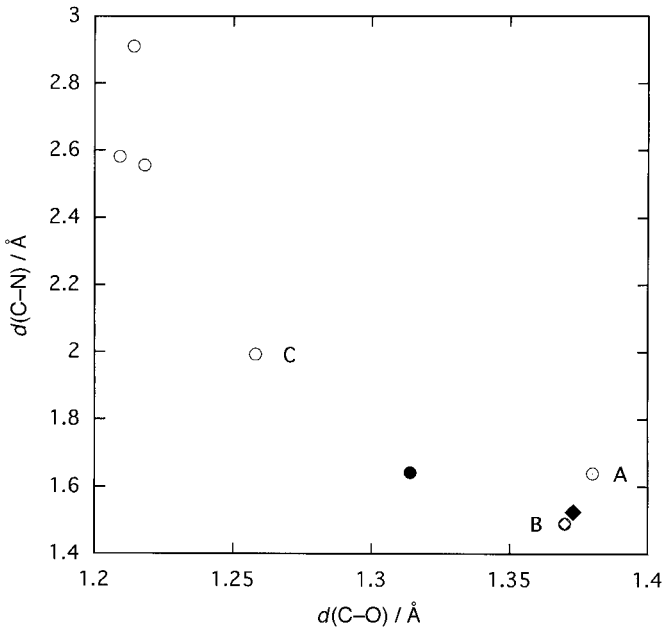


Fig. 1. *Correlation between C–N and C–O bond lengths at the former carbonyl centre for tetrahedral addition compounds derived from amino ketones* (circles, data from [1]; see the text) *and the amino aldehyde* (compound **2**, filled circle). The filled diamond shows the point for compound **2**·**Me**.

Closer inspection shows that the trend in the pattern of bond lengths represented by the smooth curve in *Fig. 1* is accompanied by increasing amounts of solvation of the developing alkoxide O-atom by H_2O. Only the three systems with $d_{(C-N)} > 2.5$ Å have no H_2O of crystallization. Clivorine (point *C*) in the crystal has a single H-bond from the developing alkoxide O-atom to a molecule of H_2O [10]: **2** has two, to two separate H_2O molecules [7]; while retusamine [8], as discussed, has a H-bonded OH group as shown in *Fig. 3* (partial structure **A**).

The systems represented by points lying at the bottom right hand corner of *Fig. 1* are best considered as quaternary ammonium aminals, with N acting as a potential leaving group. In each case, the C–N^+ bond is lengthened by electron-pair donation ($n_{(O)}$–$\sigma^*_{(C-N)}$) from the O-atom (the generalised anomeric effect, as in **2**·**Me** ↔ **5**; below) [4]. This effect is strongest when the O-atom is negatively charged, reduced by

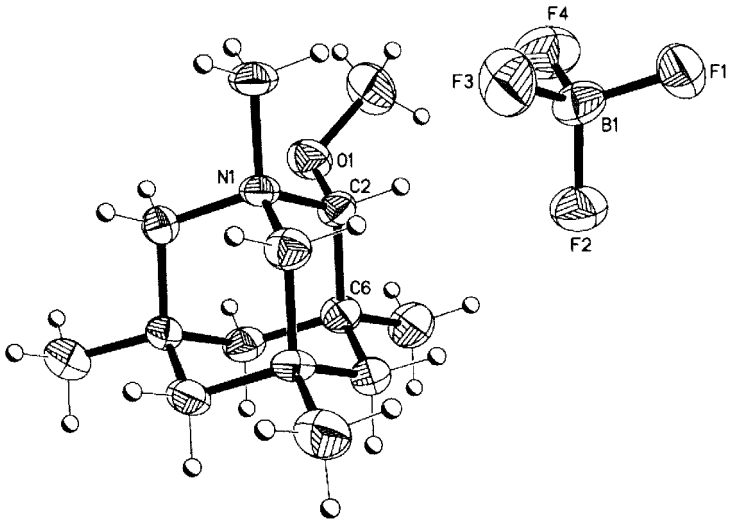
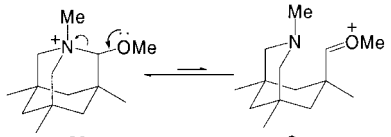


Fig. 2. *Molecular structure of* **2**·**Me** (tetrafluoroborate salt; ORTEP: ellipsoids are drawn at the 30% probability level and H-atoms represented as spheres of radius 0.12 Å. For details see the *Exper. Part*)

H-bonding, and minimised by alkylation. (The bond lengths of interest (*Fig. 1*, filled diamond) are almost identical to those of the same system in the mitomycin system (point *B*).)

Protonation (point *A*) is slightly less effective at reducing the electron-donor properties of the O-atom because the O–H bond is itself involved as a H-bond acceptor (partial structure **A**; *Fig. 3*) [8].

