The stereoselectivity of addition of benzoyloxyl radicals to *trans*-Δ^2-octalin

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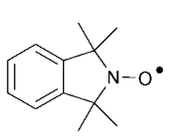
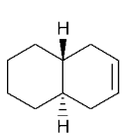
The stereochemistry of addition of benzoyloxyl radicals to the conformationally rigid cyclohexene, *trans*-Δ^2-octalin, in the presence of the free radical scavenger 1,1,3,3-tetramethyl-2,3-dihydro-1*H*-isoindol-2-yloxyl, is reported. Axial addition was favoured over equatorial addition with modest selectivity (axial : equatorial = 1.7 : 1.0). The aminoxyl trapping reaction was more selective with a ratio of *trans* : *cis* addition of 4.4 : 1.0. Interestingly, when the benzoate group is axial, axial trapping by the sterically hindered aminoxyl is strongly favoured (axial : equatorial = 7.4 : 1.0), whereas when the benzoate group is equatorial, there is only a small preference for equatorial trapping by the aminoxyl (equatorial : axial = 2.4 : 1.0). The structures of the four possible addition products were determined by ^{1}H and ^{13}C NMR spectroscopy, and confirmed in the case of the diaxial addition product [2(*ax*)-benzoyloxy-3(*ax*)-(1,1,3,3-tetramethyl-2,3-dihydroisoindol-2-yloxy)-*trans*-decalin **3**] by X-ray crystallographic analysis.

Introduction

The radical trapping technique, employing the stable aminoxyl 1,1,3,3-tetramethyl-2,3-dihydro-1*H*-isoindol-2-yloxyl **1** as radical scavenger, is a powerful technique for studying the reactions of various radicals with alkenes.[1] In previous work, we examined the reactions of benzoyloxyl radicals with cyclohexene and with 4-*tert*-butylcyclohexene. Although *trans* addition was the major reaction observed, the steroeselectivity of benzoyloxyl radical addition (axial : equatorial = 1.6 : 1.0) was much less than that observed for bromine or thiyl radical addition (axial : equatorial = 20 : 1 and *ca.* 2–4 : 1 respectively).[2] Both cyclohexene and 4-*tert*-butylcyclohexene are conformationally mobile systems, so it was of interest to examine the stereochemistry of addition of an oxyl radical to a conformationally rigid (or locked) cyclohexene. As far as we are aware, there have been no previous such studies.



1 = R_2N–O•



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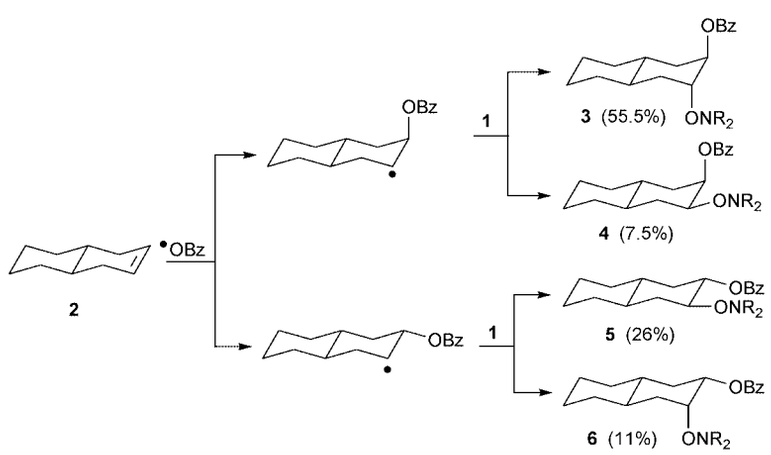
The conformationally rigid cyclohexene chosen was *trans*-Δ^2-octalin **2**, the symmetry of which limits the number of possible addition products to four.

