Tetrahedral Intermediates formed during Acyl Transfer. Reactions of Acetyl Cyanide

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Acyl transfer from acetyl cyanide to either the oxygen of PhNHOH, the nitrogen of MeNHOMe, or the sulphur of $PhCH_2SH$ proceeds *via* tetrahedral intermediates that are readily detected by ^{1}H and ^{13}C n.m.r. spectroscopy.

There is considerable current interest in the tetrahedral intermediates that form during acyl transfer reactions involving either simple substrates[1—3] or enzymes[4] (Scheme 1). Such intermediates are normally detectable only if either (i) unusual structural features result in their stabilisation, (ii) oxygen or sulphur (but not normally nitrogen[5]) nucleophiles are used, or (iii) if high energy precursors are employed.[1] We report here that weakly basic oxygen, sulphur, or nitrogen nucleophiles readily form persistent tetrahedral intermediates by direct reaction with acetyl cyanide (**1**), and that these can be easily studied using ^{1}H or ^{13}C n.m.r. spectroscopy.

We have previously reported[6] that whereas sterically non-congested hydroxylamines such as MeNHOH react with aroyl cyanides *via* direct *N*-attack to give hydroxamic acids, phenyl and other bulky aliphatic hydroxylamines provide instead the *O*-aroylated compounds. In order to understand the profound difference in chemical behaviour of the ambident nucleophile, a study of the reaction between (**1**) and (**2**) was undertaken. Using the ^{1}H Me resonance as a probe, we observed a transient intermediate (**3**) in this reaction, with $t_{1/2} < 1$ min at room temperatures. On warming, this was replaced initially by an *O*-acetyl (**4**) and eventually by the more stable *N*-acetyl product (**5**). With an ambident nucleophile such as (**2**) therefore, three of the four possible kinetic and thermodynamic products that differ by more than a simple proton transfer can be observed in one experiment.

Direct proof that (**3**) was a tetrahedral intermediate was obtained using ^{13}C n.m.r. spectroscopy.† On mixing (**1**) and (**2**) at 255 K in $CDCl_3$, a peak at δ 95 was observed, assigned to

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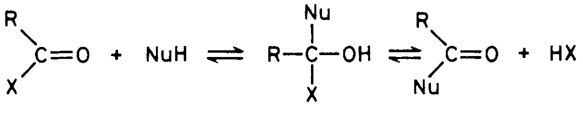
† *N.m.r. data* [50—150 mM solutions in $CDCl_3$, $|J(^{15}N-^{13}C)|$ in Hz]. (**1**): ^{1}H; δ 2.554 (COMe). ^{13}C; δ 173.8 (CO), 113.4 (CN), 32.1 (Me). (**2**): ^{13}C; 149.1 (*ipso, J* 4.9), 129.0 (*meta, J* 0), 122.6 (*para, J* 0), 114.8 (*ortho, J* 3.4). (**3**): ^{1}H; 1.804 (Me). ^{13}C; 146.2 (*ipso, J* 5.0), 129.1 (*meta, J* 0), 123.9 (*para, J* 0), 118.1 (CN), 115.8 (*ortho, J* 3.4), 94.6 (COH, *J* 2.2), 24.2 (Me, *J* 0). (**4**): ^{1}H; 2.206 (Me). ^{13}C; 170.7 (CO), 146.1 (*ipso*), 129.0 (*meta*), 124.1 (*para*), 116.7 (*ortho*), 19.2 (Me). HCN: ^{13}C; 108.5 (CN). (**5**): ^{1}H; 2.063 (Me). ^{13}C; 165.3 (CO), 138.1 (*ipso*), 129.3 (*meta*), 128.5 (*para*), 126.1 (*ortho*), 20.1 (Me).