At first sight, it seems remarkable that the data points for **2**·**Me** (*Fig. 1*, filled diamond) and that for the mitomycin system (point *B*), representing the much 'tighter' RO–C–N^+ system, fall on the same curve as the zwitterionic species. In the case of **2**·**Me**, for example, the ring-opened system is the high-energy species **3** (not observed!). The explanation is clearly that the trend represented by the original smooth curve accommodates both the fundamental stereoelectronic effects involved in the addition of the amine N-atom to C=O and the (necessary) stabilization of the developing alkoxide anion by increasingly strong bonding interactions. In the absence of these increasingly strong bonding interactions, the curve might look quite different. However, such speculation is of limited interest for the experimentalist because of the difficulty in obtaining crystals containing naked oxyanions. This solvation problem is discussed in more detail below.



2·Me **3**

Factors Driving the Cyclisation Reaction. We identified previously [7][11] two factors (in addition to the stability of the azaadamantane) that appear to be important in controlling the extent of cyclisation of **1**⇌**2**: the array of ring-Me groups on the adamantane skeleton, and H-bonding hydration of the alkoxide O-atom of **2**.

We have spent considerable time and effort on attempts to obtain anhydrous **2**. We appear to have succeeded (see the *Exper. Part*) in three successive sublimations to give a sample with microanalysis consistent with the parent molecular formula. A second, pure sample gave a microanalysis consistent with a hemihydrate. However, the only crystals we could obtain suitable for X-ray structure determination, by sublimation, turned out to be the monohydrate of **2**. This system crystallises as a tight dimer, with the alkoxide O-atoms H-bonded to two H_2O molecules shown in *Fig. 3*. [7]. This species appears to retain its H_2O even on sublimation under vacuum, and we are all but convinced that the monohydrate actually sublimes as the dimer, without dissociating [7].

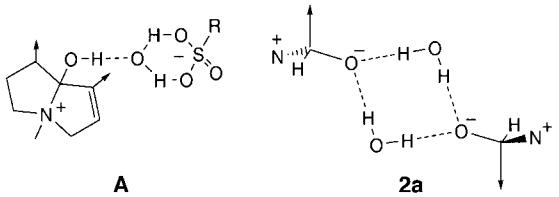


Fig. 3. *Successive stages of hydration of the developing alkoxide anion formed by the addition of amine N-atom to C=O.* Partial structures of retusamine [8] and the dimer of **2** [7], **A** and **2a**, respectively.

We know, qualitatively at least, that cyclisation is favored in polar solvents [7], which will stabilise selectively the charged, zwitterionic species **2**; and we may assume that H-bond-donor solvents will be particularly effective, since the positive charge of **2** is shielded in the quaternary ammonium system. This, and the behaviour of the various samples we have obtained, suggests that the cyclisation of **1**, driven initially by the stability of the tricyclic structure, generates the 'near-alkoxide' **2**, which is itself so powerfully stabilised by H-bonding solvation that it behaves, in effect, as a dehydrating agent, readily absorbing moisture from the atmosphere or, when dissolved, from the solvent. We observed the same effect previously when trying to find a structur-e–reactivity correlation for the dianions of phosphate monoesters. Always the ester found H_2O from somewhere before crystallising [12].

This analysis suggested the following experiments. It is possible to observe the cyclisation equilibrium by NMR, and we have followed the reaction as a function of temperature under two sets of conditions in 'dry' CD_2Cl_2. The samples of **1**⇌**2** were our best 'anhydrous' sample and the well-characterised hemihydrate, which adds a controlled amount of H_2O. Although the solvent was carefully dried, it is well-known that it can be difficult to remove the last traces of moisture. So, in a third series of measurements, we used CD_2Cl_2 saturated with H_2O (*ca.* 6 equiv. with respect to solute **1**⇌**2**). The results are summarised in *Table 1.*

At ambient temperatures the proton H–C(2) is in fast exchange, and the equilibrium constant can be calculated from the average chemical shift. (The shifts of the aldehyde and aminal H-atoms are based on their separate signals, observed at

Table 1. *Effect of H_2O on the Cyclisation Equilibrium* **1** ⇌ **2**

Anhydrous compound[a])				Hemi-hydrate (0.5 H_2O)[b])			In the presence of an excess of H_2O (*ca.* 6 equiv.)[c])		
T/°	δ_{obs}/ppm C*H*O/H–C(2) averaged peak	% cyclic form **2**	K_{obs}	δ_{obs}/ppm C*H*O/H–C(2) averaged peak	% cyclic form **2**	K_{obs}	δ_{obs}/ppm C*H*O/H–C(2) averaged peak	% cyclic form **2**	K_{obs}
30				6.85	61	1.56	6.13	68	2.13
25	7.12	44	0.78						
8				6.52	68	2.13	5.47	81	4.26
0	6.54	59.5	1.47						
–13				6.22	75	3.00	5.12	88	7.33
–20	6.1	71	2.44						
–34				5.89	82	4.56	4.96	91	10.1
–40	5.72	81	4.26						
–55				5.61	89	8.09	4.83	94	15.7
–77				5.44	92	11.5	4.69	96	24.00
	ΔH° –15.6 kJ/mol ΔS° –52 J/K/mol			ΔH° –9.1 kJ/mol ΔS° –26 J/K/mol			ΔH° –10.6 kJ/mol ΔS° –(20–28) J/K/mol		

