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Stereoelectronic interactions between hetero-atoms*

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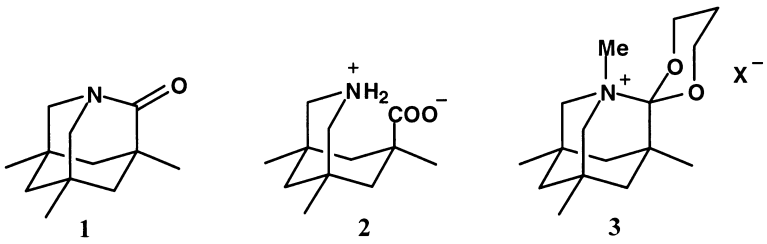
Abstract: We recently reported the preparation of the 1-aza-2-adamantanone **1** ['The Most Twisted Amide.' A. J. Kirby, I. V. Komarov, P. D. Wothers, N. Feeder. *Angew. Chem., Int. Ed. Engl.* **37**, 785–786 (1998)], and the unsurprising observation that when dissolved in water it is rapidly hydrolysed to the ring-opened amino-acid **2**. This compound is a key intermediate—one we had expected would be difficult to synthesise—on the way to target system (**3**). This last compound was designed to allow a simple test for the existence of the Reverse Anomeric Effect.



1 2 3

Scheme 1

All three compounds are now readily accessible, and each of them is extraordinary—an extreme case that proves one or more of the rules that we use to think about structure, conformation and reactivity. Highlights of their chemistry are presented and discussed in the context of the stereoelectronic effects involved in through-bond interactions between hetero-atoms.

Much of this paper is about conformational analysis [1], and I was looking forward to presenting it to an audience which included Sir Derek Barton. Since he is sadly no longer with us, I would like to dedicate it to him. The infallible mark of the great chemist is how often we find ourselves using his ideas in our everyday work. Appropriately I can also trace one of the fundamental ideas I will present back to R. B. Woodward, another of our great mentors: and specifically to a famous paper on tetrodotoxin, published in 1964 [2].

I quote:

> 'The appearance of the array in the tetrodotoxin molecule presents a clear lesson for the future in its intimation that if normally noninteracting groups are appositely attached to a rigid skeleton, or otherwise brought into forced proximity, they may be expected to co-operate in the formation of structural groupings which are not observed in simpler systems.'

We will see how prescient is this statement—and how directly relevant to the work I will describe.

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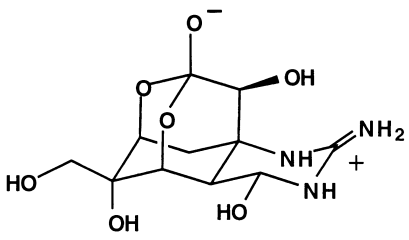
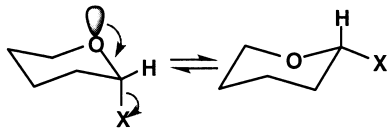


Tetrodotoxin

Scheme 2

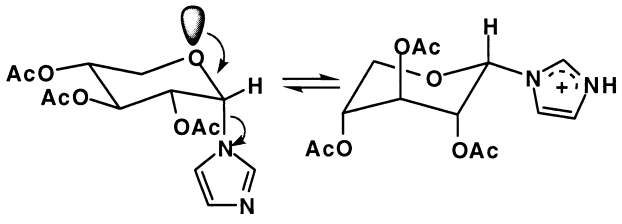
THE REVERSE ANOMERIC EFFECT

The work arose from our interest in the anomeric effect [3], the axial preference of an electronegative substituent in the anomeric position of a sugar, or generally the 2-position of a tetrahydropyran. This well-documented exception to the usual rules of conformational analysis is most simply explained in terms of an $n_O-\sigma^*_{C-X}$ interaction, not possible in the equatorial conformation (Scheme 3).



Scheme 3

An apparent exception to this exception is the reverse anomeric effect (RAE): in which positively charged electronegative substituents in the anomeric position show an increased *equatorial* preference, again compared with the corresponding cyclohexane. These are much less familiar systems, but the RAE is of particular potential importance in thinking about acid-catalysed reactions of sugars, where it would lead in principle to a reversal of the basic conformational preference, and thus of the relative ground state energies of anomers on protonation of the aglycone. Perhaps the most clear-cut evidence for this effect is the (modestly) increased amount of the equatorial anomer observed on protonation of the imidazole group of N-triacetyl-α-D-xylopyranosylimidazole [4,5] (Scheme 4).

