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Enantiomeric NMR analysis of chiral epoxides as addition compounds with *d*-ephedrine

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Adducts of *d*-ephedrine with chiral mono- and disubstituted epoxides are convenient derivatives for the determination of enantiomer ratios in epoxides by ^{1}H NMR spectroscopy.

The individual enantiomers of chiral terminal epoxides became easily available due to the Jacobsen discovery of excellent catalysts for the enantioselective hydrolysis of terminal epoxides.[1] As a consequence, chiral epoxides are of considerable importance as synthetic intermediates. In the use of these chiral intermediates, the determination of an enantiomer ratio in the scalemic samples of epoxides, as well as of the enantiomeric purity of homochiral epoxides (enantiomeric analysis), is an unavoidable procedure. No general method for the enantiomeric analysis of terminal epoxides is currently available. This situation is well illustrated by Jacobsen work,[1] in which HPLC and GLC on several chiral columns were applied to the chiral analysis of 29 terminal epoxides without derivatization or after conversion into addition products with trimethylsilylazide, 2-naphthalenethiol or 2-mercaptobenzothiazole. Recently, a new method has been proposed for the analysis consisting in the formation of the addition compounds of terminal epoxides with (4*E*,5*R*)-bis-(*N*,*N*-dimethylaminocarbonyl)-2-chloro-1,3,2-dioxaphospholane and the subsequent ^{31}P NMR analysis of the resulting diastereomer mixture.[2] The obvious drawbacks of the method are the necessity to prepare the reagent and an incomplete regioselectivity of epoxide ring opening complicating the NMR analysis.

We found that *d*-ephedrine [(1*S*,2*R*)-(+)-2-methylamino-1-phenylpropan-1-ol] is a convenient reagent for the chiral analysis

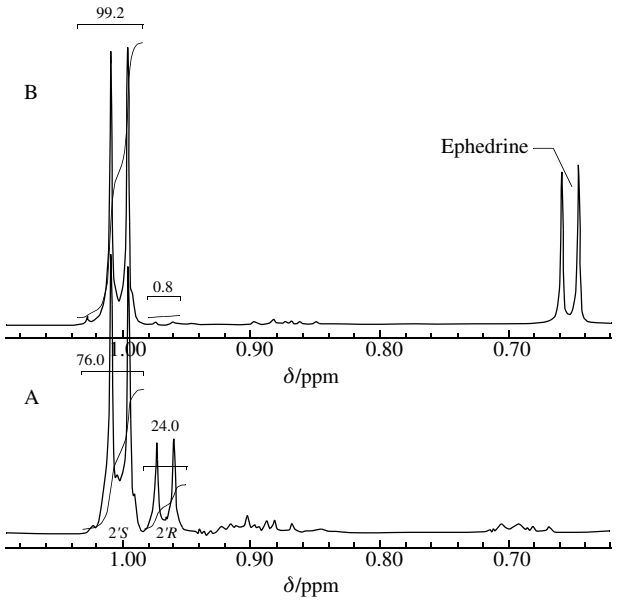
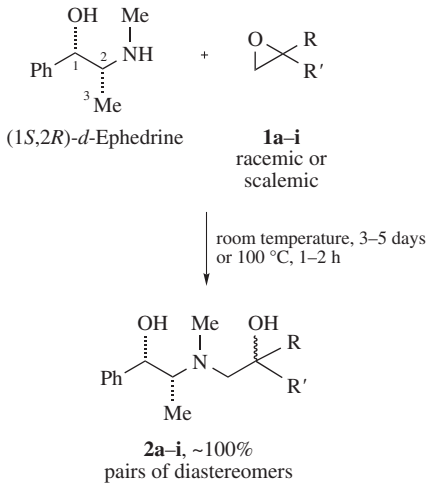


Figure 1 Parts of ^{1}H NMR spectra (C_6D_6, 500 MHz) of unpurified *d*-ephedrine adducts **2f** obtained from scalemic samples of epoxide **1f** with *ee* 52% (A) and 98.4% (B). The B sample of epoxide was obtained from the A sample by chemical and enantiomeric purification, both samples are enriched in *S*-enantiomer. The signals of C(3)H_3 groups (all are doublets with *J* 6.6 Hz) of ephedrine residues of adducts 2′*R* and 2′*S* diastereomers are shown. In the B spectrum in a high field a corresponding signal is present for the unreacted ephedrine used in the reaction in an excess.