[a]) Chemical shifts used for the C*H*O and aminal H–C(2) protons: 9.1 and 5.1; [b]) 9.6 and 5.1; [c]) 9.6 and 4.5 ppm.

temperatures below *ca.* –60°). The data show that cyclisation is more favorable at lower temperatures: only under the driest conditions is there less than 50% cyclisation, and then only at the highest temperature (25°) used. The extent of cyclisation also increases, as expected, in the presence of increasing amounts of H_2O. However, the relatively small difference between the 'anhydrous' sample and the hemihydrate suggests that even the dried solvent contains trace amounts of H_2O.

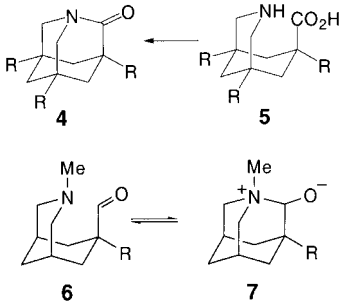
The variable-temperature data in *Table 1* allow calculation of the thermodynamic parameters for the cyclisation of **1** to **2**. The results (*Table 1*) show that the observed variation in equilibrium constant with H_2O content represents a fine balance between enthalpy and entropy control. That the enthalpy change becomes less favorable as the H_2O content of the medium increases is unexpected, and we can offer no simple explanation beyond noting that the differences are small, and such parameters, especially the entropy change, are often difficult to interpret when solvent reorganisation is a major part of the reaction. The entropy change for the cyclisation itself is expected to be close to zero.

Our earlier observations suggested that the three ring Me-groups should make a significant contribution to the high thermodynamic stability of the cyclic forms of systems like **1**, with aldehyde or carboxylic acid-derived groups held in close proximity to the tertiary amino group. Thus, we could not make the twisted amide **4** (R = H), by sublimation of the unsubstituted aminoacid **5** (R = H), which works well for the trimethyl system **5** (R = Me): similarly the MeO-exchange reaction of the corresponding methyl esters, catalyzed by the MeN group [11] is fastest for the trimethyl compound [13].

This all seems intuitively reasonable: single alkyl group substitution and especially the geminal-dialkyl effect are well-known to favor ring formation in a wide range of systems [14]. To test this proposition more quantitatively in our unusual, conforma-

Table 2. *Effect of C*–Me *Groups on the Cyclisation Equilibria* **1** ⇌ **2** *and* **6** ⇌ **7** (R = Me and R = H).

T/°C	Compound **2**				Compound **7** (R = Me)				Compound **7** (R = H)			
	δ/ppm		% cyclised	K_{obs}	δ/ppm		% cyclised	K_{obs}	δ/ppm		% cyclised	K_{obs}
	C*H*O	H–C(2)			C*H*O	H–C(2)			C*H*O	H–C(2)		
25		7.12	44	0.78		6.74	46	0.85		7.07	55	1.22
0		6.54	59.5	1.47		5.79	72.5	2.63		6.29	73	2.7
–20		6.1	71	2.44		5.49	81	4.26		5.76	83	4.8
–40		5.72	81	4.26		5.22	85	5.66		5.69		
–60		5.42				5.07				5.19		
–70		5.31			7.50	4.99				5.13		
–75	8.39	5.20										
–80	8.46	5.18	86	6.14	7.91	4.95	76	3.16		5.10		
–90	8.58	5.11	88	7.33	8.07	4.9	79	3.76	9.23	5.08		
–100	8.68	5.1	88	7.33	8.22	4.87	80	4.00	9.34	5.04	83	4.8
–110					8.31	4.87	79	3.76	9.45	5.01	78	3.5
		ΔH° –15.6 kJ/mol				ΔH° –16.5 kJ/mol				ΔH° –19.1 kJ/mol		
		ΔS° –52 J/K/mol				ΔS° –57 J/K/mol				ΔS° –62 J/K/mol		



tionally rigid system, we have prepared two homologues of **2**: **6** ⇌ **7** (R = Me and R = H), with one and no ring-Me groups. Data for the equilibrium **6** ⇌ **7** (R = Me and R = H) are compared in *Table 2* with those from *Table 1* for the same process for **1** ⇌ **2**, using anhydrous samples and solvent CD_2Cl_2.

Here, too, the results are unexpected. The equilibrium constant at 0° scarcely changes across the series, from 1.45 for the fully methylated system **1** ⇌ **2** to 1.33 for the system lacking all three Me groups. It is clear that our earlier observations were misleading: the compounds with fewer Me groups are much more volatile and reactive than the original system **2**, but evidently no less ready, thermodynamically, to cyclise.