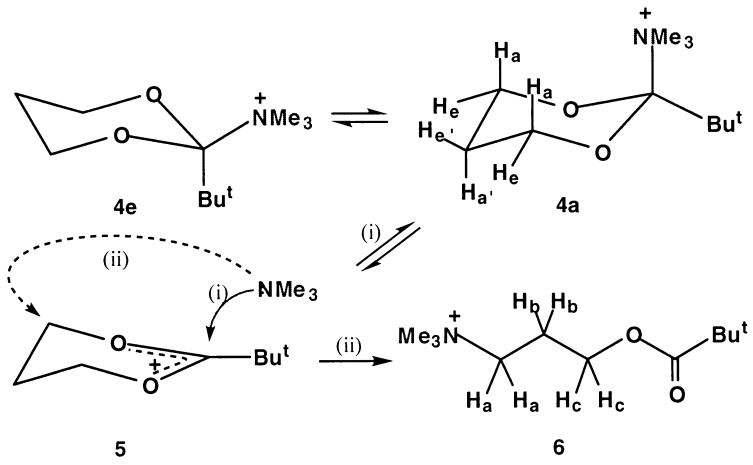


Scheme 4

The sum of the evidence for the RAE is also relatively modest, and there are contra-indications; for example the NMR titration experiments of Fabian *et al*. [6] which show that axial imidazole is more basic in an anomeric mixture of glucosylimidazoles. The current position is summarised in the excellent Review by Perrin [7].

We set out to devise a direct experimental test for the existence of the RAE in a simple sterically balanced system. To maximise stereoelectronic effects we decided to work with the dioxan ring, and to use trimethylammonium as the positively charged electronegative group. This sterically demanding group has to be balanced by an isosteric tertiary alkyl group, and this raises considerable problems, illustrated by the following results.

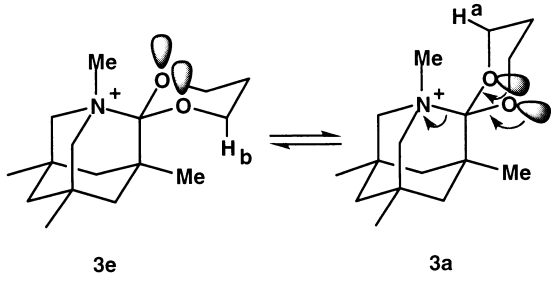
Simple systems with $X = R_3N^+$ already have a strong steric preference for the equatorial conformation. For example, the sterically balanced system **4** is not isolable: addition of trimethylamine to the dioxocarbenium ion **5** probably gives **4a** as a kinetic product (reaction (i)), but what we isolate is the



Scheme 5

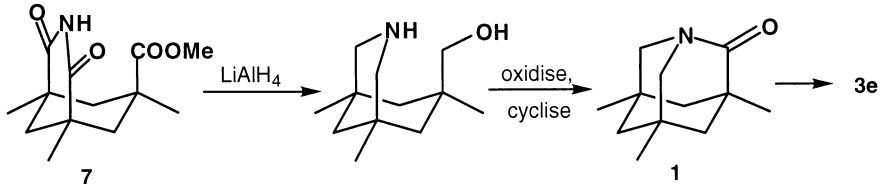
pivalate ester **6**, formed by the alternative (S_N2) reaction (ii) [8]. This is just one of a number of results that convinced us that simple systems like **4** are never likely to be stable enough to be viable test systems for this investigation (Scheme 5).

To encourage the three heteroatoms to stay together at the (quaternary) anomeric centre of interest we finally decided to embed it in the azaadamantane structure **3**. The critical test for RAE vs. normal anomeric effect now becomes simply (at least in principle) the conformational preference of the dioxan ring. The conformational equilibrium **3a**/**3e** is close to sterically neutral: though because the CH_3–N^+ bond is shorter than CH_3–C it is expected to have a slight preference for the conformation (**3e**) favored by RAE (Scheme 6).



Scheme 6

The synthesis of **3** proved a challenge [8], but, as I will describe below the final, cyclisation stage turned out to be the least of the problems. **3** was eventually prepared from the ester imide **7** of the Kemp triacid by the simple route outlined below. Dioxan ring formation involved nothing more complicated than heating **1** in acidic 1,3-propanediol, and the final product **3** could be purified by sublimation (Scheme 7) [9].