of terminal epoxides and some disubstituted epoxides by an ordinary ^{1}H NMR technique. *d*-Ephedrine is inexpensive and commercially available. As it is a biologically low-active enantiomer of natural *l*-ephedrine, it could be handled without official regulations.

d-Ephedrine adds to terminal epoxides **1a–i**† cleanly at the unsubstituted end of the epoxide ring forming quantitatively dihydroxyamine addition products (adducts) **2a–i** each as a mixture of two diastereomers (Scheme 1). This addition is best performed without solvents. For epoxides **1a–h**, it needs several days at room temperature (20–22 °C) or 1.5 h at 100 °C for completion.‡ In the cases of disubstituted epoxides **1i** and (*E*)-stilbene oxide **1j**, the formation of corresponding adducts **2i,j** is complete only after 4 h at 150 °C.‡ Various catalysts were proposed for the aminolysis of epoxides.[6] We used lithium bromide,[6(g)] which is most compatible with many functional



Scheme 1 Formation of adducts from terminal epoxides and *d*-ephedrine. For R and R′ see Scheme 2.

† Racemic epoxides **1a**,**b** from Aldrich were used; **1b** was distilled in a vacuum before use to remove a volatile impurity. Racemic **1c–j** and scalemic **1c**,**d** were prepared according to published procedures.[2(b),3–5] Preparation of scalemic **1e**,**f**, see Supplementary Materials to this paper.

groups§ and the least influencing the NMR spectrum. Indeed, lithium bromide (5 mol%) was found to catalyse the test reaction leading to the almost complete addition of *d*-ephedrine to monosubstituted epoxide **1b** in 3 h at room temperature and to disubstituted **1i** in 2 h at 90 °C.‡ All the proposed methods gave equal results for appropriate epoxides.

Reaction mixtures after *d*-ephedrine additions were ready to ^{1}H NMR study after dissolution in deuterobenzene.¶ In all of the investigated cases, the diastereomeric doubling of several adduct signals was observed (Scheme 2). 'Ephedrinic' parts of adduct molecules provide, as a rule, good reporter signals for the measurements of diastereomer ratios by spectrum integration. These signals are those of MeC^2 (δ 0.94–1.04 ppm, $\Delta\delta$ up to 0.08 ppm, doublets, *J* 6.6–7.0 Hz), HC^{1}O (δ 4.34–4.70 ppm, $\Delta\delta$ up to 0.13 ppm, doublets, *J* 4.6–6.6 Hz), MeN groups (δ 1.67–2.27 ppm, $\Delta\delta$ up to 0.32 ppm, singlets), and in most cases *ortho* protons of the phenyl group (δ 7.22–7.41 ppm, $\Delta\delta$ up to 0.05 ppm, doublets, *J* 7.0–8.7 Hz).†† The 'epoxide' parts of adduct molecules provide additional useful reporter signals. Illustrative examples are the singlet signals of COOMe groups in **2f** and **2g** remote from asymmetric centres but nevertheless suitable as the reporter signals. The solutions of the reaction mixtures from catalysed reactions contain small quantities of lithium bromide solubilised in deuterobenzene possibly due to complexation with polar adducts. This contamination results in small down-field shifts (up to +0.13 ppm) of some adduct signals but does not change the spectrum features mentioned above.

The phenomenon of diastereomeric doubling of remote proton signals is very common for *d*-ephedrine adducts **2** possibly due to the folded conformations of these adducts stabilised by the hydrogen bond of epoxide-origin hydroxyl group with ephedrine phenyl ring. This assumption is supported by the vicinal H^1–H^2 spin–spin coupling constant in adducts **2** (5.3–6.6 Hz for **2a–i**),

‡ *General procedures for the enantiomeric analysis of epoxides.*

Method A (for **1a–h**). Weighted amounts of epoxides **1a–h** (5–20 mg) and *d*-ephedrine (1.02–1.05 mol of the free base or its hemi-hydrate) were placed in a Reacti-Vial (0.5–1 ml, with a conical bottom), gently heated until the melting of *d*-ephedrine (mp 38 °C or 40 °C, anhydrous or hemi-hydrate), very thoroughly mixed with a thin steel rod, stoppered and stored at room temperature in a dark place until nearly complete epoxide consumption (3–5 days, TLC control). The reaction mixture (colourless transparent glass) was dissolved in C_6D_6 (0.4 ml), and the ^{1}H NMR spectrum was recorded at 500 MHz. If needed (see the discussion), various quantities (up to 6 mol were tested) of benzoic acid were added to an NMR solution in the ampoule, and a new spectrum was recorded.