Results and discussion

trans-Δ^2-Octalin was synthesised according to the procedure of Johnson *et al.*[3] Benzoyloxyl radicals were generated by thermolysis of benzoyl peroxide. Thus, benzoyl peroxide (182 mg, 0.11 M) and **1** (300 mg, 0.23 M), in freshly purified **2** (2.0 mL) and acetone (co-solvent, 5.0 mL) were heated at 60 °C for 27 h following successive freeze–evacuation–thaw cycles. The reaction products were isolated by reverse-phase HPLC and their structures determined by ^{1}H and ^{13}C NMR spectroscopy.

The relative yields of the alkoxyamine addition products **3**–**6** are given in Scheme 1.

It can be seen from Scheme 1 that the preferred mode of addition of the benzoyloxyl radical to *trans*-Δ^2-octalin is axial (axial : equatorial = 1.7 : 1.0). This stereoselectivity is very simi-



Scheme 1 Relative yields of products **3**–**6** from the addition of benzoyloxyl radicals to the alkene **2**.

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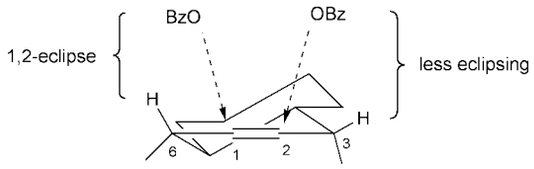


Fig. 1 Relative eclipsing interactions for (equatorial) attack on C1 *versus* (axial) attack on C2.

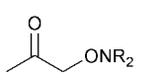
lar to that observed previously for addition to 4-*tert*-butylcyclohexene (axial : equatorial = 1.6 : 1.0).[2]

From a study of molecular models, and assuming that attack by the benzoyloxyl radical is along the Burgi–Dunitz trajectory[4] (Fig. 1), it is clear that attack on C1 from above the plane (or by symmetry, attack on C2 from below the plane, *i.e.*, equatorial approach) results in an unfavourable eclipsing interaction between the benzoyloxyl radical and the pseudo-axial hydrogen on C6. The alternative (axial approach) attack on C2 from above the plane results in less of an eclipsing interaction (with the pseudo-equatorial hydrogen on C3). This small difference in 1,2-eclipsing interactions is believed to be the main reason for the modest axial preference observed for benzoyloxyl radical addition to *trans*-Δ^2-octalin.

It could be argued that torsional effects determine the preferred mode of addition to a cyclohexene, as axial attack would lead to a radical with a chair conformation, while equatorial attack would give rise to a twist-boat radical intermediate. This argument was rejected previously[2] on the grounds that the transition state for addition of the benzoyloxyl radical to an alkene would be expected to occur early along the reaction coordinate. Thus, the stability of the cyclohexyl radical intermediate formed should play little or no part in determining the axial *versus* equatorial preference. Reversibility in the addition step and 1,2-benzoyloxy migration are also considered to be unimportant in influencing the ratio of axial : equatorial addition.[2]

It can also be seen from Scheme 1 that the stereoselectivity of the aminoxyl trapping step depends very much on the orientation of the benzoate group. Thus, when the benzoate group is axial, axial trapping by the aminoxyl is favoured (axial : equatorial = 7.4 : 1.0), whereas when the benzoate group is equatorial, equatorial trapping by the aminoxyl is favoured (equatorial : axial = 2.4 : 1.0). This preference for formation of the *trans* addition product (overall *trans* : *cis* addition = 4.4 : 1.0) was the same as that observed previously with 4-*tert*-butylcyclohexene (*trans* : *cis* addition = 4.4 : 1.0), and is thought to result from a combination of steric and dipolar repulsion factors.[2]

In addition to the products shown in Scheme 1, a number of other alkoxyamine adducts were also formed. These included the four possible hydrogen abstraction products [formed by allylic hydrogen abstraction from **2** followed by trapping with **1**], the acetone-derived adduct **7**, and small amounts of two unidentified compounds.