The full set of variable-temperature data do not fit the *Arrhenius* equation (K_{eq} levels out at lower temperatures (possibly because H_2O freezes out) so we can say little with confidence about the thermodynamics of cyclisation. However, the data points in the fast-exchange region show a reasonably linear dependence on $1/T$ and have been used to calculate the enthalpy and entropy changes shown in *Table 2*. Here, too, the free energy changes on cyclisation represent small differences between larger (but not large) values of ΔH° and $T\Delta S^\circ$; and, here too, the trend in ΔH° is unexpected, the enthalpy change becoming more favorable for the systems with fewer Me–C groups.

But the change is very small, and offset by (still smaller) changes in the entropy term. The main conclusion from *Table 2* is that the number of Me–C groups has very little effect on the cyclisation equilibrium. Such an effect would be expected to operate primarily on the enthalpy term, but neither enthalpy nor entropy term changes significantly with the number of Me groups. (This is at least consistent with structural changes that are similar in detail for the three equilibria, which presumably are also set up with similar degrees of hydration).

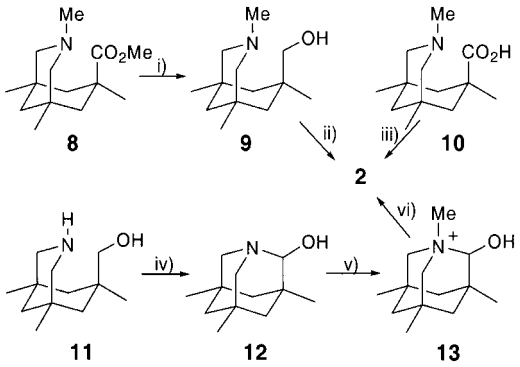
Experimental Part

General. Reagents were purified and dried as necessary by standard techniques. Melting points were determined with a *Büchi 510* melting-point apparatus and are uncorrected. Anal. TLC was carried out on pre-coated 0.25-mm thick *Merck 60 F_{254}* silica-gel plates, with visualization accomplished using I_2 vapour. IR Spectra were recorded on a *Perkin-Elmer 1310* spectrometer; the samples were prepared as solns. in the indicated solvents. One-dimensional NMR spectra and experiments (APT, NOE, low-temperature NMR measurements) were performed with the following instruments. *Bruker WM-400* (400 MHz for ^{1}H), *WP-100* (100 MHz for ^{1}H) or *Bruker WM-250* (250 MHz for ^{1}H). Two-dimensional experiments were performed on a *Bruker WM-500* (500 MHz for ^{1}H). The deuterated solvents indicated were used as reference or internal deuterium lock. Mass spectra were recorded in the University Chemical Laboratory, Cambridge. Elemental analyses were carried out by the staff of the Laboratory's Microanalytical Department.

Determination of Thermodynamic Parameters. ^{1}H-NMR Spectra were recorded for compounds **2** and **7** (R = Me and R = H) at different temperatures in CD_2Cl_2 (*ca.* 0.2M solns.). The percentage of the tricyclic forms in each case was calculated either from the position of the CHO/H–C(2) averaged peak (equilibration between the aldehydes and zwitterionic form fast on the NMR time scale), or by integrating the separate CHO and –C(2) peaks at lower temp. The data are summarized in *Tables 1* and *2*, and were used to calculate the thermodynamic parameters ΔH^0 and ΔS^0.

Synthesis. We have now generated the tetrahedral structure **2**, which we can prepare in at least three forms, by three different routes (*Scheme 1*). Two are detailed below.

Scheme 1



i) $LiAlH_4$ in Et_2O, reflux 24 h. ii) *Jones* reagent, sublimation. iii) $LiAlH_4$ in Et_2O, reflux. iv) *Jones* reagent. v) MeI in benzene. vi) Na_2CO_3, sublimation.

In each case, compound **2** produced by oxidation of **9**, reduction of **10** or removing the proton from **13**, was purified by sublimation. Careful sublimation of the compound as first produced gave a solid that appeared to be almost if not completely anhydrous. But all crystals obtained by sublimation that were suitable for X-ray structure determination turned out to be the monohydrate. Even three successive sublimations of the product from **13** gave only the hemihydrate.

1,3,5,7-Tetramethyl-1-azoniatricyclo[3.3.1.1^{3,7}]decan-2-olate (**2**). *Procedure A.* The amino alcohol **9** [11] (0.759 g, 3.6 mmol) was dissolved in acetone (30 ml) and *Jones*' reagent (prepared from 0.901 g of CrO_3, 0.85 ml of H_2SO_4 and 1.7 ml of H_2O) was added. The mixture was stirred for 2 h at r.t., then H_2O (75 ml) was added, followed by i-PrOH (20 ml) to destroy excess oxidant. After stirring for a further 0.5 h, a sat. soln. of Na_2CO_3 was added (care!) to bring the pH to *ca.* 9. The resulting mixture was evaporated, and the product was sublimed (80°, 0.05 mm) from the remained solid, then resublimed to give crystalline **2** (0.585 g, 77.9%).

