Deprotonation of Nitroalkanes by Bicyclic Amidine and Guanidine Bases; Evidence for Molecular Recognition within a Catalytic Cycle for C–C Bond Formation

Peter H. Boyle, Máire A. Convery, Anthony P. Davis,* Gladys D. Hosken and Brian A. Murray

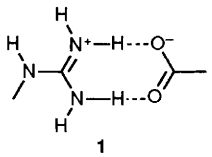
Department of Chemistry, Trinity College, Dublin 2, Ireland

Evidence from ^{1}H NMR spectroscopy, supported by X-ray crystallography, suggests that the bicyclic amidine and guanidine bases **2** and **3** react with nitroalkanes in non-polar organic solvents to give tightly-bound ion pairs **5**; it is argued that homochiral analogues of these complexes may prove valuable as intermediates in enantioselective catalytic C–C bond-forming reactions.

One of the simplest recognition motifs in biological chemistry is the pairing of a carboxylate anion with the guanidinium moiety of arginine, driven by electrostatic attraction and the formation of two parallel H-bonds (*cf.* **1**). For some time it has been appreciated that this interaction can be modelled effectively by using bicyclic amidines and guanidines such as **2**[1] and **3**[2] (Scheme 1) and, in more recent work, homochiral relatives of **3** with C_2 symmetry.[3] It has also been reported that the cations derived from these bases can complex inorganic oxoanions.[1a,2b,3c,3d,4] However, as far as we are aware, there has been no study of the interaction between such cations and carbanionic species. In particular, there is a clear electronic similarity between carboxylates and nitronate anions **4**, suggesting quite strongly that the latter might bind to the bicyclic cations as in **5**. We now report spectroscopic evidence that this does indeed occur in nonpolar and moderately polar organic solvents. We also describe an X-ray crystal structure which demonstrates the interaction in the solid state.

The results assume a special significance when it is considered that nitronates are intermediates in addition reactions of nitroalkanes in which chiral centres may be generated, and which may be induced by catalytic quantities of organic bases (Scheme 2).[5] The potential presence of a tightly organised complex such as **5** within a catalytic cycle raises the possibility that, with an appropriately designed bicyclic base, asymmetric induction might occur from catalyst to product leading to new enantioselective catalytic methodology.

In an initial series of experiments, ^{1}H NMR spectroscopy was used to investigate the interaction of nitroethane in CD_3CN with Eschenmoser's amidine **2** and, as a control, the



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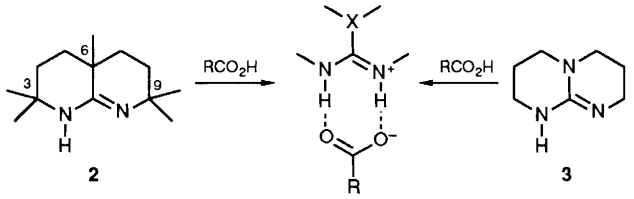
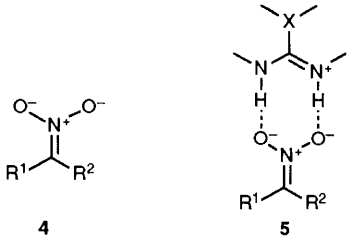


Scheme 1



4 5

'tertiary' amidine 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, **6**). In the latter case, with the concentrations of both components at *ca.* 1 mol dm^{-3}, the DBU caused the signals due to the nitroalkane α-protons to broaden somewhat (presumably due to exchange), but the spectrum showed no indication that the degree of proton transfer was substantial. This result was expected on the basis of pK_a measurements in acetonitrile by Schwesinger (DBU, 24.3; nitroalkanes, 28.6–30.4).[6]† However, when amidine **2** was added to the solution of nitroethane, the CH_2–NO_2 signal (δ 4.44, q, *J* 7.5 Hz) decreased in size and a new quartet appeared at δ 5.74 (*J* 5.8 Hz). This could be assigned with confidence to the methine proton of nitronate **7**, by comparison with the figures for the corresponding proton in silyl nitronate **8** (δ 6.15, *J* 6 Hz).[10]

