Enantioselectivity in a Free-radical Oxidation: Measurement of Small Enantiomeric Excesses

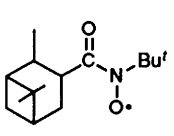
Deborah J. Brooks,[a] M. John Perkins,*[a] Susan L. Smith,[a] David M. Goodall[b] and David K. Lloyd[b]

[a] *Department of Chemistry, Royal Holloway and Bedford New College, Egham Hill, Egham, Surrey, TW20 0EX, UK*

[b] *Department of Chemistry, University of York, York YO1 5DD, UK*

Partial conversion of 2-methyl-1-phenylpropan-1-ol into isobutyrophenone by the acyl aminoxyl radicals formed on oxidation of enantiomerically pure *N*-fenchelylbenzohydroxamic acid or its *para*-nitro derivative occurs with small but measurable enantioselectivity. This has been demonstrated using HPLC with diode-laser-based polarimetric detection to examine unchanged alcohol in the reaction mixtures.

Enantioselectivity in intermolecular hydrogen-atom transfer has been demonstrated by allowing incomplete reaction of a dissymmetric radical with a racemic substrate.[1–3] Recovered substrate from such a reaction has been found to be optically active, showing that selective removal of one enantiomer has taken place. Examples include the reaction of dissymmetric alkoxyl radicals with 2-phenylbutane,[1] and oxidation of racemic benzoin by the pinanecarbonyl aminoxyl **1**.[2] We have



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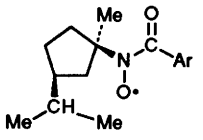


2: Ar = Ph
3: Ar = *p*-$C_6H_4NO_2$

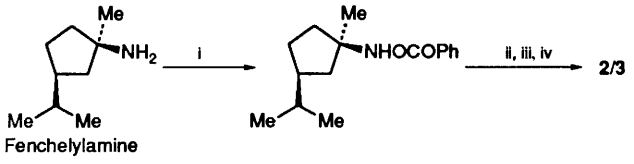
PhCHOHCRMe$_2$

4: R = H
5: R = Me

now extended the latter study by investigating the oxidation of α-phenylalcohols using the acyl fenchelyl† aminoxyls, **2** and **3**.

By incorporating chirality into the *tert*-alkyl group, we planned to investigate the effect of changing the reactivity of the oxidising radical whilst attempting to maintain essentially the same geometric constraints. Reactivity was to be altered by taking advantage of the known variation with substituent of the O–H bond strengths in *N*-aroyl-*N*-*tert*-alkylhydroxylamines.[4]

The chiral aminoxyls were prepared from fenchone‡ *via* fenchelylamine by established procedures (Scheme 1). Reactions



Scheme 1 *Reagents*: i, $(PhCO_2)_2$; ii, ArCOCl; iii, NH_2NH_2; iv, $K_3[Fe(CN)_6]/OH^-$

of the aminoxyls with *ca.* one equivalent of racemic 2-methyl-1-phenylpropan-1-ol (**4**) and the more hindered 2,2-dimethyl-1-phenylpropan-1-ol (**5**) were carried out in benzene at 60 °C (N_2), and recovered alcohol was examined for enantiomer composition.

Measurement of Small Enantiomeric Excesses.—Initial attempts to detect enantioselectivity in oxidation of benzylic alcohols using the fenchelyl aminoxyls had been unsuccessful. However, the reactions of aminoxyls **2** and **3** with racemic **4** were selected for more careful study. Chiral discrimination was expected to be small, and to estimate this we chose to use HPLC in conjunction with a recently developed diode-laser based polarimetric detector.[5] This technique promises to have particular impact in quantitative determination of small enantiomeric excess values. The use of polarimetric and spectrophotometric detectors in series to measure optical rotation (α) and absorbance (*A*) is of particular value for chromatography of complex reaction mixtures on both chiral and achiral columns, as the optical rotation trace should show response only to chiral compounds where there is an enantiomeric excess.[6] For low enantiomeric excess values, the accuracy of determining enantiomeric purity using an achiral column to determine α/A ratios of unknown and reference standard is predicted to be very high.[7] The procedure is not subject to the disadvantages of other methods which depend on the difference between two large numbers (as for example peak integration of HPLC traces using a chiral column), or the rigorous sample purification needed for direct polarimetry (which must be carried out in a way which cannot effect the enantiomeric excess). Where absolute rotations at the measurement wavelength (820 nm) (or enantiomerically pure reference materials) are not available, full or partial separation on a chiral stationary phase provides the necessary reference data. This procedure was used in preliminary experiments with alcohol **5**.

