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Direct NMR Assay of the Enantiomeric Purity of Chiral β-Hydroxy esters by Using Quinine as Chiral Solvating Agent

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Abstract: The use of quinine as a chiral solvating agent for NMR spectroscopy affords a general method for the enantiomeric purity determination of β-hydroxyesters. The ester group represents the most suitable probe for the measurements, which can be optimized by varying the molar ratio ester/quinine, the total concentration or the temperature.

The growing interest towards asymmetric syntheses has induced a concomitant effort to develop new and efficient methods to evaluate enantiomeric excesses (e.e.). NMR methods based on the use of diamagnetic chiral solvating agents[1-4] (CSAs) are today of great interest: the e.e. determination only requires the acquisition of routine NMR spectra of their mixtures with the chiral analyte in the suitable deuterated solvent: the main limiting factors being the lack of general applicability and, in some cases, their cost. Quinine has been successfully employed as a CSA in several cases[5-7]; it is commercially available at very low cost and efficiently discriminates between the enantiomers of different classes of compounds because of the simultaneous presence of different and suitable functional groups in the molecule.

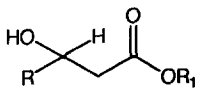
Recently, we became interested to the development of new chiral auxiliaries for the Reformatsky synthesis of optically active β-hydroxy esters[8], for which no general methods for the determination of the enantiomeric purities have been described till now[9,10]. We report here that quinine (**Q**) can be employed as an efficient CSA for the determination of the enantiomeric purities of β hydroxy esters[8]. The accurate analysis of the experimental conditions (molar ratio ester/**Q**, total concentration, temperature) which allows us to optimize the enantioseparations is also described.

RESULTS and DISCUSSION

The ^{1}H NMR spectra of quinine, β-hydroxyesters **a-l** (Scheme) and their mixtures have been recorded at 300 MHz in $CDCl_3$ as solvent. By comparing the spectra of racemic **a-h** in the free state and in the presence of the CSA, it has been established that quinine induced non-equivalence in the enantiotopic nuclei of the two enantiomers of each ester, the magnitude of which has been suitably evaluated on their *tert*-butyl absorptions; in fact, these are well recognizable sharp singlets in an almost free spectral region

(near to 1.0 ppm).

Scheme



1) R_1 = tBu ; R = Ph(a), pMe-C_6H_4(b),pCF_3-C_6H_4(c), Ph-CH=CH(e), 2-Naphthyl(f), 1-Naphthyl(g), c-Hex(h)

2) R_1 = Et(i), Me(l) ; R = Ph

As an example, in the Figure 1 the spectral regions corresponding to the *tert*-butyl resonances of free **a**(A), the equimolar mixture (R,S)-**a** /quinine (B) and the corresponding mixture containing the (S)-enantiomer of **a** (C) are shown.

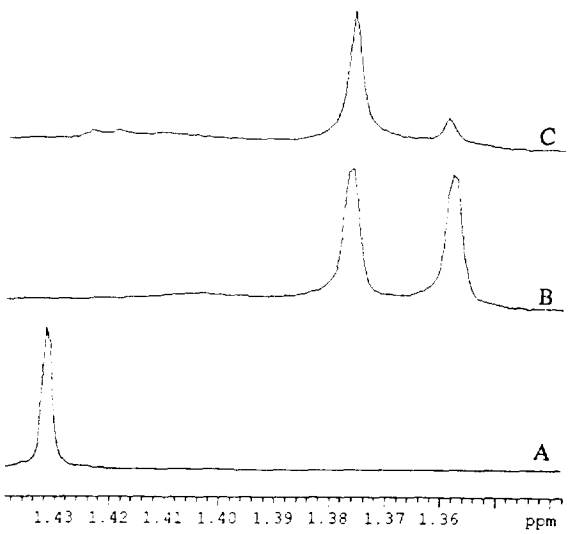


Figure 1. ^{1}H NMR resonances (300 MHz, $CDCl_3$) of *tert*-butyl protons in: free **a** (A), the equimolar mixture (R,S)-**a** / **Q** (B) and the equimolar mixture (S)-**a** / **Q** (C).

