# *syn*-Selectivity in the Epoxidation of 1-(Cyclohex-2-enyl)-2-nitroimidazole mediated by Hydrogen Bonding

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Epoxidation of 1-(cyclohex-2-enyl)-2-nitroimidazole with 3-chloroperoxybenzoic acid occurs exclusively *syn* to the nitroimidazole in the absence of water; amines react only with the *syn* epoxide.

The stereochemistry of epoxidation by peroxy acids of many cyclohexenes bearing bulky 3-substituents is generally governed by steric factors, the geometrical isomer with the epoxide oxygen *anti* to the 3-substituent being the major or exclusive product when the substituent is non-polar or a hydrogen-bond acceptor.[1–4] Hydrogen bonding is, however, involved in the exclusive *syn*-epoxidation of cyclohexen-3-ol;[4–6] similar control may be taking place in the *syn*-aziridination of this substrate.[7] One exception to this rule is the dependence on solvent of the epoxidation of 3-(*tert*-butyldimethylsilyloxy)cyclohexene by peroxytrifluoroacetic acid.[8] As part of a continuing programme of design, synthesis and evaluation of new radiosensitisers and bioreductively activated cytotoxins based on nitro-heterocycles and, in particular, study of conformationally controlled analogues of the lead compound RSU 1069 [α-(aziridin-l-ylmethyl)-2-nitroimidazole-1-ethanol],[9] we required the diastereoisomers of 1-(3-aziridinyl-2-hydroxycyclohexyl)-2-nitroimidazole and expected that those with aziridine *trans* to the hydroxy group could be formed from the appropriate epoxide.

1-(Cyclohex-2-enyl)-2-nitroimidazole **2**† was prepared by alkylation of the potassium salt of 2-nitroimidazole **1** under phase-transfer conditions,‡ in a modification of the general method of Parrick *et al.*[10] (Scheme 1). Treatment of cycloalkene **2** with the commercial grade of 3-chloroperoxybenzoic acid (MCPBA) (containing *ca.* 35% water) in boiling dichloromethane gave§ a mixture of epoxides **3a** and **3b** in ratios between 2 : 1 and 3 : 1. When the epoxidation was carried out using dried samples of the peroxyacid, the sole epoxide formed was **3a**. Mixtures of **3a** and **3b** could be separated analytically but not preparatively by chromatography. Assignment of the diastereoisomeric identities of the major and minor components of the product mixture was made by nuclear Overhauser enhancement (NOE) measurements in the 270 MHz $^1$H NMR spectra (Fig. 1), which confirmed the assignments of the resonances due to the cyclohexane 1-H, 2-H and 3-H. Particularly diagnostic are the values of the NOEs between the 1-H and 2-H in **3a,b**; the value for the *syn*-isomer **3a** is nearly three-fold larger than the corresponding value for the *anti*-isomer **3b**. These data are consistent with the distance between 1-H and 2-H in the *cis*-arrangement in **3a** being much shorter than the 1-H to 2-H (*trans*) distance in **3b** in the geometry required by the pseudochair conformation. Treatment of mixtures of **3a** and **3b** with aziridine (**CAUTION**) or with the less sterically demanding nucleophile methylamine in boiling ethanol resulted in the consumption exclusively of

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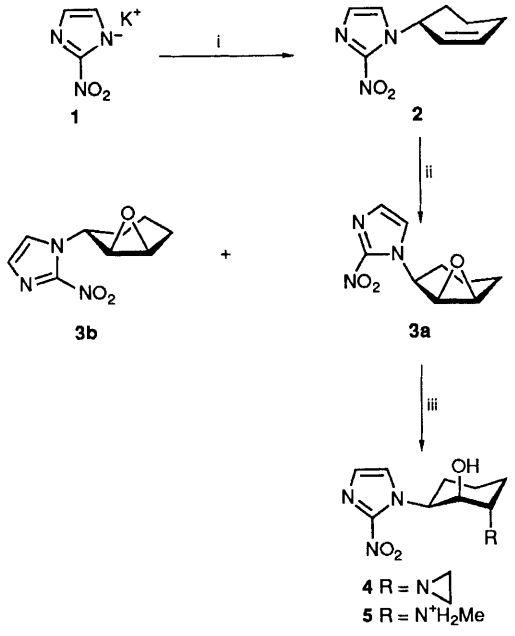
† New compounds were chromatographically homogeneous and gave satisfactory $^1$H NMR and accurate mass spectra. All compounds were racemic.