Results

A typical achiral separation of the reaction mixture from (+)-(1*S*)-**2** oxidation of racemic **4** is shown in Fig. 1. Peaks due to reactants and expected products (isobutyrophenone and *N*-fenchelylbenzohydroxamic acid) were identified by chromatography of pure compounds or by spiking portions of reaction mixture with pure samples and observing which peak increased in height. Peaks identified in Fig. 1 are: X, radical; AH, alcohol; K, ketone; XH, hydroxamic acid; and B, benzyl alcohol (marker). Other peaks are attributed to unidentified by-products. The optical rotation (OR) chromatogram is at first sight somewhat confusing, with several positive/negative peak doublets. This type of signal is frequently seen with polarimetric detection during the elution of a high-concentration peak.[5,8] It is thought to be due to the build-up of a liquid lens within the polarimeter cell[9] which causes defocussing of the laser beam and consequently scattering and depolarisation of the light.

† *cis*-1-Methyl-3-(propan-2-yl)cyclopentyl.
‡ 1,3,3-Trimethylnorbornan-2-one.

Table 1 Chromatographic data on reaction mixtures from the oxidation of racemic 2-methyl-1-phenylpropan-1-ol **4** by the enantiomeric fenchelyl aminoxyls **2** and **3**

Radical	Starting alcohol consumed (%)	OR Detector response for residual **4** (α)[a,b]	UV Detector response for residual **4** (10^{-6} A)[a]	$10^6\frac{\alpha}{A}$	$10^3\frac{\alpha/A^c}{\alpha_s/A_s}$	Enantiomer of **4** remaining (%)	Enantiomer of **4** reacted (%)
(+)-**2**	50.3	2.95 ± 0.92	1.55	1.90	3.42	(+) 50.17 (−) 49.83 ± 0.06% (in 49.7% of starting alcohol)	(+) 49.83 (−) 50.17 ± 0.06%
(−)-**2**	42.7	−1.43 ± 0.80	1.42	−1.01	−1.81	(+) 49.91 (−) 50.09 ± 0.05% (in 57.3% of starting alcohol)	(+) 50.12 (−) 49.88 ± 0.07%
(+)-**3**	27	−3.04 ± 0.99	1.70	−1.79	−3.21	(+) 49.84 (−) 50.16 ± 0.05% (in 73% of starting alcohol)	(+) 50.43 (−) 49.57 ± 0.14%
(−)-**3**	31	+3.05 ± 0.87	1.48	2.06	3.70	(+) 50.19 (−) 49.81 ± 0.05% (in 69% of starting alcohol)	(+) 49.58 (−) 50.42 ± 0.11%

[a] Arbitrary units. [b] Errors used in calculation are $t_{95}s/\sqrt{n}$, from $n = 9$ replicate measurements (see ref. 10). [c] $\alpha_s/A_s = \alpha/A$ determined for enantiomerically pure **4** ($= 5.57 \times 10^{-4}$).