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The hydrogen abstraction products accounted for approximately 13% of the total reaction products and were not further investigated. The acetone-derived adduct **7**, accounting for approximately 25% of the total reaction products, reflects the proportion of aminoxyl-induced decomposition of benzoyl peroxide.[5] The concomitant formation of these other alkoxyamine adducts, and the generation of benzoyloxyl radicals *via* aminoxyl-induced decomposition of benzoyl peroxide, are considered[2,5] not to influence the relative ratios of addition products **3**–**6**, which together accounted for 60% of the total reaction products.

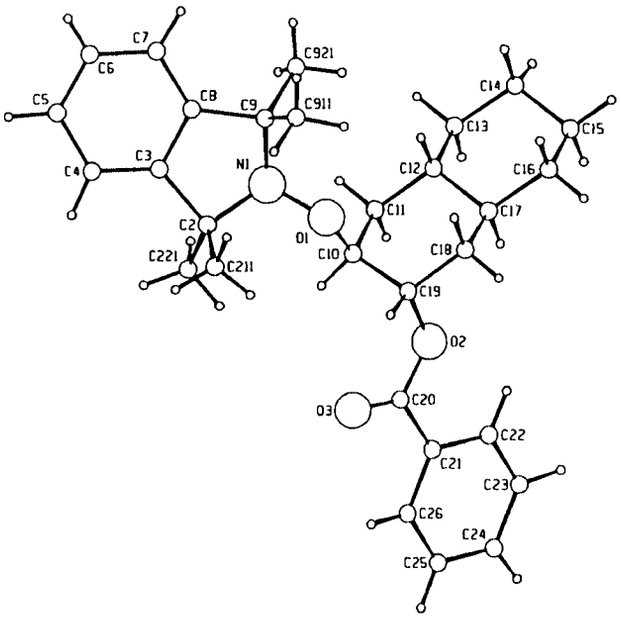

Fig. 2 Molecular projection of **3**.

Structure determination

The structures of the addition products **3**–**6** followed from their ^{1}H and ^{13}C NMR spectra, and in particular, from the two 1H multiplets that occurred in the ranges 3.9–4.3 and 5.0–5.6 ppm of the ^{1}H NMR spectra. Previous studies[1,2] have shown that protons on carbon bearing the aminoxy moiety have chemical shifts that lie in the range 3.6–4.6 ppm, while protons on carbon bearing a benzoyloxy group have chemical shifts in the range 5.0–5.7 ppm.[2] Thus, the diequatorial product **5** showed a 1H, ddd resonance at 4.0 ppm (with couplings of 10.1, 10.1, and 5.0 Hz, corresponding to two diaxial couplings and one axial/equatorial coupling) and a 1H, ddd resonance at 5.11 ppm (with couplings of 10.1, 10.1, and 5.3 Hz, corresponding to two diaxial couplings and one axial/equatorial coupling). The equatorial/axial product **6** showed a broad singlet at 4.34 ppm and a ddd at 5.08 ppm. The resonance at 5.08 ppm showed couplings of 3.2, 5.04, and 11.9 Hz, corresponding to two axial/equatorial and one diaxial coupling, which indicates that the benzoate group is equatorial. The broad singlet at 4.34 ppm had a bandwidth of 13.7 Hz, consistent with three equatorial/axial couplings, and indicating that the aminoxyl group is axial. Similarly, the axial/equatorial product **4** showed a 1H, ddd resonance at 3.91 ppm (with couplings of 2.9, 4.1, and 11.7 Hz, corresponding to two equatorial/axial couplings and one diaxial coupling, *i.e.*, equatorial aminoxy group) and an unresolved multiplet at 5.61 ppm. The narrow bandwidth of the latter (~7.0 Hz) precluded any diaxial couplings, thus indicating that the benzoate group is axial.