‡ Salt **1** was stirred with 18-crown-6 and 3-bromocyclohexene in acetonitrile for 24 h, giving, after work-up, **2** (31%) as a gum; $^1$H NMR ($CDCl_3$) δ 1.5–2.4 (6 H, m, 4,5,6-H), 5.70 (1 H, m) and 5.80 (1 H, m) (1,2-H), 6.20 (1 H, ddd, *J* 8, 4, and 3 Hz, 3-H), 7.10 (1 H, s, imidazole 4-H) and 7.25 (1 H, s, imidazole 5-H).

§ Typical experiment. Compound **2** was boiled under reflux in dichloromethane with MCPBA [commercial sample: MCPBA (55% w/w), 3-chlorobenzoic acid (10%) and water (35%)] (3 equiv.) for 20 h to give, after aqueous work-up, a mixture of **3a** and **3b** (48%) in the ratio *ca.* 3 : 1. **3a**: $^1$H NMR ($CDCl_3$) δ 1.5–2.2 (6 H, m, 4,5,6-H), 3.43 (2 H, br s, 2,3-H), 5.56 (1 H, m, 1-H), 7.17 (1 H, s, imidazole 4-H), and 7.57 (1 H, s, imidazole 5-H). **3b**: $^1$H NMR ($CDCl_3$) δ 1.45–1.65 (3 H, m, 5*ax*,5*eq*,6*ax*-H), 1.95 (1 H, ddt, 4*ax*-H), 2.12 (1 H, m, 6*eq*-H), 2.22 (1 H, ddt, 4*eq*-H), 3.25 (1 H, d, 2-H), 3.43 (1 H, m, 3-H), 5.27 (1 H, dd, 1-H), 7.22 (1 H, d, imidazole 4-H) and 7.24 (1 H, br s, imidazole 5-H).



**Scheme 1** Synthesis and reactions of epoxide stereoisomers **3a,b**. Epoxide **3b** is only formed in the presence of water. *Reagents*: i, 3-bromocyclohexene–18-crown-6–acetonitrile; ii, 3-chloroperoxybenzoic acid–dichloromethane; iii, RH–ethanol–triethylamine.

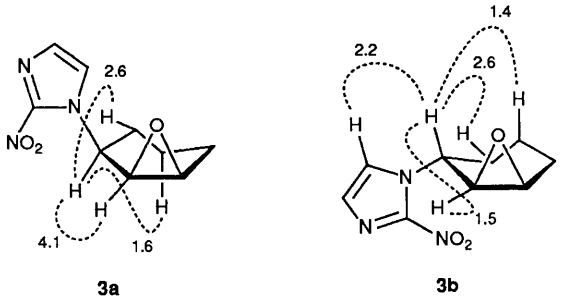


**Fig. 1** NOEs for epoxides **3a,b**. The values of the NOEs are shown as percentages on the dashed lines joining pairs of hydrogens.

the major isomeric epoxide, giving **4**† and **5**† in 81 and 52% yields respectively (based on the content of *syn*-isomer **3a** in the starting mixture of **3a** and **3b**). $^1$H NMR spectra¶ demonstrated that the addition products **4** and **5** have the structures and conformations shown in Scheme 1. In particular, the 2-D carbon–proton chemical shift correlation study on **5** showed *inter alia* that the proton resonances at δ 3.26. 4.19 and 5.33 are due to C–H, whereas that at δ 5.89 is not and can be assigned to O–H. Irradiation of the signal at δ 4.19 causes collapse of couplings at δ 5.89 and 5.33; thus, these protons comprise a CH–CH–OH system. The resonance at δ 5.33 is assigned to 1-H by chemical shift analogy with open-chain analogues (*e.g.* RSU 1069) and by observation of a *trans* diaxial coupling to 6*ax*-H. Therefore, the OH group is at