Scheme 7

In solution compound **3** shows a clear preference for a conformation closer to that (**3a**) favoured by the normal anomeric effect. In the ^{1}H NMR protons H^a and H^b of **3** show nuclear Overhauser effects of 12.3% to the $^+NCH_3$ and 2.0% to the CCH_3 group, respectively; and vicinal couplings (11.4, 5.6 Hz for H^a, 2.4, 2.4 Hz for H^b) not far from the expected magnitudes for conformation **3a**. (NOEs were obtained using the highly sensitive NOE buildup curve technique, described by Keeler and his co-workers [10].)

It might be expected that the question of the preferred ground state conformation could be simply settled by an X-ray structure determination, but this turned out not to be the case. Crystals were readily available, and we obtained structures of two different salts of **3,** only to find that the conformations of the iodide and hydrogendifluoride salts in the crystalline state differ significantly. The conformation is closer in the former case to **3e** and in the latter to **3a**. Both structures show a pronounced flattening of the dioxan ring at the two oxygen centres. This evidently results from the severe steric interactions—almost equally severe in either chair conformation—between the two $O–CH_2$ bonds and the $^{+}N–CH_3$ and $C–CH_3$ groups (in **3a** and **3e**, respectively).

The two structures are compared in the Figure with each other, and in Newman projections with the idealised chair-form structures **3a** and **3e**. Remarkably the O–C–O system of the dioxan ring is close to sp^2-hybridised, with bond angles of 120° at all three centres. Since the cation is the same in both structures the differences in conformation must result from crystal packing forces. The pattern of bond lengths at the 'anomeric' centre supports this interpretation: the $C–N^+$ bond is very long (1.59 Å) and the C–O bonds notably short (1.38 Å) in the dihydrogenfluoride salt in particular. But the flattening of the dioxan ring results in close-to-trigonal geometries of the O–C–O system, and thus in much reduced differences in the strength of the potential $n_O–\sigma^*_{C–N}$ overlap between 'axial' and 'equatorial' substituents. The only firm conclusion from the conformation of the dioxan ring is that in these special circumstances there appears to be a preference—though not a strong preference—for the conformation **3a**, favoured by the normal anomeric effect. The results of extensive *ab initio* calculations on this and related systems are consistent with this conclusion (Fig. 1) [11].

THE TWISTED AMIDE

In addition to our target compound **3** this work produced the fascinating 'twisted amide' **1**. The textbook example of such systems is Pracejus' compound, 2,2-dimethyl-6-quinuclidone **8** [13], prepared by a 12-step synthesis. The synthesis of **1** is relatively straightforward, and we have seen that the compound is thermally stable, so we have been able to look in some detail at its properties (Scheme 8).

The crystal structure [9] shows very clearly, as expected, that **1** is not an amide but a ketone, which happens to be connected to an amine nitrogen. The carbonyl group is planar ($\nu_{max} = 1732\,cm^{-1}$,

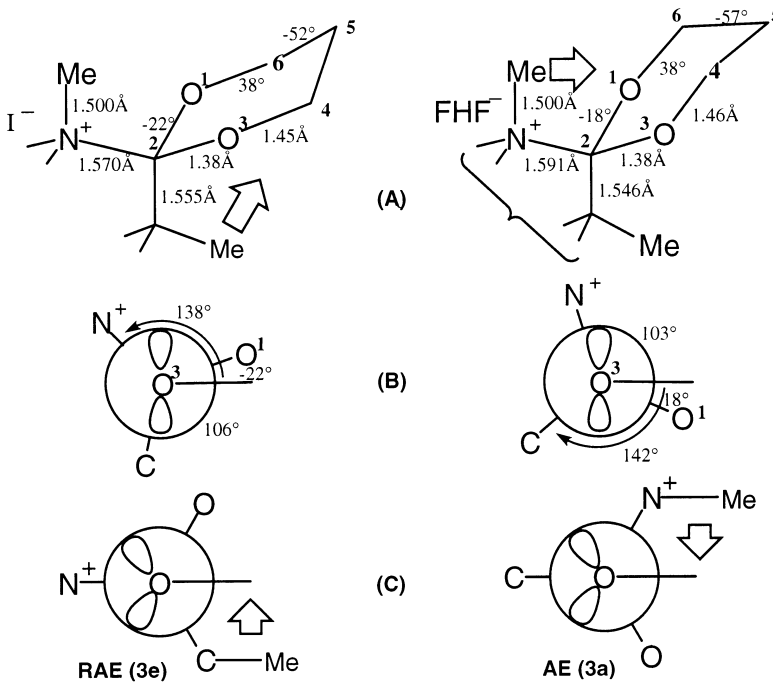
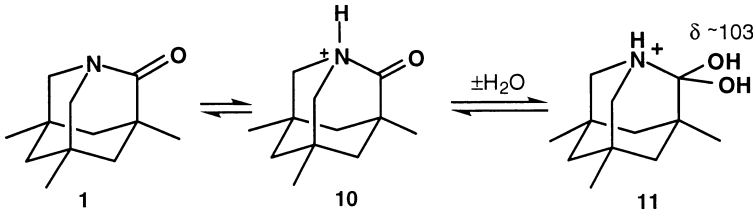