Method B (for **1a–h**). Similar to Method A, but the reagent mixture was kept for 1.5 h in an air bath at 100 °C.

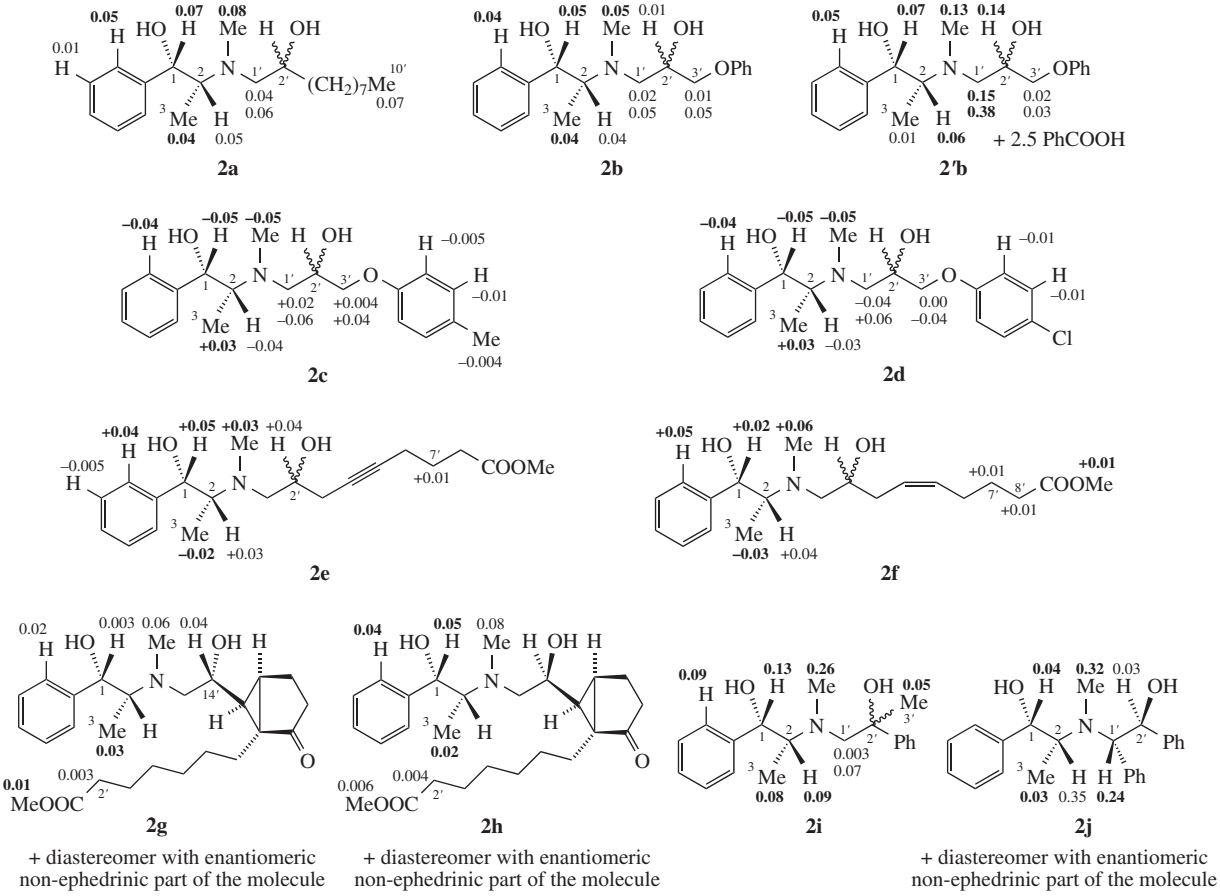
Method C (for **1i,j**). Similar to Method A, but the reagent mixture with epoxides **1i,j** was sealed under a vacuum in an ampoule and kept for 4 h in an air bath at 150 °C.