Their analysis clearly showed that quinine produced both a resolution and a shift to lower frequency of the absorptions due to the *tert*-butyl protons of the two enantiomers of **a**. The comparison between the spectra B and C unequivocally confirms that the two signals obtained in the presence of the CSA are due to the two enantiomers, which are in fast exchange on the NMR time scale between the free and bound states; thus, the relative areas of the two signals correspond to the relative amount of the two enantiomers and, hence, to the enantiomeric composition of **a**.

For all cases examined, the signals stemming from the *tert*-butyl group give rise to appreciable non-equivalences, at room temperature and in the presence of one equivalent of quinine (Table 1) and the magnitude of the splitting obtained is strongly affected by the molar ratio ester/quinine and by the

temperature.

Table 1. Shift non-equivalence ($\Delta\delta^a$, 300 MHz, $CDCl_3$, 25°C) induced in the *tert*-butyl and CH protons of the β-hydroxy-*tert*-butyl esters **a-h** in the presence of quinine, as a function of the molar ratio ester/quinine.

Ester	1:1		1:2	
	Bu^t	CH	Bu^t	CH
a	3.9	8.3	5.4	8.4
b	3.3	8.6	5.0	8.4
c	5.4	6.4	7.6	8.3
d	3.0	8.0	4.8	8.1
e	2.6	6.1	4.1	6.3
f	4.3	7.7	6.1	8.0
g	5.6	9.1	8.7	9.1
h	2.0	n.d.	2.6	n.d.

[a] Difference of the proton chemical shifts (Hz) of the two enantiomers in the presence of quinine.

As shown in the Table 1, the non-equivalence increases approximately by 50% on varying the above molar ratio from 1:1 to 1:2. By the addition of further equivalents of quinine, the *tert*-butyl non-equivalences continue to increase and at a molar ratio equal to 1:5, the expected saturation effect is observed (Figure 2).

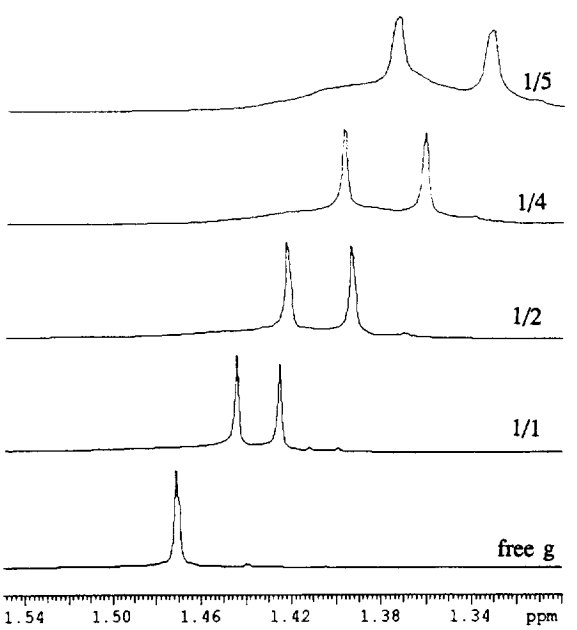


Figure 2. ^1H NMR resonances (300 MHz, $CDCl_3$) of *tert*-butyl protons of free **g** and of mixtures (R,S)-**g** / **Q** (B) in different molar ratios.

As far as the effect of the temperature is concerned, a two fold increase of the *tert*-butyl non-equivalence has been measured by lowering the temperature to -40 °C, without any sensitive loss of the spectral resolution (Table 2).

Table 2 . Shift non-equivalence ($\Delta\delta^a$, 300 MHz, $CDCl_3$, 25°C) induced in the *tert* butyl and CH protons of **g** in the presence of quinine, as a function of the molar ratio ester / quinine

group	1:1	1:2	1:4	1:5
Bu^t	5.63	8.66	11.04	12.34
CHOH	9.09	9.10	8.77	8.87

[a] Difference of the proton chemical shifts (Hz) of the two enantiomers in the presence of quinine

Both the increase of the molar ratio ester/quinine as well as the lowering of temperature (Table 2) can contribute to the increase of the non-equivalence by means of two mechanisms: a different increase of the molar fraction of bound ester for the two enantiomers and also a different degree of conformational homogeneity for them. An experimental parameter which is relevant in determining the outcome of the e.e. determinations involving the use of CSAs is the total concentration of the analysed solution. Indeed the stability constants of the two diastereoisomeric complexes formed by each enantiomer of the analyte and the CSA could be different, in principle, and hence different total concentrations could produce different bound fractions for the two enantiomers. In our case, the non-equivalence measured on the *tert*-butyl protons approximately undergoes a ten-fold increase by increasing the total concentration from 7mM to 0.7M (Table 3).