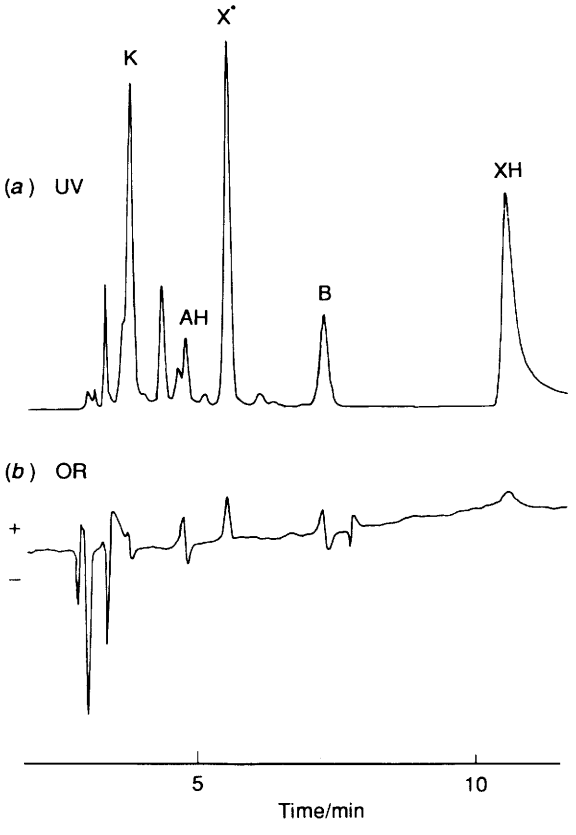


Fig. 1 Chromatograms of the reaction mixture resulting from the partially enantioselective oxidation of *rac*-2-methyl-1-phenylpropan-1-ol **4** (AH) by the fenchelyl aminoxyl (+)-**2** (X•). Products, 2-methyl-1-phenylpropanone (K); *N*-fenchelylbenzohydroxamic acid (XH). Benzyl alcohol (marker, B). Column: Spherisorb S5 CN. Mobile phase hexane: propan-2-ol (95:5), flow rate 1 cm^3 min^{-1}.

Yeung and Reitsma[8] reported that the integrated peak area of this type of artifact signal was close to zero.

Twenty determinations were made of such peak doublets due to the achiral benzyl alcohol marker in the chromatograms of the reaction mixtures from (+)-(1*S*)-**2** with **4** and (−)-(1*R*)-**2** with **4**, and the average integrated area under standardised conditions of measurement was +0.23 ± 2.52 mm^2. This suggests that any bias in the results is considerably smaller than the random error of measurement. The areas of the alcohol OR peaks were determined in the same way, measuring both the positive and negative parts and taking the difference. A similar check could not be carried out on the chromatograms of reaction mixtures from radical **3**, since the marker eluted very late in a broad, more dilute, peak which gave no OR response. A minor peak, clearly evident in the UV traces in Fig. 1, overlaps the front of the peak due to **4**. Allowance was made for its presence but this impurity will have reduced the accuracy of area determinations for oxidations using **2**.

Table 1 shows the OR and UV peak areas for the various reactions, and the ratio of OR to UV peak area (α/A). (The errors are for the 95% confidence limit).[10] By taking the α/A ratio, variations in α due to changing injection and retention are eliminated.[11] α/A was also determined for (+)-(*R*)-**4** (see Table 1 footnote) and for racemic **4** (for which, as expected, α/A was zero within limits of experimental error).

For determination of α/A for 2,2-dimethyl-1-phenylpropan-1-ol (**5**) no optically pure sample was available. However, α/A was readily determined after enantiomeric resolution by HPLC on a chiral stationary phase (Fig. 2). It was found that the oxidation of **5** was very slow under these conditions, and no significant evidence consistent with enantiomer selectivity could be found by analysis of unchanged alcohol.