Finally, the diaxial product **3** showed two broad doublets (J = 2 Hz, corresponding to an equatorial/equatorial coupling) at 4.08 and 5.49 ppm respectively. The narrow bandwidth of both of these resonances (~11 Hz) precludes a diaxial plus two other couplings, therefore, both benzoate and aminoxyl groups must be axial. The structure of **3** was confirmed by X-ray crystallographic analysis (Fig. 2).†

Conclusion

The addition of benzoyloxyl radicals to *trans*-Δ^2-octalin occurs with modest stereoselectivity, with axial addition being favoured over equatorial addition by approximately 1.7 : 1. Trapping of the resulting radical intermediates by the aminoxyl

† CCDC reference number 188/227. See http://www.rsc.org/suppdata/p2/a9/a908455j/ for crystallographic files in .cif format.

1 occurred with higher stereoselectivity, the *trans* product being favoured by approximately 4.4 : 1. These results, with a conformationally rigid cyclohexene, strongly support those of our earlier study[2] with a conformationally biased cyclohexene, and show conclusively that the stereoselectivity of addition of oxyl radicals to cyclohexenes is not as high as that observed for bromine or thiyl radical addition.

Experimental

Substrates

trans-Δ^2-Octalin was prepared from *cis*-5,8,9,10-tetrahydronaptho-1,4-quinone (itself prepared from *p*-benzoquinone and buta-1,3-diene according to the method of Henbest *et al.*[6]), according to the method of Johnson *et al.*[3] Benzoyl peroxide was obtained commercially, then purified by recrystallisation (×2) from chloroform–methanol (1 : 1), mp 106–107 °C (lit.,[7] 104–106 °C). 1,1,3,3-Tetramethyl-1,3-dihydro-2*H*-isoindol-2-yloxyl was prepared by the procedure of Griffiths *et al.*[8]

Radical trapping experiment

Benzoyl peroxide (182 mg, 1.0 equivalent) was added to a solution of *trans*-Δ^2-octalin (2.0 mL) and acetone (co-solvent, 5.0 mL) containing the aminoxyl (300 mg, 2.1 equivalents). The solution was degassed by successive freeze–thaw cycles on a high vacuum line, sealed under vacuum in a Pyrex vessel, and then heated at 60 °C for 27 h (approximately ten half-lives of the initiator). The majority of volatile material was then removed under reduced pressure prior to isolation of the reaction products by HPLC. An isocratic methanol–water (90 : 10) solvent system, with detection at 270 nm, was used to separate the reaction products.

Product analysis

Peak areas from HPLC chromatograms were converted directly into relative yields of products (differences in extinction coefficients at 270 nm due to the presence or absence of the benzoyloxy moiety were taken into account). The HPLC-separated products were identified by NMR techniques as described previously.[2] ^{1}H and ^{13}C NMR spectra (proton noise-decoupled; off-resonance decoupled) were recorded on a Bruker WM-250 (250.12 and 62.80 MHz), or a Bruker CXP 300 (300.06 MHz) instrument. All *J* values are in Hertz. Mass spectra were recorded at the University of Queensland on a Kratos MS25RFA spectrometer.

Products and new compounds

New products were characterized by the spectroscopic data listed below (determined in $CDCl_3$). The following spectral data for the isoindoline ring system were common for all *trans*-Δ^2-octalin addition products: δ_H 0.78–1.86, m, 12H, $4CH_3$; 7.02–7.09, m, 2H, H4, H7; 7.16–7.21, m, 2H, H5, H6. δ_C 24.7–30.3, ring methyls; 66.9–68.6, C1, C3; 121.3–121.7, C4, C7; 127.1–127.3, C5, C6; 145.2–145.7, C3a, C7a.

Compounds are listed in order of elution from the HPLC column under the conditions stated above [small amounts of two unidentified compounds eluted between **7** and **4**; the ^{1}H NMR spectrum of the first of these was consistent with the aldol condensation product of **7**, however, as it was clear that neither of these compounds was a decalin derivative, they were not further investigated].