MeNHOMe: ^{1}H; 2.755 (*N*-Me), 3.568 (*O*-Me). ^{13}C; 61.1 (*O*-Me), 38.8 (*N*-Me). MeOMeNCOH(Me)(CN): ^{1}H; 1.637 (*C*-Me), 2.642 (*N*-Me). 3.691 (*O*-Me). ^{13}C; 118.9 (CH), 85.0 (COH), 61.2 (*O*-Me), 35.7 (*N*-Me), 24.3 (*C*-Me). AcN(Me)(OMe): ^{1}H; 2.181 (*C*-Me), 3.220 (*N*-Me), 3.720 (*O*-Me). ^{13}C; 171.9 (CO), 61.1 (*O*-Me), 31.9 (*N*-Me), 19.8 (*C*-Me).

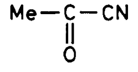
MeOH: ^{13}C; 50.9 (*O*-Me). MeOCOH(CN)(Me): ^{13}C; 117.3 (CN), 92.5 (COH), 52.1 (*O*-Me), 28.1 (*C*-Me). MeOAc: ^{13}C; 172.1 (CO), 51.8 (*O*-Me), 20.9 (*C*-Me).

$PhCH_2SH$: ^{1}H; 3.75 (CH_2, d, *J* 7.6), 1.78 (SH, t, *J* 7.6). ^{13}C; 141.0 (*ipso*), 128.6, 127.9 (*ortho/meta*), 126.9 (*para*), 29.0 (CH_2). $PhCH_2SCOH(CN)(Me)$: ^{1}H; 4.239, 4.145 (CH_2, *J* −13.1), 1.886 (Me). ^{13}C; 136.5 (*ipso*), 129.05, 129.0 (*ortho/meta*), 127.8 (*para*), 118.5 (CN), 73.3 (COH), 36.0 (CH_2), 28.8 (Me). $PhCH_2SCOMe$: ^{13}C; 175.3 (CO), 20.3 (Me).

the new sp^3 carbon centre.[7] After warming the solution to 285 K for a few seconds and recooling, this peak was replaced by a carbonyl peak at δ 170.7 due to (**4**) and on further warming by one at δ 165 due to (**5**) (Figure 1). Further experiments indicate that (**3**) arises by *O*- rather than *N*-attack from (**2**): (i) Ph^{15}NHOH gives an intermediate with ^{15}N–^{13}C couplings of 2.2 and *ca.* 0 Hz to the sp^3 and Me carbons respectively. Comparison with observed ^{1}J, ^{2}J, and ^{3}J couplings of 5, 3.4, and *ca.* 0 Hz to the Ph ring suggests that two bonds, not one, separate the ^{15}N and the sp^3 carbon atom.[8] (ii) Using MeOH an intermediate is observed to form slowly at room temperature, with a ^{13}C peak at δ 92.5 corresponding to the sp^3 carbon. (iii) With MeNHOMe, where attack by oxygen is not possible, a rather more unstable intermediate was detected at 245 K, presumably resulting from *N*-attack. This species had a rather broad sp^3 resonance at δ 85, indicating possibly restricted rotation about the N–O bond or the formation of diastereoisomers due to slow inversion at the nitrogen atom.[9]



Scheme 1

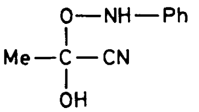


$\mathrm{Me{-}C({=}O){-}CN}$

(**1**)

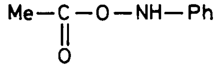
PhNHOH

(**2**)



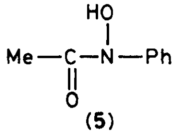
$\mathrm{Me{-}C(OH)(O{-}NH{-}Ph){-}CN}$

(**3**)



$\mathrm{Me{-}C({=}O){-}O{-}NH{-}Ph}$

(**4**)



$\mathrm{Me{-}C({=}O){-}N(OH){-}Ph}$

(**5**)

The relative stability of these tetrahedral intermediates is probably due to the poor leaving group ability of CN$^-$ and the weakly basic properties of hydroxylamines. A strongly basic nucleophile such as Et$_2$NH or piperidine at 245 K reacts almost instantly with (**1**), with no intermediate being detectable, and addition of two equivalents of the tertiary base DABCO (1,4-diazabicyclo[2.2.2]octane) at 255 K to a solu-

