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Synthesis and Studies of the 15-Crown-5 Complex of the Sodium Salt of 2-Nitroimidazole

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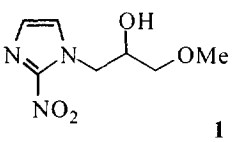
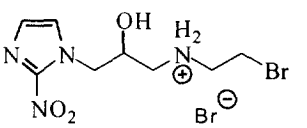
Abstract: The 15-crown-5 complex of the sodium salt of 2-nitroimidazole has been isolated and its solid state structure determined by X-ray crystallography. This shows bonding interactions between the sodium atom and the imidazolate through a ring nitrogen and one of the nitro-oxygen atoms. The sodium ion is seven co-ordinate and is located slightly out of the least-squares plane of the crown ether. In solution, the complex acts as a naked anion allowing the heterocyclic ring to be N-alkylated under mild conditions. © 1997 Published by Elsevier Science Ltd.

Following Nakamura's[1] identification of the antibiotic azomycin as the hitherto unknown 2-nitroimidazole system, there has been considerable interest in studying the biological activity of derivatives of this system. N-Alkylated derivatives such as misonidazole **1** have been particularly studied because of the discovery that this material is a radiosensitiser and chemosensitiser of hypoxic tumour cells.[2,3] Since the hypoxic cells found in the interior of tumours are usually more resistant to the effects of radiation than non-hypoxic cells, this property has proved to be valuable in the treatment of some cancers by radiotherapy.



1



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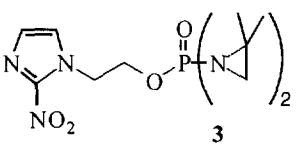

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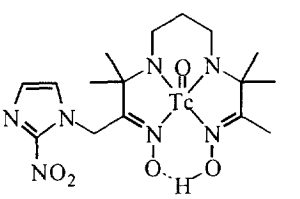
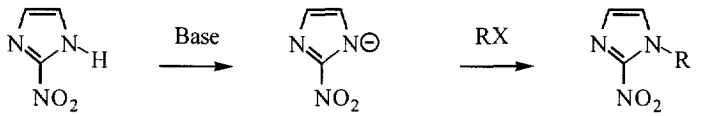


4

More recently, second generation bifunctional radiation sensitisation agents have been developed which combine the targeting ability of the 2-nitroimidazole unit for hypoxic cells with the radiation sensitising activity of other chemical units. This has led to the development of radiation sensitisation agents, such as **2**[4] and **3**[5]. The ability of compounds like misonidazole to bind covalently to viable hypoxic cells has also led to the development of a strategy for the imaging of hypoxic tissue. By incorporating an appropriate halogen isotope in such molecules potential imaging agents for myocardial hypoxia have been developed for both PET[6] and SPECT[7] imaging and more recently the attachment of a nitroimidazole unit to a range of ligand systems has also been investigated with the aim of producing ^{99m}Tc-based imaging agents such as **4**.[8]

A key step in the synthesis of many of these compounds is the alkylation of the anion of 2-nitroimidazole (Scheme 1). This anion is typically formed by the action of base on 2-nitroimidazole in hot dimethylformamide, this solvent being necessary to overcome the limited solubility of 2-nitroimidazole in most solvents. Unfortunately, yields from the alkylation of the anion are only modest and the introduction of substituted alkyl groups can be difficult. A procedure using the tetrabutylammonium salt of the nitroimidazole in dimethylformamide, originally developed for the 4-nitro-substituted systems,[9] has been shown to improve N-alkylation of 2-nitroimidazole[10] but relatively long reaction times are required. More recently, a method for increasing the nucleophilicity of the imidazole anion by complexing its metal salts with crown ethers in a polar aprotic solvent has been reported.[10] Under these conditions alkylation of the anion occurs quite quickly in good yields.

Scheme 1



While investigating this approach for attaching the 2-nitroimidazole nucleus to a range of hydrophilic ligand systems, we discovered that it was easy to isolate the crown ether complex of the sodium salt of 2-nitroimidazole. This complex was easy to handle and, unlike the free nitroimidazole, was soluble in many organic solvents such as acetone, chloroform, dichloromethane, acetonitrile, and dimethylformamide, although surprisingly it is relatively insoluble in ethyl acetate. It therefore has many attractions as a precursor for N-alkylated derivatives of 2-nitroimidazole. The complex appears to be very stable in both the solid and in solution and no decomposition was observed over a period of many months.