2-(2-Oxopropoxy)-1,1,3,3-tetramethyl-2,3-dihydro-1*H*-isoindole 7. δ_H (250.12 MHz) 1.44, s, 12H, ring CH_3; 2.26, s, 3H, $CH_3C(O)$; 4.59, s, 2H, CH_2O; 7.06, m, 2H, H4, H7; 7.23, m, 2H, H5, H6. Identical to an authentic sample by ^{1}H NMR.[5]

2(*ax*)-Benzoyloxy-3(*eq*)-(1,1,3,3-tetramethyl-2,3-dihydro-1*H*-isoindol-2-yloxy)-*trans*-decalin 4. (Found: *M* 447.277. $C_{29}H_{37}NO_3$ requires 447.277). δ_H (250.12 MHz) 0.78–1.79, m, 12H, cyclic methylene protons; 1.21, 1.23, 1.42, 1.49, 4 × 3H, $4CH_3$; 2.07, m, 2H, cyclic methylene protons; 3.91, ddd, 1H, HC(ONR$_2$), *J* 2.9, *J* 4.1, *J* 11.7; 5.61, m, 1H, HC(OBz); 7.04, m, 2H, H4, H7; 7.18, m, 2H, H5, H6; 7.45, t, 2H, *J* 6.9, 7.55, d, 1H, *J* 7.4, 8.11, d, 2H, *J* 8.1, benzoyloxy. δ_C (62.8 MHz) 25.1, 30.1, 4 × CH_3; 26.3, 29.3, 29.6, 33.9, 34.4, 36.5, 41.5, decalin ring carbons; 67.9, **C**$(CH_3)_2$; 72.1, **C**(OBz); 83.5, **C**(ONR$_2$); 121.6, C4, C7; 127.2, C5, C6; 128.4, *meta* benzoyloxy; 129.7, *para* benzoyloxy; 130.1, *ipso* benzoyloxy; 132.9, *ortho* benzoyloxy; 145.4, isoindoline C3a, C7a. The ester carbon was not observed.

2(*eq*)-Benzoyloxy-3(*eq*)-(1,1,3,3-tetramethyl-2,3-dihydroisoindol-2-yloxy)-*trans*-decalin 5. (Found: *M* 447.277. $C_{29}H_{37}NO_3$ requires 447.277). δ_H (300.06 MHz) 0.83–1.75, m, 12H, cyclic methylene protons; 1.16, 1.25, 1.48, 1.60, 4 × 3H, $4CH_3$; 2.08, ddd, 1H, HC**H**HCOBz, *J* 2.3, *J* 5.0, *J* 11.7; 2.47, dd, 1H, HC**H**HC(ONR$_2$), *J* 5.0, *J* 11.1; 4.00, ddd, 1H, **H**C(ONR$_2$), *J* 5.0, *J* 10.1, *J* 10.1; 5.11, ddd, 1H, **H**C(OBz), *J* 5.3, *J* 10.1, *J* 10.1; 7.02, m, 2H, H4, H7; 7.16, m, 2H, H5, H6; 7.43, m, 2H, 7.53, m, 1H, 8.09, m, 2H, benzoyloxy. δ_C (62.8 MHz) 24.7, 25.1, 29.9, 30.3, 4 × **C**H_3; 26.0, 26.1, 32.9, 33.1, 37.9, 39.0, 40.4, decalin ring carbons; 66.9, 68.2, **C**$(CH_3)_2$; 75.3, **C**(ONR$_2$); 80.2, **C**(OBz); 121.3, 121.7, C4, C7; 127.1, C5, C6; 128.2, *meta* benzoyloxy; 129.8, *para* benzoyloxy; 131.0, *ipso* benzoyloxy; 132.7, *ortho* benzoyloxy; 145.7, isoindoline C3a, C7a.