Discussion

We have been interested in exploring the factors which might influence enantioselectivity in hydrogen-atom transfers of the kind described here. Amongst these factors is the position of the transition state on the reaction co-ordinate. Consideration of the generalised reactions [eqns. (1) and (2)] suggests that: (*a*)

$$(+)\text{-}(S)\text{-X}^\bullet + (+)\text{-}(R)\text{-AH} \xrightarrow{k_1} (+)\text{-}(S)\text{-XH} + \text{A}^\bullet \quad (1)$$

$$(+)\text{-}(S)\text{-X}^\bullet + (-)\text{-}(S)\text{-AH} \xrightarrow{k_2} (+)\text{-}(S)\text{-XH} + \text{A}^\bullet \quad (2)$$

both have similar reactant energies (at least in dilute solution and with reaction association unimportant); (*b*) both have the same product energies (identical products); and therefore (*c*) any discrimination is by virtue of the different energies of the

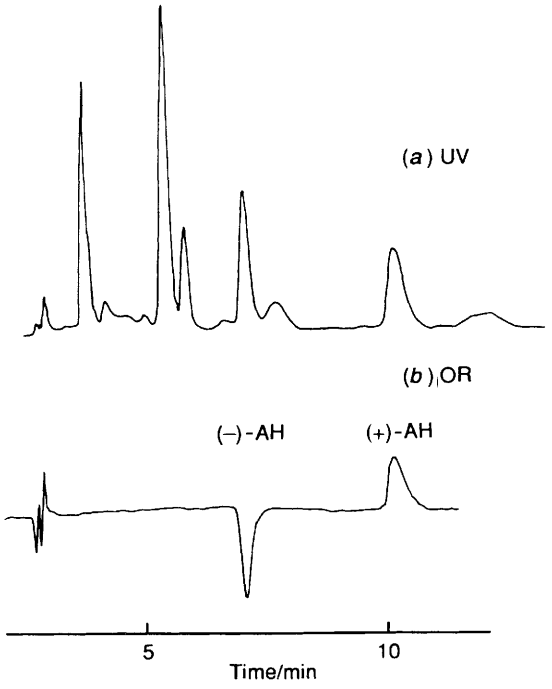


Fig. 2 Enantiomer separation of 2,2-dimethyl-1-phenylpropan-1-ol **5** in a complex mixture from reaction of alcohol **5** with radical **2**. Daicel OD chiral column (25 cm × 0.46 cm). Mobile phase hexane - propan-2-ol (95:5), flow rate 1 cm^3 min^{-1}, 15 μg of each enantiomer injected.

diastereomeric transition states. We have called pairs of similar reactions for which the heats of reaction are the same, but which exhibit different activation barriers, 'equithermal' and have also argued that the greatest kinetic discrimination should be encountered in the thermoneutral case.[12] In such circumstances the transition states for the pair of reactions will be neither reactant-like nor product-like but midway along the reaction co-ordinate. The experiments described here, involving benzylic hydrogen abstraction from alcohols **4** and **5**, were part of a programme to test this extension to the Hammond postulate experimentally.[12]

The rate constant ratio k_1/k_2 may be calculated from percentages of enantiomer reacted, p. From values of p in the

$$k_1/k_2 = p_+/p_- \text{ [reactions of (+)-2 or (+)-3]}$$
$$= p_-/p_+ \text{ [reactions of (−)-2 or (−)-3]}$$