¶ **4**: $^1$H NMR [$(CD_3)_2SO$] δ 1.12 (1 H, dd, aziridine-H *syn* to N-cyclohexane bond), 1.16 (1 H, dd, aziridine-H *syn* to N-cyclohexane bond), 1.45–1.90 (7 H, m, 2 × aziridine-H *anti* to N-cyclohexane bond + 4*ax*,4*eq*,5*ax*,5*eq*,6*eq*-H), 2.17 (1 H, dq, 6*ax*-H), 3.34 (1 H, m, 3-H), 3.91 (1 H, m, 2-H), 5.11 (1 H, d, OH), 5.49 (1 H, d *ca.* t, 1-H), 7.15 (1 H, d, imidazole 4-H), and 7.67 (1 H, d, imidazole 5-H). **5**: $^1$H NMR [$(CD_3)_2SO$] δ 1.6–1.9 (5 H, m, 4*ax*,4*eq*,5*ax*,5*eq*,6*eq*-H), 2.19 (1 H, br q, 6*ax*-H), 2.63 (1 H, br s, $NCH_3$), 3.26 (1 H, m, 3-H), 4.19 (1 H, m, 2-H), 5.33 (1 H, 1-H), 5.89 (1 H, d, OH), 7.20 (1 H, s, imidazole 4-H), 7.72 (1 H, s, imidazole 5-H), and 9.20 (1 H, br) and 9.35 (1 H, br) ($^+NH_2$).

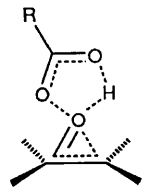


**Fig. 2** General transition state for epoxidation of alkenes by peroxy acids

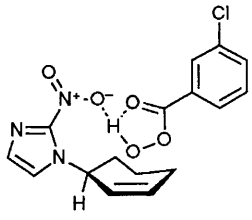


**Fig. 3** Stereocontrol by hydrogen bonding in the reacting complex between cycloalkene **2** and MCPBA

C-2 and **5** has the structure shown; other regio- and stereo-isomers are not consistent with these observations. Both compounds have approximately the conformations indicated in Scheme 1, with nitroimidazole in the equatorial arrangement and hydroxy and nitrogen functions axial; this contrasts with the conformation reported by Lier *et al.*[1] for the analogous *t*-3-amino-*c*-2-phenoxycyclohexan-*r*-1-ol.

The mechanism of the epoxidation of alkenes is considered to involve the peroxy acid in the conformation with an intramolecular hydrogen bond, with rates of reaction being lower in hydrogen-bond accepting solvents.[11] There is also general consensus on the structure of the transition state being similar to that shown in Fig. 2, although 1,3-dipolar cycloaddition has also been proposed.[12] The specificity of epoxidation of **2** by MCPBA in the anhydrous reaction can be rationalised in terms of control through the hydrogen-bonded complex shown in Fig. 3. Examination of models of this structure reveals that the peroxide oxygen is appositely located for the epoxidation process shown in Fig. 2. The presence of trace amounts of water in the reaction mixture, occasioned by the use of undried commercial MCPBA, would tend to disrupt this controlling hydrogen bond, relatively disfavouring epoxidation *syn* to the nitroimidazole.

Thus, stereocontrol is possible through hydrogen bonding of the weak acid MCPBA to an appropriately located hydrogen-bond acceptor, such as the nitro group. This contrasts with the reported[8] lack of such control with MCPBA but good control with the stronger acid peroxytrifluoroacetic acid in the epoxidation of 3-(*tert*-butyldimethylsilyloxy)cyclohexene; this selectivity is abolished when a hydrogen-bond acceptor, such as tetrahydrofuran, is used as the solvent. The demonstration of *syn*-stereospecificity in the epoxidation of **2** with MCPBA suggests either that the nitro group is a more powerful hydrogen-bond acceptor than is a silyl alkyl ether or that the geometry of the intermediate complex is more appropriate for reaction. Further studies on the generality and mechanism of this stereospecificity are being pursued.

The complete lack of reactivity of the amine nucleophiles with isomer **3b**, compared with ready addition to isomer **3a**, is consistent with a preference for ring-opening to give a *trans*-diaxial product in analogy with precedents for opening of other epoxides[3,4,13] with nucleophiles. The corresponding *trans*-diaxial reaction of nucleophiles with the *anti*-isomer **3b**

would require approach to C-2; this is precluded on steric grounds.

The epoxidation of cyclohexene **2** with MCPBA in the presence or absence of small amounts of water represents a new opportunity for exploitation of hydrogen bonding of this readily handled peroxy acid in stereocontrolled synthesis.

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