The studies were extended to cover the reaction of nitroethane with **2** and **6** in C_6D_6, and with guanidines **3** and **9** in CD_3CN and C_6D_6. The results are summarised in Table 1. It can be seen that there is a major difference in behaviour between bases **2** and **3** on the one hand, and the 'control' molecules **6** and **9** on the other. In all the experiments involving **2** and **3**, the NMR spectra contained sharp multiplets due to nitronate **7** (as well as the methine quartet, the doublet due to $CH_3CHNO_2^-$ could be resolved in many cases). Proton transfer was substantial in both solvents with amidine **2**, and essentially quantitative with guanidine **3**. In the experiments involving **6** and **9**, proton transfer was only observed in one case (entry 7), in which the stronger base and the more polar solvent were employed (moreover, in this example the spectrum of the anion was qualitatively different from the other cases, the methine appearing as a broad singlet). Perhaps the most striking contrast is between entries 6 and 8; nitroethane in C_6D_6 is deprotonated quantitatively by **3**, but left untouched by its 'tertiary' analogue **9**.

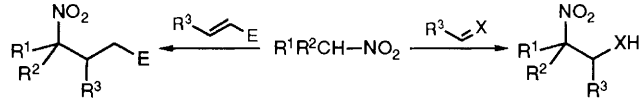
It does not seem reasonable to explain these data simply on the basis of pK_a differences between the four bases. Although

† Although nitroalkanes are remarkably acidic in water, so that proton transfer presumably would occur in that solvent (*cf.* the aqueous pK_a values of $MeNO_2$, 10.2,[7] and acetamidine, 12.52[8]), they are far less so in nonhydroxylic solvents.[9] It is generally understood that the difference is due to the stabilisation of nitronate anions by hydrogen bonding.

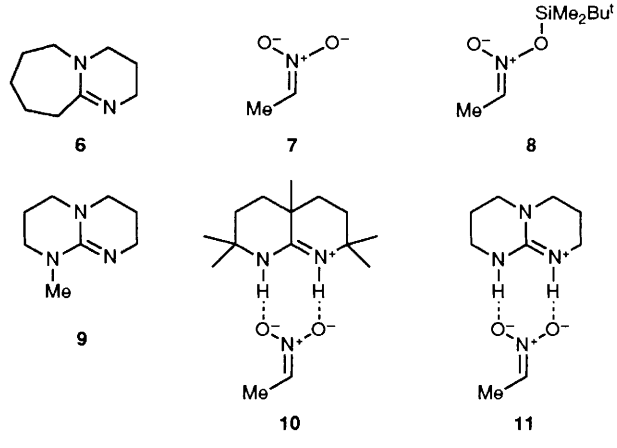
Table 1 Interaction of nitroethane with amidine and guanidine bases in CD_3CN and C_6D_6, as observed by ^1H NMR spectroscopy

Entry	Base	Solvent	Concentrations[a]/ mol dm^{-3}	Result[b]
1	**2**	CD_3CN	0.41, 0.41	[Nitro] : [nitronate], 1 : 1
2	**2**	C_6D_6	0.43, 0.43	[Nitro] : [nitronate], 3 : 1
3	**6**	CD_3CN	1, 1	CH_2–NO_2 signal broadened
4	**6**	C_6D_6	1, 1	No observable interaction
5	**3**	CD_3CN	—[c], 0.23	*Ca.* quantitative proton transfer
6	**3**	C_6D_6	—[c], 0.7	*Ca.* quantitative proton transfer
7	**9**	CD_3CN	0.3, 0.3	[Nitro] : [nitronate], 2.4 : 1
8	**9**	C_6D_6	0.7, 0.7	No observable interaction

[a] Initial concentrations, first figure refers to nitroethane, second to base. [b] Ratios by NMR integration. [c] Incremental addition of nitroethane.



Scheme 2 E = electron-withdrawing group



6 7 8 9 10 11

it has been shown by Schwesinger that, in acetonitrile, **3** (pK_a 25.96) is a slightly stronger base than **9** (pK_a 25.43),[6] the difference is surely insufficient to account for their contrasting behaviour in these experiments.‡ As far as we are aware, the pK_a of **2** has not been measured in a nonpolar solvent, but there is no reason to suppose that it would be substantially more basic than DBU. The most credible explanation for the results in Table 1 is that the exceptional ability of **2** and **3** to deprotonate the nitroalkane is due to the formation of complexes **10** and **11**, in which the nitronate is stabilised by formation of two, specifically directed H-bonds.