Procedure B. To a suspension of the amino acid **10** [11] (0.1 mmol), $LiAlH_4$ (0.6 mmol) was added carefully, and the mixture was refluxed under Ar for 2 h. H_2O was added to quench the excess reducing agent, the product was extracted with CH_2Cl_2, the extract was dried over 3 g of K_2CO_3, evaporated without filtration, and the dry product was sublimed to give crystalline **2**, as before; 0.585 g (77 % yield).

Procedure C (not described), starting from the amino alcohol **11** [11], gave an identical product, M.p. 63°.

Data of **2**. IR: 2956, 2200, 1459, 1216. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.61 (*s*, H−C(2)); 2.74 (*d*, *J* = 10.83, H−C(8), H−C(8a)); 2.23 (*s*, MeN); 2.08 (*dd*, *J* = 10.83, 2.45, H_{eq}−C(8), H_{eq}−C(9)); 1.86 (*dd*, *J* = 12.6, 2.45, H_{eq}−C(4), H_{eq}−C(10)); 1.17 (*dt*, *J* = 11.8, 2.45, H_{eq}−C(6)); 1.095 (*dt*, *J* = 11.8, 2.45, H_{ax}−C(6)); 1.025 (*dd*, *J* = 12.6, 2.45, H_{ax}−C(4), H_{ax}−C(10)); 0.86 (*s*, Me−C(5), Me−C(7)); 0.85 (*s*, Me−C(3) (assigned from COSY, HMQC, HMBC). ^{13}C-NMR (100.59 MHz, $CDCl_3$): 130.0; 63.58; 47.46; 46.41; 44.29; 39.89; 31.07; 26.57; 26.32. EI-MS: 209 (4%, M^+) 208 (13%, $[M-H]^+$), 181 (68%, $[M-CO]^+$), 180 (51%, $[M-H-CO]^+$), 58 (100, $C_3H_5N^+$). FAB-MS (positive): 419 (18, $[2M+H]^+$), 210 (100, $[M+H]^+$), 93 (8), 58 (6). HR-FAB-MS: 210.18590 ($C_{13}H_{23}NO+H$; calc. 210.18578).

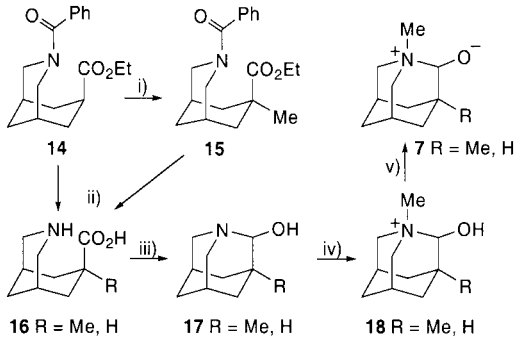
^{1}H-NMR Spectra of a triply-sublimed sample, taken in carefully dried solvents, showed additional peaks assigned to H_2O: a br. *s* (4.33 ppm) in CD_2Cl_2 and a *s* (1.56 ppm) in C_6D_6), which careful integration showed to be equivalent to 0.5 H_2O. Microanalysis was consistent with this conclusion: calc. for the hemihydrate: $C_{13}H_{23}NO\cdot 0.5\ H_2O$: C 71.51, H 11.08, N 6.42; found: C 71.91, H 11.08, N 6.42. The compound prepared by *Procedure A* had essentially the same spectral data, except that no H_2O peak is visible in the ^{1}H-NMR taken in CD_2Cl_2, and the analysis is most consistent with an anhydrous product: calc. for $C_{13}H_{23}NO$: C 74.59, H 11.02, N 6.69; found: C 73.55, H 11.07, N 6.64.