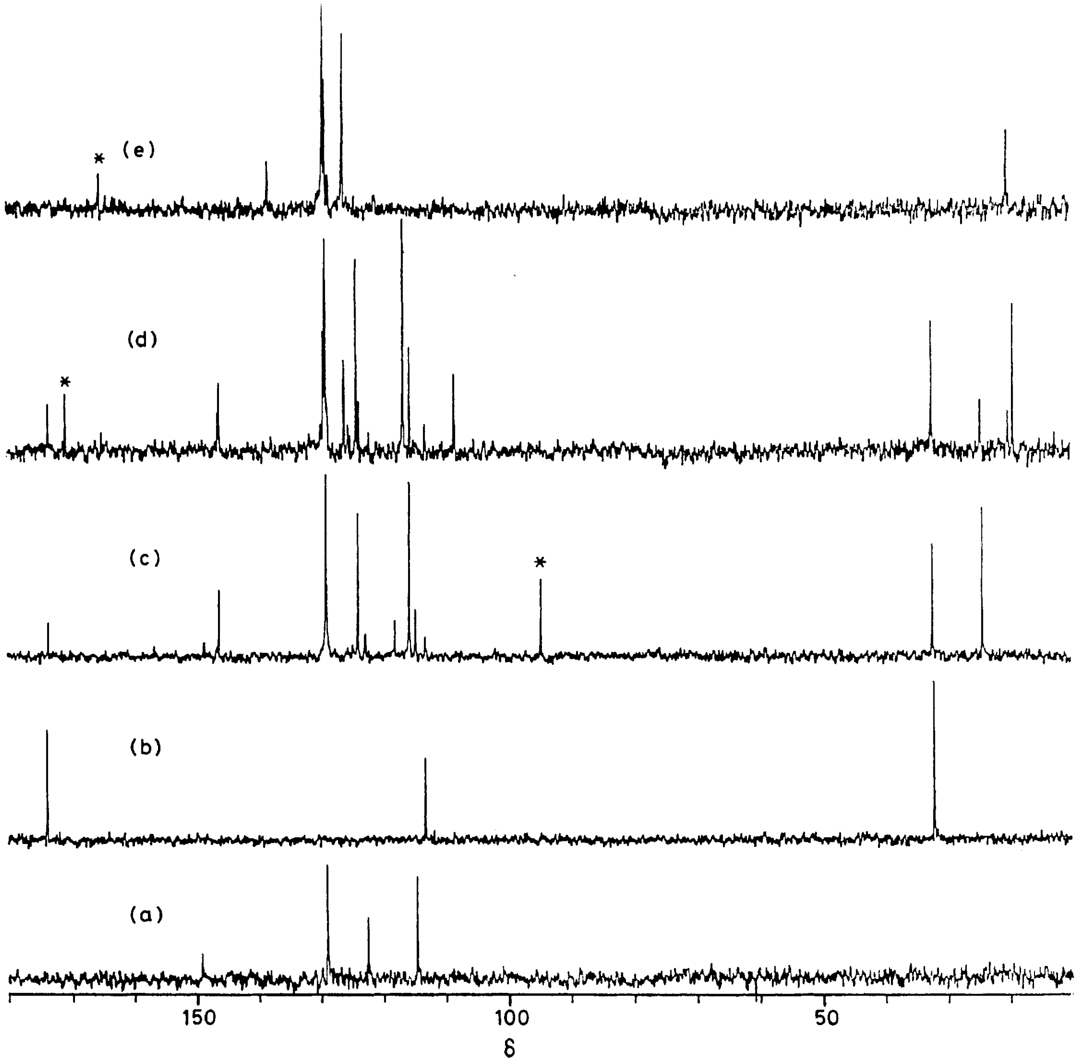


Figure 1. ^{13}C Spectra in CDCl$_3$ at 255 K for (a) (**2**), (b) (**1**), (c) a mixture of (**1**) and (**2**) corresponding to the formation of (**3**), recorded after mixing, (d) spectrum of (**4**) obtained after warming to 285 K and recooling, and (e) spectrum of authentic (**5**). Peaks marked with an asterisk are those referred to in the text; those due to CDCl$_3$ are not shown.

