

Synthesis of Perdeuterio-1,4-diazabicyclo[2,2,2]octane (DABCO-²H₁₂)

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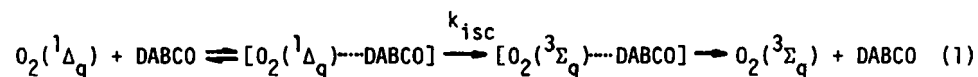
Summary

1,4-Diazabicyclo[2,2,2]octane (DABCO) is an efficient quencher of singlet oxygen, O₂(¹Δ_g), and is used as an indicator of O₂(¹Δ_g) intermediacy in both chemical and biochemical oxidative processes. The quenching is physical in character and the fully deuteriated derivative, DABCO-²H₁₂, is a molecule of potential mechanistic importance. Its synthesis with >98% isotopic purity is described.

Key words: 1,4-diazabicyclo[2,2,2]octane, perdeuteration, singlet oxygen

Introduction

The mechanism of reaction of singlet oxygen, O₂(¹Δ_g), with organic/biological substrates has been the subject of intensive research over the last two decades (1-3). Quenching may be physical or chemical in character, the archetypal physical quencher being 1,4-diazabicyclo[2,2,2]octane (DABCO)⁴. Inhibition of oxidative effects by the latter is used as a test of the intermediacy of O₂(¹Δ_g) and a consensus of opinion (5-7) favours the mechanism summarised in eq. 1 for the quenching process. However, the key factors influencing the rate constant for

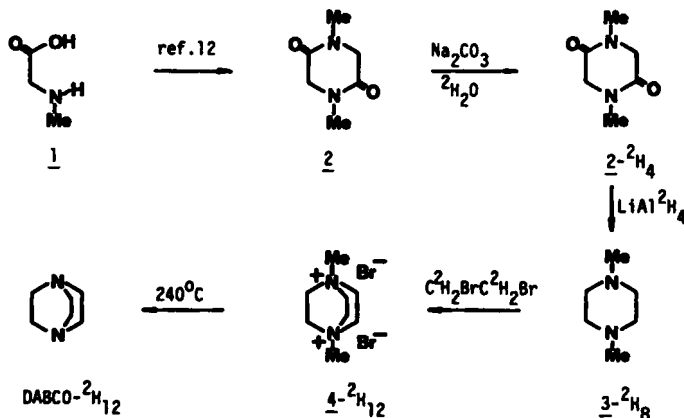


intersystem crossing, k_{isc} , are as yet ill-defined. In the light of the known importance, in solvent quenching, of the conversion of the electronic excitation energy of O₂(¹Δ_g) into C-H vibrational modes (8-11), the fully deuteriated analogue, DABCO-²H₁₂, becomes a molecule of key mechanistic interest. Its synthesis with an isotopic purity of >98% is described below.

Results

The synthetic route (Scheme 1) began with the formation of 1,4,-dimethyl-2,5-dioxopiperazine (**2**) from 2-methylamino-ethanoic acid (sarcosine; **1**).¹² Four of the twelve deuteriums were introduced in each of three consecutive steps. All

Scheme 1



intermediates were characterised by comparison of mass and nmr spectra, m.p. or b.p. and glc behaviour (except **4-²H₁₂**) with the corresponding undeuteriated material. The chemical homogeneity of the final product, DABCO-²H₁₂ was demonstrated by glc and m.p. It was shown by mass spectrometry (Figure 1) to contain DABCO-²H₁₀ (3%), DABCO-²H₁₁ (9%) and DABCO-²H₁₂ (88%). This corresponds to an isotopic purity of >98%

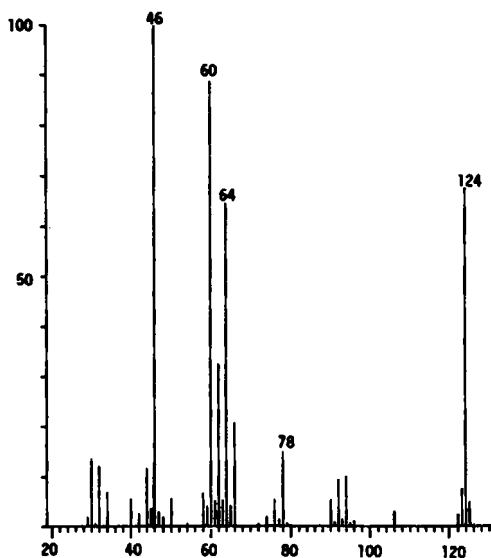


Figure 1 Electron-impact mass spectrum of DABCO-²H₁₂

Experimental Section

Electron impact mass spectra and nmr spectra were recorded on AEI MS12 and Perkin-Elmer R12A instruments respectively. Gas chromatographic analysis was performed with a Pye-Unicam 204 instrument using a 30 m x 0.33 mm (i.d.) capillary column coated with cross-bond DP1701 (OV-17), 0.15 μm thickness, 80°C, 12.5 psi (helium).