Method D (for **1a–j**). Similar to Method A, but anhydrous LiBr (5 mol%) was added to the reagent mixture, and the suspension was stirred (until complete LiBr dissolution) for 3 h at room temperature (epoxides **1a–h**) or 2 h at 90 °C (epoxides **1i,j**). Such reaction mixtures sometimes formed turbid solutions in C_6D_6 readily clarified by cotton wool filtration.

§ An attempt to catalyse the addition by magnesium, tin(II) and zinc triflates[6(a)] or silica gel[6(h)] (10% m/m each) was unsuccessful probably due to the preferential coordination of these catalysts with a hydroxyl group of *d*-ephedrine.

¶ Adducts **2** tend to form fine crystalline deposits on storage in a (deutero)-chloroform solution possibly due to hydro(deutero)chloride salt formation; therefore, chlorine-containing solvents should be avoided.

†† Typical ^{1}H NMR spectrum (500 MHz, C_6D_6) δ: 1:1 diastereomer mixture **2b** (1st/2nd isomers or both isomers) 0.94/0.97 (2d, 2×1.5H, C$^3H_3$, *J* 6.6/6.6 Hz), 1.94/2.00 (2s, 2×1.5H, N–Me), 2.37/2.39 and 2.51/2.46 (4dd, 4×0.5H, C$^{1'}H_2$, *J* 12.8/12.8, 3.9/9.0 and 12.8/12.8, 9.0/3.9 Hz), 2.65/2.69 (2qd, 2×0.5H, H^2, *J* 6.6/6.6, 5.9/6.1 Hz), 3.61/3.66 and 3.76/3.75 (4dd, 4×0.5H, C$^3H_2$, *J* 9.2/9.5, 5.0/4.8 and 9.2/9.5, 5.3/5.4 Hz), 3.82/3.83 (2quintets, 2×0.5H, H$^{2'}$, *J* 4.7/4.7 Hz), 4.43/4.48 (2d, 2×0.5H, H^1, *J* 5.9/6.1 Hz), 6.83–6.88 (m, 3H, *o*+*p*-$H_{Ph\ epoxidic}$), 7.08–7.20 (m, 5H, *m*+*p*-H_{Ph}), 7.23/7.28 (2d, 2×1H, *o*-$H_{Ph\ ephedrinic}$, *J* 7.6/7.2 Hz). ^{1}H NMR spectra of epoxides **1a–j** and adducts **2a**,**c–j** in C_6D_6 could be found in Supplementary Materials to this paper.



Scheme 2 Pairs of diastereomeric adducts of *d*-ephedrine with chiral epoxides. Chemical shift differences ($\Delta\delta$/ppm) of diastereomer signals in ^{1}H NMR spectra in C_6D_6 are shown at the corresponding protons. $\Delta\delta$ with a sign correspond to $\delta(2'R) - \delta(2'S)$ differences (in cases when individual diastereomers were available). $\Delta\delta$ for the used or assumed reporter signals are bolded.

which differs distinctly from that in *d*-ephedrine (3.2–3.7 Hz; corresponds to a gauche conformation of these protons, predicted by the semi-empirical PM3 method).

The signals of residual *d*-ephedrine (δ 0.55–0.71, 2.00–2.07 and 4.68–4.76 ppm for MeC^2, MeN and HC^{1}O groups, respectively) taken in a small excess appear in the NMR spectra of crude adducts **2** well apart from the above mentioned reporter signals of adducts and thus do not interfere with the analysis. Moreover, in the cases of incomplete consumption of racemic epoxides **1** in the addition reaction, the integral intensities of diastereomer signals of adducts already formed never deviated measurably from a 1:1 ratio thus demonstrating very low (if any) enantioselectivity of *d*-ephedrine addition to epoxides **1**.