final column of Table 1, $k_1/k_2 = 0.993 \pm 0.002$ and 0.995 ± 0.003 (radical **2**) and 1.017 ± 0.006 and 1.017 ± 0.004 (radical **3**). Overall mean values with 95% confidence limits[10] are $k_1/k_2 = 0.994 \pm 0.003$ (radical **2**); 1.017 ± 0.004 (radical **3**). Both rate constant ratios differ from unity by 2 to 4 times the 95% confidence limits, giving clear evidence for enantioselectivity. As measured by the difference between k_1/k_2 and unity, the enantioselectivity for reaction of alcohol **4** with radical **3** is approximately three times the magnitude and opposite in sign to that for reaction with radical **2** (0.017 as against −0.006). The results obtained, which show that similar radicals of the same chirality exhibit different enantiomeric preferences for alcohol **4**, indicate that any geometric preference determined by the chirality of the fenchelyl group is substantially modified by other factors which differentiate between **2** and **3**. These factors may include the conjugation between the aroyl and aminoxyl groups, which may change sufficiently between benzoyl and nitrobenzoyl to influence the preferred conformation of the molecule as well as association between radical and alcohol. Indeed, when the UV spectra of the enantiomers of **2** were recorded in the presence of enantiomerically pure **4**, there was clear evidence of diastereomeric association. Thus spectral shifts were observed for reactant pairs (+)-**2**:(+)-**4** and (−)-**2**:(−)-**4**, but were absent for their diastereomeric analogues (+)-**2**:(−)-**4** and (−)-**2**:(+)-**4**. Chiral discrimination in association may therefore be stronger than, and in the opposite sense to, that in reaction. Chiral discrimination in association in this case may be similar to that in Pirkle-type complexes.[13] A stable three-point interaction $C_6H_5 \cdots C_6H_5$ coplanar, $C{=}O \cdots H{-}O$ hydrogen bonding, $CH(CH_3)_2 \cdots (CH_3)_2CH$ hydrophobic packing is available in (+)-**2**:(+)-**4** and (−)-**2**:(−)-**4**, whereas the $CH(CH_3)_2$ groups are occluded in the diastereomers. Hydrogen-atom transfer cannot occur directly between partners in the complex, and model building with likely transition state geometry[14] suggests that stereoselectivity will be weaker than in the hydrogen-bonded complex.

We conclude that the systems explored here are inappropriate ones with which to develop the analysis of equithermal reactions discussed in ref. 12.

The selectivities found in this work were very small, and were significantly less than those reported in earlier examples.[1-3] This is not particularly surprising, in view of the relatively minor and remote asymmetry of the aminoxyls. More crowded chiral *tert*-alkylamine precursors, mostly derived from terpenes, have been investigated, but none led to hydroxamic acids in acceptable yields.

Most importantly, perhaps, these experiments have shown the power of the polarimetric HPLC detector as a means of determining very small enantiomeric excesses, whether or not optically pure reference material is available.

Experimental

Fenchelyl Aminoxyls.—(+)-(1*S*)-Fenchone was converted into (+)-fencholamide* (93%; m.p. 94 °C) by the method of Semmler,[15] and the corresponding (+)-isocyanate (98%; pale yellow oil) was then obtained by von Wallach's method.[16] This was hydrolysed using excess aqueous hydrochloric acid (12%, 100 °C, 4 h) to give, after basification and extraction into diethyl ether, (+)-fenchelylamine (93%, amber oil). The crude amine (6.8 g) was added dropwise with stirring to a solution of pure benzoyl peroxide (5.83 g) in dry benzene (100 cm^3).[17] The mixture was stirred at room temperature for 72 h, after which ether (100 cm^3) was added and the precipitated amine salt was removed and washed with ether (2 × 50 cm^3). The combined filtrate was washed with water, aqueous $NaHCO_3$, water, dried (Na_2SO_4) and evaporated to leave a yellow oil. Column chromatography (silica gel, 20% ethyl acetate–80% light petroleum b.p. 60–80 °C) gave *O*-benzoyl-*N*-fenchelylhydroxylamine as a colourless oil (ν/cm^{-1} 3200 and 1700). This hydroxylamine (1.60 g) was benzoylated in benzene (50 cm^3) using benzoyl chloride (0.9 g) and pyridine (0.5 g) (reflux 24 h). The reaction mixture was poured into aqueous HCl, and the product extracted into diethyl ether and isolated by column chromatography (silica gel, $CHCl_3$) as a colourless oil (1.9 g, 85%) (ν/cm^{-1} 1760 and 1640).