Fig. 1 Conformations in the crystal about the anomeric centre in two salts of **3**, compared with idealised conformations favouring the anomeric (AE) and reverse (RAE) effect [12].



Scheme 8

$\delta^{13}C = 200$ p.p.m.) and the nitrogen normally pyramidal (the sum of the three bond angles at $N = 325.7°$). The N–C and C=O bond lengths are 1.475(11) and 1.196(5) Å: substantially longer and shorter, respectively, than expected (1.352, 1.233 Å) for the amide group of an unconstrained tertiary δ-lactam. And the twist angle [14] $\tau = 90.5°$ indicates that the nitrogen lone pair lies in the nodal plane of the π-orbital of the C=O group. The strong $n-\pi^*$ overlap characteristic of a normal, planar amide group is thus prevented.

The compound also reacts as a (relatively reactive) ketone, undergoing for example a normal Wittig reaction; and it is readily converted to the 'acetal' **3** under normal, acidic conditions when dissolved in 1,3-propanediol [9]. The reactivity of the amino-nitrogen on the other hand is clearly reduced. Methylation with methyl iodide does not give the N-methylammonium derivative, presumably because the reaction is reversible: we were only able to make it using Meerwein's reagent, and the methyl group is readily removed by nucleophiles. N-demethylation of N-methylammonium compounds is normally a very slow process.

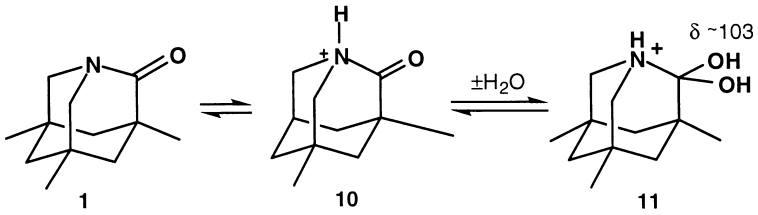
This is not the behaviour expected for even a reasonably basic amine, and thus raises interesting—and as yet unanswered—questions about the pK_a of the amine nitrogen of **1**. It is not possible to measure this directly: the twisted amide is rapidly hydrolysed in even mildly acidic aqueous solution. Pracejus obtained a pK_a of 5.33 for **8**, using the following rather elegant procedure [13]. He dissolved **8** in an aqueous solution containing half an equivalent of HCl and then measured the pH of the resulting solution, after 1 and then 2 min. The pH fell as the compound was hydrolysed, but a small extrapolation to zero time gave the pH of the initial solution of what should be the half-protonated base, and thus its pK_a, as 5.33. When this technique was applied to our compound the pH also fell rapidly: extrapolating back to zero time gave an initial pH of about 4.7. However, this is not the pK_a of **1**. When the experiment was run in D_2O the ^{1}H NMR showed that no. **1** remained after 45 s (the earliest time we could record the high-field spectrum). Hydrolysis is complete within this time, and the solution contains only the amino-acid **9**, which titrates normally to give pK_as of 4.57 and 10.56 for the carboxyl and secondary amine groups, respectively.

Much evidence suggests that our twisted amide **1** is generally more stable than the Pracejus compound **8**, so we suspect that his estimated pK_a of 5.33 is not correct. (Though the C=O group of **8** does differ from that of **1**, and may be more sterically hindered.) We are actively pursuing the question of the basicity of the amine nitrogen in this unique situation. An initial contribution in this area is the measurement of the ionisation potential (IP). Paul Rademacher at Essen [15] has recently obtained the PE spectrum of **1**, and finds, as expected, a substantial difference in the ionisation potentials of lone pair electrons on N and O (8.30 and 9.45 eV, respectively).