tion of (**3**) also results in rapid conversion of the intermediate into (**4**).[10] We found however that the reaction between a less electrophilic species such as PhCOCN and (**2**), or between a softer nucleophile such as $PhCH_2SH$ and (**1**) was very slow, even at room temperatures. In the latter case, $t_{1/2}$ at 300 K was *ca.* 5 days, giving an intermediate with a ^{13}C peak at δ 73.3.‡ Whereas the CH_2 protons in the reactant $PhCH_2SH$ and the product $PhCH_2SCOMe$ are magnetically equivalent, this is not the case in the intermediate ($\Delta\delta$ 0.094 p.p.m., J_{AB} −13.1 Hz), showing very clearly that this species must be chiral! We conclude that acyl cyanides may be convenient precursors for the generation and study of simple tetrahedral intermediates formed from a variety of weakly basic nucleophiles.

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References

1 B. Capon, A. K. Ghosh, and D. A. Grieve, *Acc. Chem. Res.*, 1981, **14**, 306.

2 R. A. McClelland and L. J. Santry, *Acc. Chem. Res.*, 1983, **16**, 394.

3 J. P. Guthrie, *Acc. Chem. Res.*, 1983, **16**, 122.

4 D. H. Rich, M. S. Bernatowicz, and P. G. Schmidt, *J. Am. Chem. Soc.*, 1982, **104**, 3535.

5 *Cf.* ref. 1. An observable intermediate in acyl transfer to nitrogen has been reported only once, O. S. Tee, M. Trani, R. A. McClelland, and N. E. Seaman, *J. Am. Chem. Soc.*, 1982, **104**, 7219.

6 S. Prabhakar, A. M. Lobo, and M. M. Marques, *Tetrahedron Lett.*, 1982, 1391.

7 Typical values for *O,O*-hemiacetals and *O,O,O*-hemiorthoesters are in the range δ 118—95, *cf.* ref. 1. See also R. C. Glen, P. Murray-Rust, F. G. Riddell, R. F. Newton, and P. B. Kay, *J. Chem. Soc., Chem. Commun.*, 1982, 25. In ref. 4, a value of δ 99 is reported for a *O,O*-hemiacetal intermediate involved in binding to an enzyme.

8 The magnitude of ^{15}N–^{13}C coupling constants depends on the degree of s character in the C–N σ bond, *cf.* G. A. Webb, in 'NMR and the Periodic Table,' eds. R. K. Harris and B. E. Mann, Academic Press, London, 1978, ch. 3, p. 73. In general, coupling to an sp^3 carbon would be expected to show a smaller coupling than to an sp^2 carbon, in agreement with our ^2J values observed.

9 M. Iwamura, M. Katos, and H. Iwamura, *Org. Magn. Reson.*, 1980, **14**, 392.

10 *Cf.* V. M. Kanagusabapathy and R. A. McClelland, *J. Chem. Soc., Chem. Commun.*, 1985, 691.

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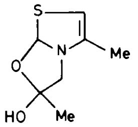
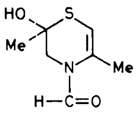
‡ M. B. Doughty and D. S. Lawrence, *J. Chem. Soc., Chem. Commun.*, 1985, 454 report a compound (A) which apparently contains *O,S,N*-orthoamide and *O,O*-hemiacetal features, with ^{13}C shifts of δ 160.6 and 76.4 respectively for the carbon atoms. Our results, and those of others (ref. 7) suggest that these resonances are due to an amide carbonyl and an *O,S*-hemithioacetal. We propose that their compound is in fact (B).

Added in proof: *X*-ray analysis of a sample of this compound kindly provided by Dr. M. B. Doughty (H. S. Rzepa and D. J. Williams, unpublished results) indicates it to have structure (B) in the solid state, but with the configuration of the formyl group reversed. N.m.r. studies in solution (H. S. Rzepa, unpublished results) show that form (B) predominates, but that *ca.* 10% appears to exist as form (A), in thermodynamic and stereospecific equilibrium with (B).



(A)



(B)