This *N,O*-dibenzoylfenchelylhydroxylamine (0.16 mol) was then stirred with hydrazine hydrate (0.13 mol) in absolute ethanol (50 cm^3) for 1.5 h at 40 °C. The mixture was cooled and poured into ice to give *N*-fenchelylbenzohydroxamic acid, obtained as needles, m.p. 116–117 °C from hexane–MeOH: 92%; ν/cm^{-1} 3400 and 1620; δ($CDCl_3$) 0.5–2.10 (17 H, m), 0.7 (6 H, dd), 1.25 (3 H, s), 7.1–7.4 (5 H, m) and 8.3 (1 H, brs); $[\alpha]_D^{25}$ + 6.6 (c = 0.05 in $CHCl_3$); (Calc. for $C_{16}H_{23}NO_2$: C, 73.5; H, 8.8; N, 5.3. Found: C, 73.7; H, 8.9; N, 5.2). Correlation

* *cis*-1-Methyl-3-(propan-2-yl)cyclopentanecarboxamide.

with the configuration of the starting fenchone shows this to have the (*S*)-configuration at C-1 of the fenchelyl group.

The corresponding *p*-nitrobenzohydroxamic acid was prepared similarly; m.p. 129.5–131 °C; $[\alpha]_D^{25}$ +12.2 (*c* = 0.05 in $CHCl_3$); (Calc. for $C_{16}H_{22}N_2O_4$: C, 62.7; H, 7.2; N, 9.15. Found: C, 62.25; H, 7.1; N, 8.9%).

The enantiomeric hydroxamic acids $[\alpha]_D^{25}$ −6.6 and −12.7 respectively were prepared similarly from (−)-fenchone.

The aminoxyls were prepared by shaking a solution of the appropriate hydroxamic acid (0.04 mmol) in reagent grade benzene with excess aqueous alkaline $K_3Fe(CN)_6$.[18] The solutions were washed thoroughly (water) and dried (Na_2SO_4); solvent was then removed under reduced pressure, without heating, and replaced by CCl_4 (2 cm^3). The CCl_4 solutions were used for the alcohol oxidations (0.04 mmol).

Oxidation of 2-Methyl-1-phenylpropan-1-ol (**4**).—Racemic **4** (0.04 mmol) was added to each of the CCl_4 solutions of aminoxyls (0.04 mmol). The solutions were purged with nitrogen, stoppered under an atmosphere of nitrogen, and stored at 60 °C for 72 h. The reaction mixtures were then analysed as described below. Complete reaction would yield as products 0.02 mmol of ketone and 0.04 mmol of hydroxamic acid, plus 0.02 mmol of residual alcohol (50% of starting value).

Chromatography.—Achiral chromatography was performed on a Spherisorb S5 CN (25 × 0.46 cm) column with 95:5 hexane–propan-2-ol (enantiomers of **2** and **3** reacted with **4**) or 93:7 hexane:ethyl acetate (preliminary experiments with **5**) mobile phase at a flow rate of 1 cm^3 min^{-1}. Five separations of each combination of radical and alcohol were performed. Chiral chromatography of the five standard and reaction mixtures was performed on a Daicel OD (25 × 0.46 cm) chiral stationary phase. The mobile phase was 95:5 hexane–propan-2-ol at a flow rate of 1 cm^3 min^{-1}. The rest of the chromatographic system comprised a pump (ACS model 352) and an injection valve (Rheodyne 7125) with a 20 mm^3 sample loop. Detection was by UV photometry (ACS model 750/12) at 254 nm and by polarimetry (ACS model 750/25 ChiraMonitor) at 820 nm. The reaction mixtures were prepared for chromatography by removing the carbon tetrachloride in which the reaction took place and dissolving the residue in an equal volume of 95:5 hexane–propan-2-ol. Benzyl alcohol was added to each sample as a standard marker at a concentration of 2 mg cm^{-3}.

Ultraviolet Spectroscopy.—Qualitative examination of the UV spectra of aminoxyls **2** in CCl_4 showed that there was a small bathochromic shift (to *ca.* 317 nm) from the normal absorption maximum (336 nm) when either (+)-**2** was admixed with one mole equivalent of (+)-**4**, or (−)-**2** was admixed with one mole equivalent of (−)-**4** at ambient temperature. Using similar concentrations no perceptible change was observed for (+)-**4** with (−)-**2** or (−)-**4** with (+)-**2**.

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