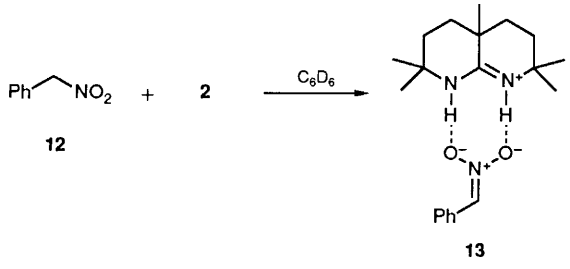
As part of our search for a crystalline analogue of **10** or **11** suitable for structure determination by X-ray diffraction (see below) we undertook some experiments involving phenylnitromethane **12**. This nitroalkane was expected to be more susceptible to deprotonation than nitroethane, and was indeed found to react nearly quantitatively with amidine **2** in C_6D_6 to give complex **13** (Scheme 3). An advantage of this

‡ The difference of 0.53 pK_a units translates to an equilibrium constant of only 3.4 for proton transfer between the two bases.

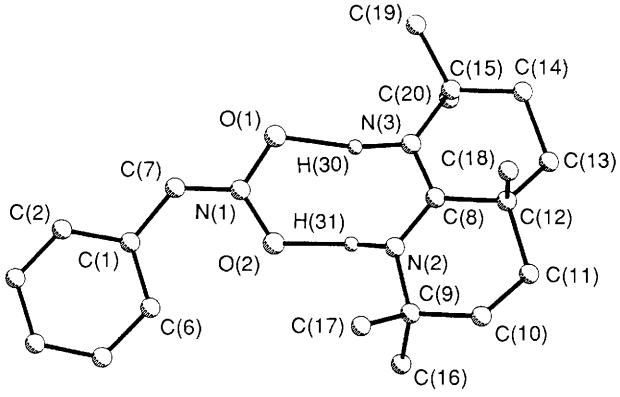
Table 2 Chemical shifts for the amidine–amidinium methyl groups in **2**, and in its reaction products with nitroalkanes in C_6D_6

	δ(3-Me, 9-Me)[b]	δ(6-Me)[b]
Bicyclic amidine **2**	1.12, 1.07	1.15
Phenylnitromethane-derived complex **13**	1.23, 1.16	0.70
Nitroethane-derived complex **10**	1.19, 1.12[a]	0.89[a]

[a] By extrapolation from the spectrum of a solution in which **2** was estimated to be 93% protonated. [b] See formula (Scheme 1) for numbering.



Scheme 3



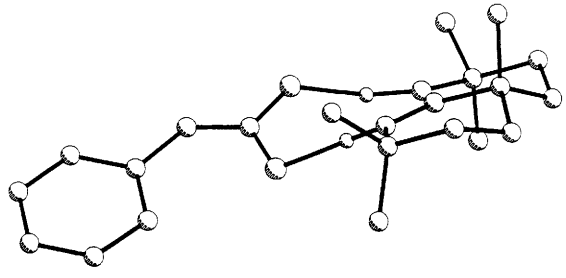
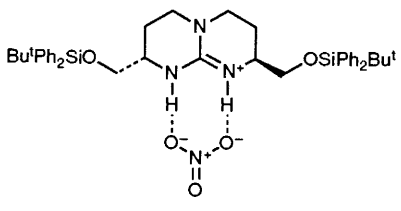


Fig. 1 The X-ray crystal structure of complex **13**, viewed from two different perspectives.

system was that the extent of reaction facilitated the study of the NMR signals due to the amidinium portion of complex **13**. In all the experiments reported herein, only one set of signals was observed for the amidine or guanidine, implying that (unlike the nitroalkane–nitronate interconversion) exchange between protonated and unprotonated forms of the bases was fast on the NMR time-scale (this could occur by direct reaction between free base and corresponding complex, or alternatively by proton exchange between free base and a low concentration of separated cation). On incremental addition



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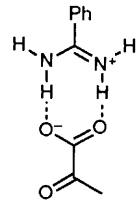
O···H 2.01, 2.06 Å
O···N 2.81, 2.82 Å



15

O···H 1.98,1.79 Å
O···N 2.90, 2.78 Å

of **12** to **2**, it was possible to follow the movement of the three signals due to the methyl groups in the amidine up to the point where the base was completely protonated (slight excess of **12**). The results are given in Table 2. In general it would be predicted that protonation of **2** should cause all three signals to move downfield.[1a] While this expectation is borne out in the case of the methyl groups on C-3 and C-9 (although the effect is small), the resonance due to the methyl on C-6 moved sharply upfield by *ca.* 0.45 ppm. It was possible to get equivalent figures for the reaction of **2** with nitroethane by employing a very large excess of the latter (Table 2). Again the C-6 methyl resonance moved upfield, but this time by only *ca.* 0.26 ppm.