2(*eq*)-Benzoyloxy-3(*ax*)-(1,1,3,3-tetramethyl-2,3-dihydroisoindol-2-yloxy)-*trans*-decalin 6. (Found: *M* 447.277. $C_{29}H_{37}NO_3$ requires 447.277). δ_H (250.12 MHz) 0.83–1.83, m, 13H, cyclic methylene protons; 1.23, 1.36, 1.40, 1.46, 4 × 3H, $4CH_3$; 2.28, ddd, 1H, HC**H**HCONR$_2$, *J* 3.6, *J* 3.6, *J* 14.1; 4.34, vbrs, 1H, **H**C(ONR$_2$); 5.08, ddd, 1H, **H**C(OBz), *J* 3.2, *J* 5.0, *J* 11.9; 6.99, m, 1H, 7.08, m, 1H, H4, H7; 7.18, m, 2H, H5, H6; 7.43, t, 2H, *J* 7.2, *J* 7.2, 7.55, tt, 1H, *J* 7.3, *J* 7.3, *J* 2.5, *J* 2.5, 8.11, dd, 2H, *J* 8.6, *J* 1.5, benzoyloxy. δ_C (62.8 MHz) 25.2, 29.6, 4 × **C**H_3; 26.2, 26.7, 30.1, 32.6, 33.5, 36.1, 36.4, decalin ring carbons; 41.4, **C**H_2COBz; 67.8, 68.6, **C**$(CH_3)_2$; 75.5, **C**(ONR$_2$); 79.5, **C**(OBz); 121.3, 121.7, C4, C7; 127.2, C5, C6; 128.2, *meta* benzoyloxy; 129.9, *para* benzoyloxy; 132.8, *ortho* benzoyloxy; 145.7, isoindoline C3a, C7a. The benzoate *ipso* and ester carbons were not observed.

2(*ax*)-Benzoyloxy-3(ax)-(1,1,3,3-tetramethyl-2,3-dihydroisoindol-2-yloxy)-*trans*-decalin 3. Mp 111–113 °C. (Found: *M* 447.277. $C_{29}H_{37}NO_3$ requires 447.277). δ_H (250.12 MHz) 1.03, m, 2H; 1.24–1.86, m, 11H, cyclic methylene protons; 1.38, 1.40, 1.49, 1.58, 4 × 3H, $4CH_3$; 1.99, d, 1H, HC**H**HCONR$_2$, ^3J 10.1; 4.08, d, 1H, **H**C(ONR$_2$), ^3J 2.0; 5.49, d, 1H, **H**C(OBz), ^3J 2.0; 7.09, m, 2H, H4, H7; 7.21, m, 2H, H5, H6; 7.44, t, 2H, *J* 7.7, *J* 7.7; 7.55, t, 1H, *J* 7.3, *J* 7.3; 8.04, d, 2H, *J* 8.4, benzoyloxy. δ_C (62.8 MHz) 25.4, 4 × CH_3; 26.5, 33.4, 33.5, 33.6, 33.9, 36.9, 37.2, decalin ring carbons; 67.8, **C**$(CH_3)_2$; 71.0, **C**(ONR$_2$); 79.3, **C**(OBz); 121.6, C4, C7; 127.3, C5, C6; 128.4, *meta* benzoyloxy; 129.6, *para* benzoyloxy; 131.0, *ipso* benzoyloxy; 132.9, *ortho* benzoyloxy; 145.2, isoindoline C3a, C7a.

Crystal data

3 $C_{29}H_{37}NO_3$, M_r 447.62, monoclinic $P2_1/n$, *a* 14.904(6), *b* 10.051(1), *c* 17.289(9) Å, β 98.12(2)°, *V* 2564(2) Å^3, $Z = 4$, μ(Mo-Kα) 0.7 cm^{-1}, temperature 296(2) K, 4500 unique reflections, 1928 reflections with $I > 2.5\sigma(I_o)$ gave *R*1 0.040 and *wR*2 0.044.

Acknowledgements

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