2-Methoxy-1,3,5,7-tetramethyl-1-azoniatricyclo[3.3.1.1^{3,7}]decane Tetrafluoroborate (**2**·**Me**). The methylation of the nominally alkoxide O-atom of **2** needed *Meerwein*'s reagent. The reaction was carried out in a flame-dried flask under Ar. Compound **2** (50 mg, 0.24 mmol) and trimethyloxonium tetrafluoroborate (42.4 mg, 0.29 mmol), were placed in the reaction flask, and dry CH_2Cl_2 (2 ml) was added. The mixture was stirred at r.t. for 1 h, then a new portion of the alkylating agent (10 mg, 0.07 mmol) was added. The mixture was stirred overnight, then treated with MeOH (5 ml). All volatile products were evaporated, and the solid residue was dissolved in CH_2Cl_2 (0.5 ml) and filtered. The product was precipitated from the filtrate soln. with Et_2O, filtered, and dried under vacuum to give crystals of **2**·**Me** (59.9 mg, 80.6%). M.p. 161–162°. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.47 (*s*, H−C(2)); 3.75 (*s*, MeO); 3.50 (*d*, *J* = 12.3, H_{eq}−C(9)); 3.13 (*d*, *J* = 12.3, H_{ax}−C(9)); 3.12 (*d*, *J* = 12.3, H_{eq}−C(8)); 2.99 (*s*, MeN); 2.80 (*d*, *J* = 12.3, H_{ax}−C(8)); 1.78 (*d*, *J* = 13.4, H_{eq}−C(6)); 1.64 (*d*, *J* = 13.09, H_{eq}−C(10)); 1.49 (*d*, *J* = 13.4, H_{eq}−C(4)); 1.26 (*d* + *d*, *J* = 13.4, H_{ax}−C(4), H_{ax}−C(6)); 1.01 (*d*, *J* = 13.09, H_{ax}−C(10)); 0.99 (*s*, Me−C(3)); 0.94 (*s*, Me); 0.93 (*s*, Me) (assigned from COSY, HMBC, HMQC). ^{13}C-NMR (100.59 MHz, $CDCl_3$): 101.46 (C(2)); 68.4 (C(9)); 63.5 (MeO); 61.9 (C(8)); 49.1 (MeN); 46.35 (C(6)); 45.70 (C(4)); 40.32 (C(10)); 36.45 (C(3)); 30.82 (C(5), C(7)); 25.55 (Me); 24.79 (Me); 23.73 (Me) (assigned from APT, HMBC, HMQC).

The preparation of the homologues of **2** lacking two or all three ring Me−C groups, required a different approach [15]. These systems (**6** ⇌ **7**, R = Me and H) were synthesized as outlined in *Scheme 2*. (There is a possibility of racemization of **14** during its hydrolysis to **16**. None was observed; the tricyclic product **17** was formed in high yield.)

Ethyl 3-Benzoyl-7-methyl-3-azabicyclo[3.3.1]nonane-7-carboxylate (**15**). A soln. of BuLi (17.6 ml of 1.6M (*ca.* 15%) in hexanes) was added to a soln. of i-Pr_2NH (3.67 ml in 200 ml of Et_2O) at 0° (ice-water bath). After stirring at 0° for *ca.* 1 h, a soln. of **14** [14] (3.9 g in 100 ml of Et_2O) was added dropwise, the ice bath was removed, and the soln. was stirred for a further 2 h at r.t. Freshly distilled Me_2SO_4 (2.65 ml) was carefully added to the stirred mixture. The reaction was exothermic, and a white precipitate formed immediately. Stirring was continued overnight, then the precipitate was filtered off. The filtrate was washed with H_2O, 5% NH_3 and 1N HCl, brine, then dried ($MgSO_4$) and evaporated. The colourless viscous oil obtained (3.4 g, 85% yield) was subjected to acid hydrolysis (aq. HBr) without further purification. The product could be purified by column chromatography (SiO_2; AcOEt/hexane 1:1): crystals. R_f 0.34 (SiO_2; AcOEt/hexane, 1:1). IR ($CDCl_3$): 2912, 2857 (CH); 1710 (C=O); 1621 (C=O); 1453 (Ph); 1416. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.48 (*dd*, *J* = 7.0, 1.7, 2 H_o); 7.36 (*m*, 2 H_m, 1 H_p); 4.47 (*d*, *J* = 13.7); 4.23 (*dq*, *J* = 7.07, 3.42, 1 H, MeCH_2); 4.13 (*dq*, *J* = 7.07, 3.42, 1 H,

Scheme 2



i) LDA, Et_2O, 0°, 2 h, then Me_2SO_4, 24 h. ii) 45% aq. HCl, reflux, 6 days. iii) $LiAlH_4$, Et_2O, reflux, 2 h. iv) MeI, benzene, 10 h. v) Na_2CO_3, sublimation.

MeCH_2); 3.63 (*d*, *J* = 12.4, H_{eq}–C(4)); 3.04 (*dd*, *J* = 14.1, 1.3, H_{eq}–C(4)); 3.02 (*dd*, *J* = 13.7, 4.1, H_{ax}–C(2)); 2.75 (*dd*, *J* = 12.4, 3.3, H_{ax}–(6)); 2.63 (*dd*, *J* = 14.2, 1.3, H_{eq}–C(8)); 2.12 (*s*, H–C(1)); 1.89 (*s*, H–C(5)); 1.61 (*m*, CH_2(9)); 1.47 (*dd*, *J* = 3.3, 14.7, H_{ax}–C(6)); 1.38 (*dd*, *J* = 14.2, 4.1, H_{ax}–C(8)); 1.26 (*t*, *J* = 7.08, *Me*CH_2); 1.15 (*s*, Me–C(7)). (Assignments were made on the basis of a DQF-COSY spectrum.) ^{13}C-NMR ($CDCl_3$, 100 MHz): 171.7; 173.3; 137.4; 128.8; 128.2; 126.7; 61.1; 52.5; 46.9; 40.8; 39.2; 38.6; 32.9; 32.3; 28.3; 27.6; 14.0. 1-D NOE Experiment (Me–(7)): H_{ax}–C(8) 11%; H_{eq}–C(8) 5%; no NOE between Me–C(7) and CH_2(9). EI-MS: 315 (27, M^+, 286 (4), 242 (6), 211 (14), 210 (100), 182 (5), 136 (10), 105 (85). EI-HR-MS: 315.18333 ($C_{19}H_{25}NO_3$; calc. 315.1834305).