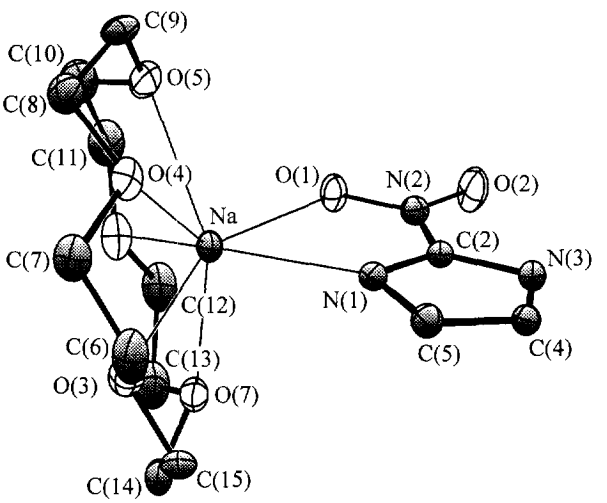


Figure 1

The crystallinity of the complex enabled its structure to be determined by X-ray diffraction.† Selected bond lengths, bond angles and the torsion angles of the crown ether are shown in Tables 1—3; Figure 1 shows the atom labelling scheme and the molecular structure. The Na—O bond lengths (2.425—2.490 Å) to the crown ether are consistent with those found in other oxygen crown ether complexes.[11] The sodium lies

1.108(1)Å out of the least squares plane of the crown ether. The torsions about the C—C bonds in the crown ether are all near to 60°, indicating the expected gauche conformations. The torsions about the C—O bonds are within 23° of being trans except for C(9)—O(5) where the torsion is 82.2(5)°.

Table 1 - Selected Bond Distances (Å)

Na	O(1)	2.473(3)	Na	N(1)	2.480(3)	Na	O(3)	2.468(3)
Na	O(4)	2.425(3)	Na	O(5)	2.490(3)	Na	O(6)	2.441(3)
Na	O(7)	2.444(3)	O(1)	N(2)	1.232(4)	O(2)	N(2)	1.218(4)
N(2)	C(2)	1.399(4)	N(1)	C(2)	1.332(4)	N(3)	C(2)	1.338(4)
N(1)	C(5)	1.357(5)	N(3)	C(4)	1.327(6)	C(4)	C(5)	1.386(6)
O(3)	C(6)	1.359(7)	O(3)	C(15)	1.444(7)	O(4)	C(7)	1.465(6)
O(4)	C(8)	1.391(6)	O(5)	C(9)	1.494(6)	O(5)	C(10)	1.360(8)
O(6)	C(11)	1.479(7)	O(6)	C(12)	1.357(7)	O(7)	C(13)	1.430(8)
O(7)	C(14)	1.39(1)	C(6)	C(7)	1.451(9)	C(8)	C(9)	1.420(8)
C(10)	C(11)	1.46(1)	C(12)	C(13)	1.51(1)	C(14)	C(15)	1.50(1)

Table 2. - Selected Bond Angles (°)