The sensitivity of the proposed method was demonstrated by the determination of the enantiomeric composition of a sample of epoxide **1f** greatly enriched in *S*-enantiomer. A 0.8% concentration of diastereomer (2′*R*)-**2f** was easily measured in the corresponding adduct mixture **2f** by the direct integration of MeC^2 doublet signals at δ 0.97 (2′*R*) and 1.00 (2′*S*) ppm in the ^{1}H NMR spectrum at 500 MHz (Figure 1). Epoxide **1f** (in a racemic form) is an intermediate in the synthesis of a constanolactone synthon.[5]

An additional possibility to use adducts **2** for enantiomeric analysis consists in the recording of the ^{1}H NMR spectrum of corresponding benzoates.[‡‡] These salts could be most conveniently prepared by the addition of one or more equivalents of solid benzoic acid to an adduct solution after the measurement of its NMR spectrum. Benzoic acid induces various changes in the ^{1}H NMR spectra of adducts, as demonstrated by the spectrum of adduct **2b** with benzoic salt (**2′b**).[§§] The first change is a significant downfield shift of the most signals in the spectrum that progressively increases with the amount of added benzoic acid. The largest downfield shift (1.4 ppm with 6 mol of BzOH) was observed for the signal of H^1 that is not the closest to the nitrogen atom. Presumably, benzoic acid acts not only as a salt-forming agent but also as a shift reagent. The second change is a great alteration of spin-spin coupling constants around C^1–C^2 and C$^{1'}$–C$^{2'}$ bonds manifesting the formation of a single preferred conformation of **2′b** analogous to that described for the salts of other α-aminoalcohols.[7] The third change is a significant increase in the diastereomeric separation of some signals (*e.g.*, from 0.05 to 0.13 for N–Me and from 0.05 to 0.38 for C$^{1'}$H signals of **2b**, see **2′b** in Scheme 2). All these changes can be used for the enantiomeric analysis, for example, to clear reporter signals from overlapping with other signals in a spectrum.

In general, a method is developed for the enantiomeric analysis of chiral epoxides using an ordinary ^{1}H NMR technique. The method consists in the conversion of epoxides into adducts with *d*-ephedrine by the thermal or catalytic reaction without solvents and direct NMR analysis of reaction mixtures for the diastereomer ratio. The separation and shape of diastereomer

‡‡ Other acids similar in strength could be used. However, a salt of much stronger trifluoroacetic acid with 1:1 diastereomer mixture **2b** produced a four-component NMR spectrum due to a persistent in NMR time-scale protonation, which results in the formation of an additional asymmetric centre at the nitrogen atoms of adduct molecules. Such a spectrum is not suitable for enantiomeric analysis due to complexity.

§§ *1:1 diastereomer mixture* **2b** *with addition of BzOH* (2.5 mol), ^{1}H NMR (500 MHz, C_6D_6) δ: (1st/2nd isomers or both isomers) 0.71/0.725 (2d, 2×1.5H, C^3H_3, *J* 6.8/6.8 Hz), 2.38/2.51 (2s, 2×1.5H, N–Me), 2.72/2.87 and 3.42/3.04 (4dd, 4×0.5H, $C^{1'}H_2$, *J* 13.0, 2.0/12.9, 9.8 and 13.0, 10.3/12.9, 1.3 Hz), 3.22/3.28 (2qd, 2×0.5H, H^2, *J* 6.8, 1.3/6.8, 2.0 Hz), 3.81/3.83 and 3.98/3.96 (4dd, 4×0.5H, $C^{3'}H_2$, *J* 9.5, 7.7/9.7, 7.1 and 9.5, 4.5/9.7, 4.5 Hz), 4.41/4.55 (2br. s, 2×0.5H, H$^{2'}$), 5.72/5.78 (2d, 2×0.5H, H^1, *J* 1.3/2.0 Hz), 6.84 (m, 3H, *o*+*p*-$H_{Ph\ epoxidic}$), 7.04–7.18 (m, 12.5H, *m*+*p*-H_{Ph}), 7.45/7.50 (2d, 2×1H, *o*-$H_{Ph\ ephedrinic}$, *J* 7.5/7.6 Hz), 8.31 (dd, 5H, *o*-H_{BzOH}, *J* 7.9, 1.6 Hz), 9.36 (s, 4.5H, OH + NH).

signals can be improved by the addition of benzoic acid. The applicability of the method was demonstrated with several monosubstituted and two disubstituted epoxides.

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Supplementary Materials Available: Experimental data of scalemic epoxides **1e**,**f** preparation and of ^{1}H NMR spectra (in C_6D_6) of epoxides **1a–j** and diastereomeric pairs of adducts **2a**,**c–j**. This material is available free of charge *via* http://www.turpion.org/suppl/mc/2151/suppl2151.pdf

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