7-Methyl-3-azabicyclo[3.3.1]nonane-7-carboxylic Acid (**16**; R = Me). Conc. aq. HBr soln. (*ca.* 45%, 20 ml) was added to **15** (3.5 g), and the mixture was stirred under reflux for 6 d. At the end of this period, all starting material had dissolved. The PhCOOH formed was removed by steam distillation, and the remaining mixture evaporated, the product extracted with H_2O (3 × 20 ml), the extract concentrated by evaporation to *ca.* 10 ml, and pH adjusted to 7.45. H_2O was removed under vacuum, MeOH (5 ml) was added and the soln. transferred to a sublimation apparatus, evaporated to dryness, then sublimed (60–120°, oil pump). The sublimed product was resublimed twice (60°, oil pump) to obtain *3-methyl-1-azatricyclo[3.3.1.1^{3,7}]decan-2-one* as white crystals possessing a strong camphor-like smell (0.75 g, 41.7% yield). This compound was dissolved in H_2O (20 ml), and the soln. was evaporated in high vacuum. Crystals of **16** (R = Me) obtained were dried in a desiccator over P_2O_5.

3-Methyl-1-azatricyclo[3.3.1.1^{3,7}]decan-2-ol (**17**; R = Me) and *1-Azatricyclo[3.3.1.1^{3,7}]decan-2-ol* (**17**; R = H) were prepared by $LiAlH_4$ reduction of **16** (R = Me and H, resp.), as described for **2** (*Procedure B*, above).

Data of **17** (R = Me): ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.54 (br. *s*, OH); 4.09 (*s*, H–C(2)); 3.45 (*d*, *J* = 12.5, 1 H, CH_2N); 2.67 (*d*, *J* = 12.5, 1 H, CH_2N); 3.18 (*d*, *J* = 13.4, 1 H, CH_2N); 2.95 (*d*, *J* = 13.4, 1 H, CH_2N); 2.07 (*d*, *J* = 12, H_{eq}–C(6)); 1.50–1.85 (*m*, 6 H); 1.26 (*d*, *J* = 12, H_{ax}–C(6)); 0.8 (*s*, Me–C(3)).

Data of **17** (R = H): ^{1}H-NME (400 MHz, $CDCl_3$): 6.27 (br., *s*, 1 H); 4.12 (*d*, 1 H); 3.09 (*m*, 2 H); 2.65 (*m*, 1 H); 2.35 (*m*, 1 H); 2.24 (*m*, 1 H); 1.89 (*dt*, *J* = 12.42, 2.06, 1 H); 1.33 (*dd*, *J* = 12.42, 2.77, 2 H); 1.20 (*d*, *J* = 12.42, 1 H); 1.15 (*dt*, *J* = 12.42, 2.06, 2 H); 0.83 (*dd*, *J* = 12.42, 2.77, 2 H).

2-Hydroxy-1,3-dimethyl-1-azoniatricyclo[3.3.1.1^{3,7}]decane iodide (**18**; R = Me) and *2-hydroxy-1-methyl-1-azoniatricyclo[3.3.1.1^{3,7}]decane iodide* (**18**, R = H) were synthesized from **17** (R = Me and H, resp.) by refluxing the starting compound (0.1 mmol) in benzene (20 ml) with an excess of MeI (1 mmol) for 10 h. After cooling the mixtures to r.t., the crystals formed were filtered and used in the next step without further purification.

Data of **18** (R = Me): ^{1}H-NMR ($CDCl_3$, 250 MHz): 6.62 (br. *s*, OH); 5.31 (*s*, H–C(2)); 3.79 (*d*, *J* = 12.5, CH_2N); 3.06 (*d*, *J* = 12.5, CH_2N); 2.91 (*s*, MeN); 1.15–2.20 (*m*, 8 H); 0.92 (*s*, Me–C(3)).

Data of **18** (R = H): ^{1}H-NMR ($CDCl_3$, 250 MHz): 5.95 (br. *s*, OH); 5.17 (*s*, H–C(2)); 3.50–3.80 (*m*, 2 CH_2N); 3.11 (*s*, MeN); 1.50–2.30 (*m*, 9 H).