(a) 1,4-Dimethyl-2,5-dioxopiperazine-²H₄ (2-²H₄) A nitrogen purged solution of 1,4-dimethyl-2,5-dioxopiperazine (2, 22 g) and anhydrous sodium carbonate in water-²H₂ (Aldrich; 99.8%; 60 ml) was stirred at 85°C for 10 min. The combined dichloromethane extracts (6 x 30 ml) were dried over anhydrous magnesium sulphate and concentrated to dryness to yield white needles (19.8 g; 90%), m.p. 145-147°C (ethyl acetate). δ(CDCl₃) 2.91 (S; 6H); corresponding undeuteriated preparation 2.91 (S; 6H), 3.89 (S; 4H). m/z(%) 147 (6.2), 146 (100), 145 (1.4), 89 (12.4), 84 (12.2), 61 (59.1), 49 (20.7), 47 (60.9), 46 (21.5), 45 (86.6), 44 (46.2), 43 (61.8).

(b) 1,4-Dimethylpiperazine-²H₈ (3-²H₈) A solution of 2-²H₄ (9.75 g) in dry tetrahydrofuran (400 ml) was added to a slurry of lithium aluminium deuteride (Fluka; > 99%; 10 g) in the same solvent (400 ml). After stirring overnight, the excess deuteride was destroyed by addition of saturated sodium hydroxide solution. Suspended material was removed by filtration and the dried (anhydrous magnesium sulphate) filtrate concentrated under vacuum. Distillation of the residue gave a colourless pungent liquid (3.5 g; 43%), b.p. 130-132°C, homogenous by glc. δ(CDCl₃) 2.21 (S; 6H); corresponding undeuteriated preparation 2.21 (S; 6H), 2.39 (S; 8H). m/z (%) 123 (3.8), 122 (45.2), 121 (5.0), 96 (21.7), 95 (17.4), 77 (21.2), 75 (12.3), 46 (29.7), 45 (100), 44 (16.2), 43 (40.6), 42 (18.3), 41 (17.6).

(c) 1,4-Diazabicyclo[2,2,2]octane-²H₁₂-dimethobromide (4-²H₁₂) A mixture of 3-²H₈ (1.0 g) and 1,2-dibromoethane-²H₄ (MSD Canada Ltd; 99%; 1.57 g) was maintained at 140° for 2 h. The resulting solid product was recrystallised twice, including one treatment with charcoal, from 95% ethanol to give white crystals (1.9 g; 75%), m.p. >260°C. δ(D₂O) 3.31 (S; 6H); corresponding undeuteriated preparation 3.31 (S; 6H), 3.98 (S; 12H).

(d) 1,4-Diazabicyclo[2,2,2]octane-²H₁₂ The dimethobromide (4-²H₁₂; 1.1 g) was heated at 240°C between 10⁻² and 10⁻³ Torr for 8 h. and the volatile white product collected in a trap cooled with acetone/dry ice. Resublimation gave DABCO-²H₁₂ as pure white crystals (0.44 g; 80%), m.p. (sealed tube) 157-158°C, single peak by glc. m/z (%) 125 (4.9), 124 (67.9), 123 (7.5), 94 (10.0), 78 (15.0), 66 (20.6), 64 (64.8), 62 (32.5), 60 (89.3), 46 (100), 44 (11.7).

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References

1. Wasserman H. H. and Murray R. W. (eds.) - Singlet Oxygen, Academic Press, New York, 1979
2. Gorman A. A. and Rodgers M. A. J. - Chem. Soc. Rev. 10: 205 (1981).
3. Frimer A. A. (ed.) - Singlet O₂, CRC Press Inc., Boca Raton, 1985
4. Ouannes C. and Wilson T. - J. Amer. Chem. Soc. 90: 6527 (1968)
5. Furakawa K. and Ogryzlo E. A. - J. Photochem. 1: 63 (1972)
6. Young R. H., Martin R. L., Feriozi D., Brewer D. and Kayser R. - Photochem. Photobiol. 17: 233 (1973)
7. Gorman A. A., Gould I. R., Hamblett I. and Standen M. C. - J. Amer Chem. Soc. 106: 6956 (1984)
8. Merkel P. B. and Kearns D. R. - J. Amer. Chem. Soc. 94: 7244 (1972)
9. Ogilby P. R. and Foote C. S. - J. Amer. Chem. Soc. 105: 3423 (1983)
10. Hurst J. R. and Schuster G. B. - J. Amer. Chem. Soc. 105: 5756 (1983)
11. Rodgers M. A. J. - J. Amer. Chem. Soc. 105: 6201 (1983)
12. Sannie C. - Mem. Pres. Soc. Chim. 487 (1941)