Regio- and Face-Selective 1,3-Dipolar Cycloadditions to Levoglucosenone

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Benzonitrile oxide and C,N-diphenylnitrone undergo highly regio- and face-selective cycloaddition reactions with levoglucosenone; in each case the major product results from approach *anti* to the 1,6-bridge of levoglucosenone, the oxygen of the 1,3-dipole becoming attached to the β-carbon of the enone unit.

Levoglucosenone† (**1**) is a chiral bicyclic D-glucose derivative prepared by pyrolysis of cellulose. Although its formation[1] and some aspects of its chemistry, such as its thermal stability,[2] addition,[3] and Diels–Alder reactions,[4] have been investigated in detail, its potential as a reactive dipolarophile has so far been neglected. We now report that it undergoes highly selective cycloaddition reactions with benzonitrile oxide (PhC≡N$^+$–O$^-$) and C,N-diphenylnitrone (PhCH=N$^+$-Ph–O$^-$).

There are four possible adducts between levoglucosenone and benzonitrile oxide: two regioisomers (**2**) and (**3**)‡ resulting

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† Levoglucosenone = 1,6-Anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose.

‡ Systematic names: (**2**) and (**4**) 5-phenyl-3,9,11-trioxa-4-azatricyclo-[6.2.1.0^{2,6}]undec-4-en-7-one; (**3**) and (**5**) 3-phenyl-5,9,11-trioxa-4-azatricyclo[6.2.1.0^{2,6}]undec-3-en-7-one; (**7**) 4,5-diphenyl-3,9,11-trioxa-4-azatricyclo[6.2.1.0^{2,6}]undecan-7-one.
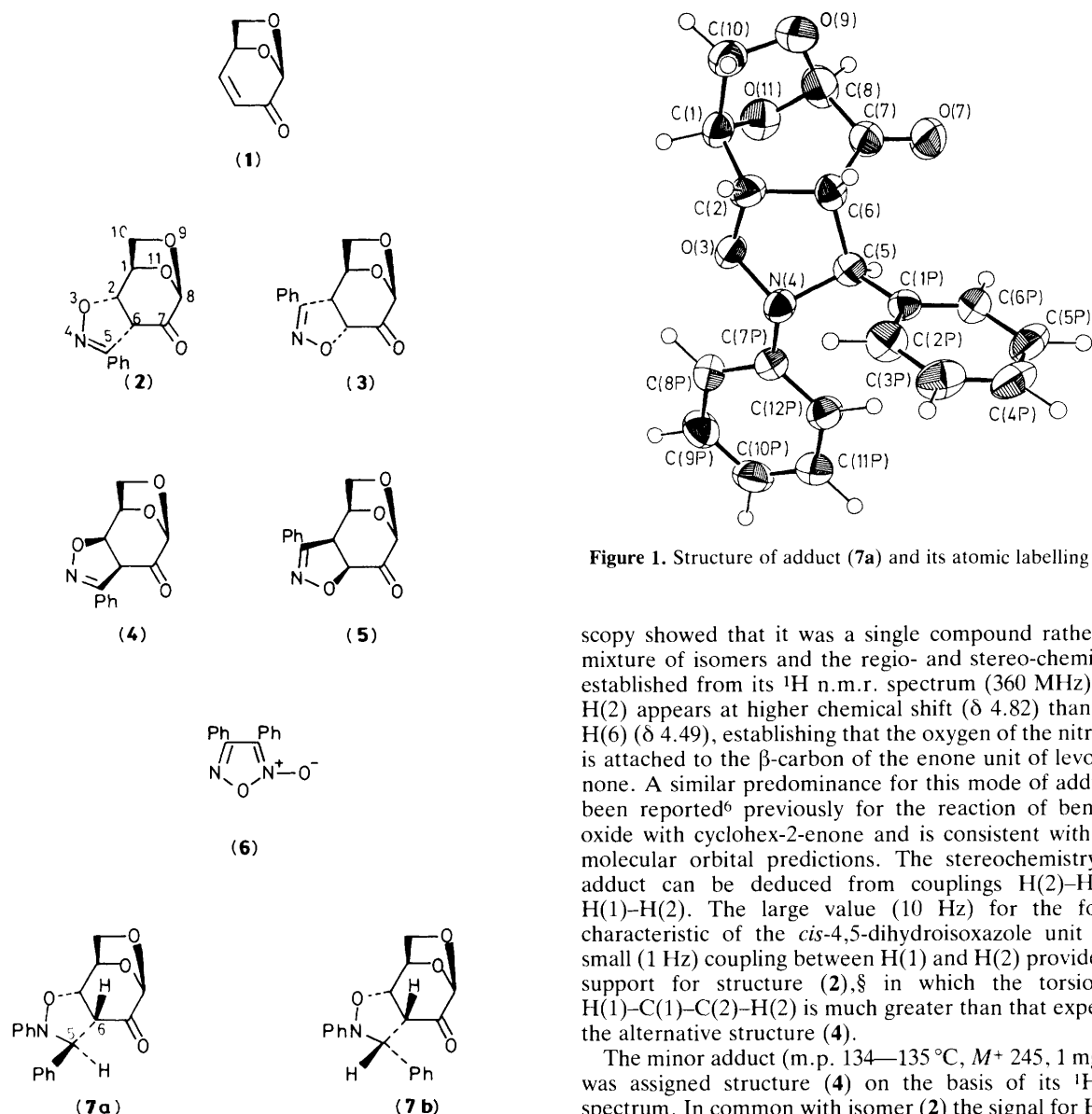
Figure 1. Structure of adduct (7a) and its atomic labelling scheme.