THE TWISTED AMIDE IN SOLUTION

The rapid hydrolysis of our twisted amide **1** under the Pracejus conditions is not surprising. Whatever the actual pK_a we expect the bridgehead nitrogen to be a basic centre, and thus protonated to some extent under the conditions. The C=O group of the conjugate acid **10** will then become highly electrophilic, and hydrolysis is the readily predicted result. But at just slightly lower pH hydrolysis to the amino-acid **9** is not observed. Instead **1** is converted to a single compound, characterised by a new signal in the ^{13}C NMR spectrum, which we have identified as the hydrate **11** of the conjugate acid **10** of our 'ketone' (Scheme 9).

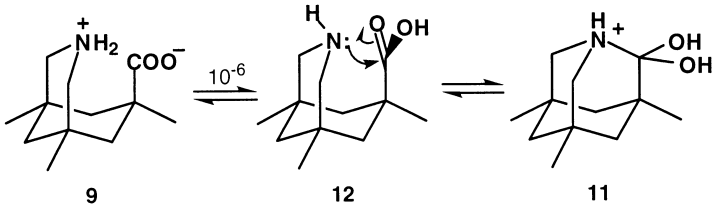
Structures like **11** are familiar as the short-lived, high energy intermediates thought to be involved in the acid-catalysed hydrolysis of normal amides. They are not normally detectable, let alone isolable. Yet



Scheme 9

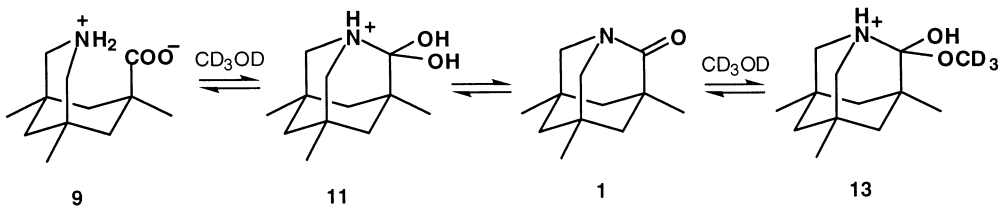
11 was isolated simply by dissolving the twisted amide **1** in dilute aqueous HCl and evaporating to dryness. It could be crystallised, and we even have a crystal structure of the chloride [16]. {This is incidentally relevant to the discussion (above) of the anomeric effect. **11**, with much reduced steric demands on the space around the anomeric centre compared with **3**, also shows the significant lengthening of the C–N^+ bond (1.552(4) Å), the related shortening of the two C–O bonds (1.382(4) Å) at the anomeric centre and the conformation about these C–O bonds expected for a normal anomeric effect.}

Evidently the stability of the azaadamantane structure is sufficient to make **11** the thermodynamically most stable derivative of **1** in acid. Remarkably, this holds true not only for **1**, but even for its ring-opened derivatives. Thus when a solution of the amino-acid **9** is acidified it is completely converted into **11**, faster than we can record the high field NMR spectrum (< 30 s). This is not only an extraordinary reaction for an amino-acid: it is also extraordinarily fast. Just how fast is shown by the following experiment. In solution in D_2O at pD 4.28 and 25 °C **9** and **11** are both present, as we can see by their characteristic ^{13}C and ^{1}H NMR spectra. On warming this solution corresponding proton peaks broaden and then coalesce. Evidently **9** and **11** are being interconverted at NMR rates. The rate constant for this equilibration can be calculated as 280 s^{-1} at the coalescence point (60–63 °C, N^+—CH_2 signals). This is quite extraordinarily fast for the formation of such a species from the zwitterionic form of an amino-acid. The actual mechanism is presumably straightforward, involving the small amount of neutral amino-acid **12**, but this implies an extraordinarily efficient intramolecular reaction. (We estimate an effective molarity [17] in the region of 10^{12} M.) (Scheme 10).



Scheme 10

Even the twisted amide can be regenerated from the amino-acid. This is most easily demonstrated in methanol, where solvolysis of **1** produces not the amino-acid zwitterion but its methyl ester, so the solvolysis equilibrium favours the cyclic form (Scheme 11).



Scheme 11

When the amino-acid zwitterion **9** is dissolved in methanol-d_4 its NMR signals disappear, with a half-time of some 30 min at the probe temperature of 23 °C. NMR spectra show the appearance of two products, in a 4:1 ratio: the twisted amide **1** (20%) and a second, major product probably corresponding to

13. Evidently, when the thermodynamics are favourable for the formation of the C–N bond the kinetic barriers to amide formation and hydrolysis are seen to be very small.

ACKNOWLEDGEMENTS

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