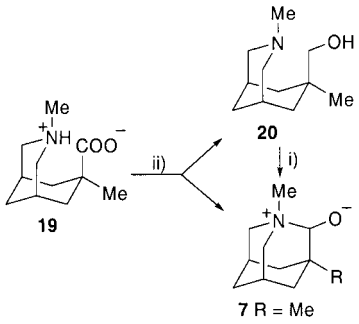
1,3-Dimethyl-1-azoniatricyclo[3.3.1.1^{3,7}]deca-2-olate (**7**; R = Me) and *1-methyl-1-azoniatricyclo [3.3.1.1^{3,7}]deca-2-olate* (**7**; R = H) were obtained from **18** (R = Me and H resp.). The starting salts (200 mg) were dissolved in 15% aq. KOH (10 ml), and the products were extracted with CH_2Cl_2 (4 × 30 ml). The extracts were dried (K_2CO_3), evaporated, and compounds **7** were sublimed to give amorphous solids.

Data of **7** (R = Me): ^{1}H-NMR (CD_2Cl_2, 250 MHz, 25°): 6.74 (*s*, H–C(2)); 2.98 (*d*, *J* = 12, 1 H); 2.50 (two overlapping *d*, 2 H); 2.17 (*s*, MeN); 1.96 (*d*, *J* = 12, 2 H); 1.25–1.55 (*m*, 7 H); 0.8 (*s*, Me–C(3)).

Data of **7** (R = H): ^{1}H-NMR (CD_2Cl_2, 250 MHz, 25°): 7.07 (*s*, H–C(2)); 2.45–3.35 (*m*, 7 H); 2.21 (*s*, MeN); 1.30–2.25 (*m*, 6 H).

Compounds **7** (R = Me and H) are both thermally stable, but extremely volatile and basic compounds. Like **2**, compound **7** (R = Me) is the final product from the reduction of the corresponding amino acid **19** or from oxidation of the amino alcohol **20** (*Scheme 3*). The oxidation proceeded in high yield, but formation of **7** (R = Me) by reduction was accompanied by overreduction to the amino alcohol **20** (*Scheme 3*).

Scheme 3



i) *Jones* reagent, 2 h, basic workup, sublimation. ii) $LiAlH_4$, Et_2O, reflux, 2 h.

Table 3. *Crystal Data and Structure Refinement for* **2**·**Me**

Empirical formula	$C_{14}H_{26}BF_4NO$	
Formula weight	311.17	
Temp.	150 K	
Wavelength	0.71069 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit-cell dimensions	$a = 8.498(3)$ Å	$\alpha = 90°$
	$b = 12.406(3)$ Å	$\beta = 105.47(2)°$
	$c = 15.475(3)$ Å	$\gamma = 900$
V	1572.4(7) Å^3	
Z	4	
Density (calculated)	1.314 Mg/in^3	
Absorption coefficient	0.112 mm^{-1}	
$F(000)$	664	
Crystal size	0.30 × 0.25 × 0.15 mm	
θ Range for data collection	2.73 to 22.49°	
Index ranges	$0 \le h \le 9$, $0 \le k \le 13$, $-16 \le l \le 16$	
Reflections collected	2214	
Independent reflections	2053 ($R_{int} = 0.1019$)	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2043 / 0 / 190	
Goodness-of-fit on F^2	1.072	
Final R indices [$I > 2\sigma(I)3$]	$R1 = 0.0716$, $wR2 = 0.1597$	
R indices (all data)	$R1 = 0.1348$, $wR2 = 0.2141$	
Largest diff. peak and hole	0.272 and −0.246 eÅ^{-3}	

Crystal-Structure Determination[1]) (*Table 3*). Crystals of **2**·**Me** were grown by pouring a $CHCl_3$ solution into Et_2O. Fine crystals formed over 24 h. Monoclinic, $C_{14}H_{26}BF_4NO$, M_r 311.17 g mol^{-1}, crystal size 0.30 × 0.25 × 0.15 mm, space group $P2_1/c$, $a = 8.498(3)$ Å, $b = 12.406(3)$ Å, $c = 15.475(3)$ Å, $\beta = 105.47(2)^\circ$, $V = 1572.4(7)$ Å^3, $Z = 4$; $D_x = 1.314$ Mg m^{-3}. Data were collected at 150(2) K with a *Rigaku AFC7R* diffractometer equipped with an *Oxford Cryosystems Cryostream* cooling device. No. of reflections measured = 2214, observed = 2053 ($I > 2\sigma(I)$), $\theta_{max} = 22.5^\circ$ (MoK_α radiation). The structure was solved with SHELXS-97 [16] and refined with SHELXL-97 [15]; No. of refined parameters = 190, R factor = 0.072, $wR = 0.16$, diff. density$_{max}$ = 0.272 e Å^{-3}, diff. density$_{min}$ = −0.246 e Å^{-3}.

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[1]) Supplementary crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-101432. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).