Table 3. Induced shift non-equivalence ($\Delta\delta^a$, 300 MHz, $CDCl_3$, 25°C) in the *tert*-butyl and CH protons of **g** in the presence of an equimolar amount of quinine, as a function of the total concentration C (M)

C	0.703	0.351	0.070	0.035	0.014	0.007
Bu^t	11.26	8.88	4.63	2.60	1.74	0.86
CHOH	8.68	8.88	9.09	0.00	0.00	0.00

[a] Difference of the proton chemical shifts (Hz) of the two enantiomers in the presence of quinine

Significative non-equivalences are also measured in other alkyl or aromatic resonances of the substrates **a-h**, but, in most cases, these absorptions show complicate coupling patterns or they are partially superimposed to the quinine signals, thus making difficult the e.e. determination. As an example, in the presence of one equivalent of quinine, the methine protons of all the substrates analysed show greater non-equivalences relatively to the *tert*-butyl protons (Table 1).

Unfortunately, these cannot be usefully employed for the determination of the enantiomeric purities, because the spreadening of the methine signals, caused by the complicate coupling pattern (Figure 3 illustrates an example), makes them partially superimposed in spite of the relevant non-equivalence; furthermore, their

complicate structure prevent us from determining the enantiomeric composition by the simple comparison of the heights of the line multiplets.

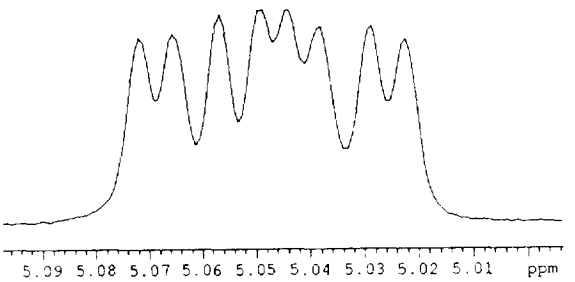


Figure 3. ^1H NMR resonances (300 MHz, $CDCl_3$) of the methine protons of an equimolar mixtures (R,S)-**a** / **Q**.

It is also important to note that the non-equivalences measured on the methine protons are nearly insensitive to the molar ratio, temperature and total concentration variations and hence any optimization of the separations obtained is not possible.

For all the cases discussed (esters **a-h**), the ester *tert*-butyl group was employed as probe of the quinine induced non-equivalence, however others ester groups can be also considered. Indeed for the β-hydroxyesters **i-l**, containing an ester ethyl or methyl group respectively, relevant non-equivalences of the alkyl absorptions were measured (being 9.6 Hz for the methyl protons of the ethyl group of **i** and 9.5 Hz for that one of **l**).

All above data clearly indicate that quinine is an efficient and convenient chiral solvating agent for the determination of the enantiomeric compositions of β-hydroxy esters. The method presents general applicability, indeed it has been employed successfully for a large number of esters, having different structures, and the accuracy of the determination only depends on the presence, in the substrates analysed, of a suitable NMR probe for the determination of the non-equivalence. To this regard, an ester *tert*-butyl seems to be particularly suitable: satisfactory non-equivalences can be always obtained by varying the molar ratio ester/CSA, the total concentration or the temperature. The simple structure of this group and its position in the NMR spectrum allows us to overcome the main intrinsic difficulty in the use of quinine as CSA, i.e. its complicate and dispersed NMR spectrum. In addition the simplicity in performing and optimizing the measurement and the low cost of the CSA, makes very attractive the use of quinine for the e.e. determination of β-hydroxy esters.