scopy showed that it was a single compound rather than a mixture of isomers and the regio- and stereo-chemistry was established from its ¹H n.m.r. spectrum (360 MHz). Proton H(2) appears at higher chemical shift (δ 4.82) than that for H(6) (δ 4.49), establishing that the oxygen of the nitrile oxide is attached to the β-carbon of the enone unit of levoglucosenone. A similar predominance for this mode of addition has been reported[6] previously for the reaction of benzonitrile oxide with cyclohex-2-enone and is consistent with frontier molecular orbital predictions. The stereochemistry of the adduct can be deduced from couplings H(2)–H(6) and H(1)–H(2). The large value (10 Hz) for the former is characteristic of the cis-4,5-dihydroisoxazole unit and the small (1 Hz) coupling between H(1) and H(2) provides strong support for structure (2),§ in which the torsion angle H(1)–C(1)–C(2)–H(2) is much greater than that expected for the alternative structure (4).

The minor adduct (m.p. 134—135 °C, M⁺ 245, 1 mg, 0.6%) was assigned structure (4) on the basis of its ¹H n.m.r. spectrum. In common with isomer (2) the signal for H(2) is at higher chemical shift than that for H(6) (δ 5.49 cf. 4.56); it must therefore have the same regiochemistry but opposite stereochemistry at the ring junctions. The observed coupling of 6 Hz for H(1)–H(2), consistent with the predicted smaller torsion angle, provides further supporting evidence for this assignment. Neither of the other two possible adducts (3) and (5), could be detected. The reaction is apparently regiospecific and highly face selective, attack from the less hindered lower face being greatly preferred (ca. 100:1).

There are eight possible products for the corresponding reaction with C,N-diphenylnitrone: exo- and endo-isomers for each pair of regioisomers resulting from 'upper' and 'lower' face attack. Treatment of levoglucosenone (0.71 g) with C,N-diphenylnitrone (1.14 g) in toluene under reflux yielded a single 1:1 adduct (m.p. 176—177 °C, M⁺ 323, 1.23 g, 68%). From its ¹H n.m.r. spectrum {δ 4.64 [H(2)], 4.86 [H(5)], 3.34 [H(6)]; $J_{1,2}$ 1.3, $J_{2,6}$ 6.8, $J_{5,6}$ 4.5 Hz} it was identified as either the endo or exo-adduct (7). The absence of a significant nuclear Overhauser effect (<2%) between protons H(5) and

from 'lower face' approach of the 1,3-dipole to the alkene double bond, i.e. from the side opposite the 1,6-anhydro bridge, and the two corresponding isomers (4) and (5)‡ from 'upper face' attack.

In order to minimise the competing dimerisation to diphenylfurazan N-oxide (6), benzonitrile oxide was generated in the presence of an excess of dipolarophile by dehydrochlorination of benzohydroxyimoyl chloride, a well-established source[5] of benzonitrile oxide. A solution of the hydroximoyl chloride (56 mg) in benzene was added by means of a syringe pump during 25 h to a refluxing solution of levoglucosenone (171 mg) and triethylamine (0.05 g) in benzene and the mixture heated for a further 16 h. Removal of triethylamine hydrochloride by filtration, followed by preparative t.l.c. [silica; eluant hexane–EtOAc (3:1)] of the residue afforded unreacted levoglucosenone (106 mg) and two 1:1 cycloadducts.

The structure of the major component (m.p. 177—178 °C, M⁺ 245, 62 mg, 71% based on benzonitrile oxide) was identified as (2) from its n.m.r. spectra. ¹³C N.m.r. spectro-

H(6) was taken as evidence in favour of the *endo* structure (**7a**). This assignment was confirmed by *X*-ray crystallography¶ (Figure 1), thus establishing not only the regio- and face specificity of the reaction, but also the *endo*-approach of reactants (torsion angle H(5)–C(5)–C(6)–H(6) 129°). None of the other seven possible 1 : 1 adducts was detected.

The degree of specificity in these reactions is remarkably high. Recently reported[10,11] examples involving cycloadditions to α,β-unsaturated lactones show comparable selectivity for benzonitrile oxide[10] but significantly less for nitrones.[11,12] Levoglucosenone is a reactive dipolarophile, it is

readily available, and should prove to be a valuable source of carbohydrate derivatives.

¶ *Crystal data* for $C_{19}H_{17}NO_4$: orthorhombic, space group $P2_12_12_1$, $a = 9.2952(4)$, $b = 11.0635(4)$, $c = 15.1210(6)$ Å, $U = 1555.0$ Å^3, $D_c = 1.381$ g cm^{-3}, $Z = 4$; 1313 data measured to $\theta = 60°$ using Cu-K_α radiation, semi-empirical absorption correction using ψ scans, refinement based on 1256 data with $F \geqslant 6\sigma(F)$. At convergence, $R = 0.0571$ and $R_w = 0.0950$, respectively, for 195 parameters. Direct methods[7] yielded the positions of all non-H atoms; iterative cycles of least-squares refinement and difference Fourier syntheses indicated H-atoms which were thereafter refined in fixed, calculated positions with a common isotropic thermal parameter.[8] The phenyl rings were constrained to be ideal, rigid hexagons. The final difference Fourier synthesis revealed no feature above 0.27 e Å^{-3}. Molecular geometry calculations utilised CALC[9] and illustrations were prepared using ORTEPII.[10] Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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