Either of the above experiments would, by themselves, provide strong support for complex formation, in that it would be hard to explain the movement of the C-6 methyl resonance without invoking a through-space effect from anion to cation. The fact that the size of the effect is dependent on the carbon framework of the anion provides an even clearer indication that our hypothesis is correct.

Finally, one of the first indications of complex formation was the observation that the amidine **2** and nitroethane, which are both liquids, undergo an apparently instantaneous reaction on mixing to give a colourless solid mass. Similar behaviour was noted for **2** and 2-nitropropane. Although neither combination could be persuaded to yield crystals suitable for X-ray diffraction, the pairing of **2** and phenylnitromethane **12** proved more productive. Treatment of **2** with one equivalent of **12** in benzene yielded colourless transparent needles which clouded on evacuation or prolonged exposure to the atmosphere but could be analysed by X-ray crystallography if maintained in an atmosphere of the solvent.

The resulting structure is shown from two perspectives in Fig. 1.§ A molecule of benzene is present in the unit cell and is

§ *Crystal data*: $C_{20}H_{31}O_2N_3 \cdot C_6H_6$, M = 423.598, monoclinic, a = 10.382(2), b = 5.993(1), c = 20.392(4) Å, β = 104.37(2)°, U = 1229.1(4) Å^3 (by least-squares refinement on the setting angles of 22 reflections, λ = 0.71069 Å), space group *Pn* (no. 7), Z = 2, D_c = 1.144 g cm^{-1}, $F(000)$ = 460. Colourless air-sensitive (loss of solvent) platelets. μ(Mo-Kα) = 0.4 cm^{-1}. *Data collection and processing*: Enraf-Nonius CAD4 diffractometer, ω–2θ mode with ω scan width = 0.8 + 0.35 tanθ, maximum collection time 60 s, graphite monochromated Mo-Kα radiation; 2005 reflections measured from two crystals ($1 \leq \theta \leq 22$, $\pm h$, $+k$, $+l$), 1454 unique (merging R = 0.0486 for two data sets after individual decay corrections), giving 1298 with $|F_o| > 5\sigma(|F_o|)$. *Structure analysis and refinement*: Direct methods followed by difference Fourier synthesis. Full-matrix least-squares refinement with all non-hydrogen atoms anisotropic and hydrogens except bridging N*H* in calculated positions, each environment having overall refined U_{iso} [CH U = 0.083(9), CH_2 U = 0.078(7), CH_3 U = 0.104(7), bridging U = 0.08 (1) Å^2], the solvent molecule isotropic with common U_{iso} [C 0.097(1), H 0.27(2) Å]. The weighting scheme $w = 1/[\sigma^2(F_o) + 0.002F_o^2]$ gave flat analysis of variance. The final R values are 0.0565, 0.0617. The programs SHELXS and SHELX-76 are used by kind permission of Prof. G. F. Sheldrick (University of Göttingen). Atomic coordinates, bond lengths and angles, and thermal parameters, have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

omitted for clarity. The relative positions of the two ions clearly indicate the expected hydrogen bonding pattern, as in **13**. The interionic distances O(1)–H(30) (1.64 Å), O(2)–H(31) (1.76 Å), O(1)–N(3) (2.77 Å) and O(2)–N(2) (2.76 Å) may be compared with those in analogous structures such as **14**[3d] and **15**.[11]¶ The internal geometry of the anion is similar to that reported for lithium phenylnitronate by Boche and coworkers.[12]

The C(12)–C(8) and N(1)–C(7) bonds are almost colinear [angles C(12)–C(8)–N(1) 173°, C(8)–N(1)–C(7) 170°] but the two π-systems are not coplanar, being somewhat twisted relative to each other along the C(12)–C(8) and N(1)–C(7) axes [dihedrals O(2)–N(1)–C(8)–N(2) 37°, O(1)–N(1)–C(8)–N(3) 27°]. This is also consistent with our expectations. While hydrogen bonds generally tend to adopt an extended arrangement (which would imply coplanarity in this case), this is not rigidly enforced and a good deal of variation occurs. Relevant examples are to be found in the work of Etter on the crystal structures of nitroanilines.[13]

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¶ Owing to the difficulty in accurately locating hydrogen atoms by X-ray crystallography, the O·····N rather than the O·····H distances provide the more meaningful comparisons.

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