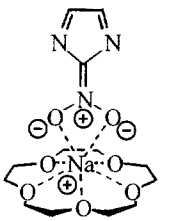
O(1)	Na	O(3)	150.9(1)	O(1)	Na	O(4)	135.2(1)
O(1)	Na	O(5)	83.8(1)	O(1)	Na	O(6)	84.2(1)
O(1)	Na	O(7)	92.5(1)	O(1)	Na	N(1)	65.51(9)
O(3)	Na	O(4)	67.1(1)	O(3)	Na	O(5)	125.3(1)
O(3)	Na	O(6)	104.0(1)	O(3)	Na	O(7)	66.8(1)
O(3)	Na	N(1)	95.5(1)	O(4)	Na	O(5)	68.1(1)
O(4)	Na	O(6)	114.3(1)	O(4)	Na	O(7)	132.1(1)
O(4)	Na	N(1)	100.0(1)	O(5)	Na	O(6)	68.5(1)
O(5)	Na	O(7)	134.5(1)	O(5)	Na	N(1)	121.9(1)
O(6)	Na	O(7)	66.0(1)	O(6)	Na	N(1)	144.9(1)
O(7)	Na	N(1)	96.6(1)	C(2)	N(1)	C(5)	101.9(3)
O(1)	N(2)	O(2)	120.8(3)	O(1)	N(2)	C(2)	19.5(3)
O(2)	N(2)	C(2)	119.7(3)	C(2)	N(3)	C(4)	101.0(3)
N(1)	C(2)	N(2)	120.4(3)	N(1)	C(2)	N(3)	117.8(3)
N(2)	C(2)	N(3)	121.8(3)	N(3)	C(4)	C(5)	111.3(3)
N(1)	C(5)	C(4)	107.9(4)	C(6)	O(3)	C(15)	114.6(5)
C(7)	O(4)	C(8)	113.4(4)	C(9)	O(5)	C(10)	117.3(5)
C(11)	O(6)	C(12)	112.2(6)	C(13)	O(7)	C(14)	111.0(6)
O(3)	C(6)	C(7)	107.2(4)	O(4)	C(7)	C(6)	108.5(4)
O(4)	C(8)	C(9)	107.9(4)	O(5)	C(9)	C(8)	112.3(4)
O(5)	C(10)	C(11)	111.3(5)	O(6)	C(11)	C(10)	107.7(4)
O(6)	C(12)	C(13)	105.5(5)	O(7)	C(13)	C(12)	109.1(4)
O(7)	C(14)	C(15)	107.3(5)	O(3)	C(15)	C(14)	107.1(4)

Table 3. - Torsion Angles of Crown-Ether Ring (°)

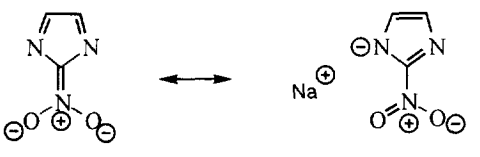
C(15)	O(3)	C(6)	C(7)	178.2(4)	O(3)	C(6)	C(7)	O(4)	-62.3(5)
C(8)	O(4)	C(7)	C(6)	165.9(4)	C(7)	O(4)	C(8)	C(9)	-178.3(3)
O(4)	C(8)	C(9)	O(5)	58.7(5)	C(10)	O(5)	C(9)	C(8)	82.2(5)
C(9)	O(5)	C(10)	C(11)	-171.7(4)	O(5)	C(10)	C(11)	O(6)	62.7(5)
C(12)	O(6)	C(11)	C(10)	-167.7(4)	C(11)	O(6)	C(12)	C(13)	-172.2(4)
O(6)	C(12)	C(13)	O(7)	-56.8(5)	C(14)	O(7)	C(13)	C(12)	157.9(4)
C(13)	O(7)	C(14)	C(15)	-159.4(4)	O(7)	C(14)	C(15)	O(3)	60.1(5)
C(6)	O(3)	C(15)	C(14)	177.7(4)					

Chelating interaction of the sodium ion with the imidazolate occurs through a ring nitrogen and one of the oxygen atoms of the nitro group, making the sodium ion seven-coordinate. The imidazolate anion is planar [maximum deviation from the least squares plane of the non-hydrogen atoms is 0.028(2)Å for N(1)], as in nitroimidazole itself[12] but unlike the situation in the N-alkylated system misonidazole[13] where a small dihedral angle (*ca.* 7.9°) is observed between the planes of the nitro-group and the 5-membered ring. Interaction of the nitro-oxygen, O(1), with the sodium is reflected in a slight elongation of the N(2)—O(1) bond compared with the N(2)—O(2) bond. The sodium ion is only 0.178(1)Å out of the nitroimidazolate plane.

Figure 2



The ^{1}H NMR spectrum of the complex in deuteriochloroform shows only two proton resonances, one of which was assigned to the nitrogen heterocycle, the other to the crown ether. Likewise the ^{13}C NMR resonances for C(4) and C(5) are coincident and downfield (*ca.* 5 ppm) from their position in the free imidazole. This downfield shift is even more marked in the case of the C(2) resonance where a shift of *ca.* 13 ppm is observed. The simplicity of the NMR spectra may be due to rapid exchange between two asymmetrical structures, or to the anion being inherently symmetrical; this could arise either by a change in the solution structure so that the sodium ion is coordinated equally to the two nitro-oxygen atoms (Figure 2 and **5a**), or by ionic dissociation to give a symmetrical free anion.



5a **5b**

It is interesting to note that earlier workers had concluded from infra-red studies on the sodium salts of nitroimidazoles that in such systems the sodium ion is coordinated to the nitro group as in **5a** rather than the heterocyclic ring as in **5b**.[14]

EXPERIMENTAL

NMR spectra were obtained on a JEOL EX270 spectrometer.

The preparation of the 15-crown-5 complex of the sodium salt of 2-nitroimidazole

This material was prepared by a modification of the method of Parrick.[10] 2-Nitroimidazol-1-yl sodium (0.27 g, 2.0 mmol) was dissolved in dry acetonitrile (5 ml) containing 15-crown-5 (0.48 g, 2.2 mmol) and heated under reflux at 80 °C for 5 min. After cooling, volatile components were removed under reduced pressure and the residue washed with ethyl acetate, and then dried under reduced pressure (40 °C at 0.1 mbar) to give the complex (0.69 g, 97%) as a yellow solid. An analytically pure sample of this material was obtained by adding a solution of the complex (100 mg) in chloroform (0.5 ml) to ethyl acetate (30 ml) at room temperature. After standing overnight, yellow needle-shaped crystals (60 mg), m.p. 145-146 °C, were recovered by filtration and dried. These crystals were subsequently shown to be suitable for X-ray analysis. $\delta_H(CDCl_3)$ 3.67(20 H, s, CH_2x10), 7.13(2 H, s, 4-H, 5-H); $\delta_C(CDCl_3)$ 68.74(t, J_{CH} 143, CH_2x10), 132.75(dd, J_{CH} 182 and 14, C-4, C-5), 157.70(t, J_{CH} 15,C-2). Found: C, 44.25; H, 6.36; N, 11.58. $C_{13}H_{22}N_3NaO_7$ requires C, 43.94; H, 6.24; N, 11.83%

X-ray Crystal Structure Determination

The crystal was glued to a glass fibre and mounted on the diffractometer head. All measurements at 291 K.

Crystal Data.- $C_{13}H_{22}N_3Na\ O_7$, M 355.33, Orthorhombic, a 9.559(2), b 11.713(3), c 16.020(4) Å, V 1794(1) Å^3 (by least-squares refinement on diffractometer angles of 25 centred reflections, $22° < \theta < 25°$, λ = 0.71073 Å), space group $P2_12_12_1$, Z 4, D_x 1.32 g cm^{-3}. Lemon-yellow rectangular tablets. Crystal dimensions: 0.80 x 0.40 x 0.30 mm, μ(Mo-Kα) 0.119 mm^{-1}.

Data Collection and Processing. Enraf-Nonius CAD4 diffractometer, $\omega/2\theta$ mode, graphite monochromated Mo-Kα radiation; 3663 reflections measured ($1.74° < \theta < 25°$, h 0 to 11, k 0 to 13, l -19 to 19), 3165 unique [merging R 0.015 after absorption correction ("DIFABS", max., min. transmission factors 1.12, 0.68)], giving 2594 with $F > 3.0\ \sigma(F)$. Crystal decay, 2.3% corrected during processing.

Structure Analysis and Processing. The space group was determined as $P2_12_12_1$ from systematic absences and confirmed by comparison of figures of merit from direct methods solutions in a number of rotational orthorhombic space groups. Direct methods[20] yielded all non-hydrogen atom positions. The structure was refined isotropically and an absorption correction applied by Walker and Stuart's method[21] (Difabs). Anisotropic refinement of the non-hydrogen atoms and Fourier difference synthesis revealed the two hydrogen atoms of the imidazole and several of the hydrogens of the crown ether; only the imidazole

hydrogen atoms (isotropic) refined in a satisfactory manner and the crown ether hydrogen atoms were placed in calculated positions and not refined. Anomalous scattering was insufficient to allow determination of absolute configuration. Full matrix least-squares refinement with $w = 4Fo^2/(\sigma^2(Fo^2) + 0.0016\ Fo^4)$ converged with R and R_w values 0.050, 0.073. A final difference density synthesis yielded max. and min. ΔF 0.42, -0.33 $eÅ^{-3}$. Programmes and sources of scattering factors are given in references 15 to 21.

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† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratories, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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