EXPERIMENTAL SECTION

Preparation of (S)-3-phenyl-3-hydroxy *tert*-butylpropanoate, (S)-a. Under an Argon atmosphere, a THF solution (10 ml) of pure *tert*-butoxycarbonylmethylzinc bromide (1.47 mmol) was added to 0.49 mmol of the

chiral ligand (1S,2S)-1-phenyl-2-N,N-dimethylamino-3-*tert*-butyldimethylsilyloxy-1,3-propanediol[8] in 10 ml of THF. After 45 min at room temperature, the mixture was cooled to 0°C and added of 0.49 mmol of benzaldehyde, stirring it for 20h. The reaction was treated with 10% HCl, and the mixture was extracted with ethylacetate. The organic layer was washed until neutral with $NaHCO_3$ (10%) and H_2O, dried (Na_2SO_4) and evaporated under reduced pressure. By purification of the crude product on Silica gel LC using dichloromethane as eluent, chemically pure **(S)-a** was obtained (0.47 mmol, 96% yield) having $[\alpha]_D^{25}$ -28.2 (c= 2.1; $CHCl_3$), E.e. 65% (lit.[10] for $[\alpha]_D^{22}$ -32.5 , E.e. 75%).

^{1} H NMR δ 1.43 (s, 9H, 3 CH_3), δ 2.61 (dd, J_{gem}=16Hz, J_{vic}=7.8Hz, 1H, CH_2), δ 2.67 (dd, J_{gem}=16 Hz, J_{vic}=4.8Hz, 1H, CH_2), δ 3.42 (bs, 1H, OH), δ 5.07 (dd, J_{vic}=7.8Hz, J_{vic}=4.8Hz, 1H, CH), δ 7.22-7.39 (m, 5H, Ph).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.27; H, 8.10. Found: C, 70.67; H, 8.15.

Preparation of racemic *tert*-butylβ-hydroxyesters a-h. Typical procedure is as follows: a solution of *tert*-butyl bromoacetate (38 mmol) and 19 ml of THF was added slowly under an Argon atmosphere to activated Zn dust (38 mmol). The mixture was stirred for about one hour at room temperature until the precipitation of colorless mycrocristalline solid was observed. The product was filtered, washed with THF, dried under vacuum and stored under Argon atmosphere at -20°C. Aldehyde (0.5 mmol) was added to a THF solution (10 ml) of Reformatsky reagent (0.5 mmol) and the mixture was stirred for five hours. The reaction was quenched with HCl (10%), $NaHCO_3$ (10%), water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporate under reduced pressure. The residue was purified by distillation under vacuum . The chemical yields were in the range 80 - 90%.

Preparation of racemic *tert*-butyl β-hydroxyesters i and l.

The preparation of **i** and **l** has been carried out by using the same procedure above reported for the *tert*-butyl β-hydroxy esters **a-h**, but without isolating the Reformatsky reagent. The chemical yields were ≥ 70%.

NMR measurements ^{1}H NMR spectra were recorded on a Varian Model VXR 300 at 300 MHz in deuterated chloroform. The temperature was controlled (accuracy ±1 °C) by the Varian control unit.

3-phenyl-3-hydroxy tert-butylpropanoate, **a.** ^{1} H NMR δ 1.43 (s, 9H, 3 CH_3), δ 2.61 (dd, J_{gem}=16Hz, J_{vic}=7.8Hz, 1H, CH_2), δ 2.67 (dd, J_{gem}=16 Hz, J_{vic}=4.8Hz, 1H, CH_2), δ 3.42 (bs, 1H, OH), δ 5.07 (dd, J_{vic}=7.8Hz, J_{vic}=4.8Hz, 1H, CH), δ 7.22-7.39 (m, 5H, Ph).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.27; H, 8.10. Found: C, 70.67; H, 8.15.

3-(p-methylphenyl)-3-hydroxy-tert-butylpropanoate, **b.** ^{1} H NMR δ 1.43 (s, 9H, 3 CH_3), δ 2.59 (dd, J_{gem}=16.6Hz, J_{vic}=8.4Hz, 1H, CH_2), δ 2.66 (dd, J_{gem}=16.6 Hz, J_{vic}=4.4Hz, 1H, CH_2), δ 3.45 (bs, 1H, OH), δ 5.03 (dd, J_{vic}=8.4Hz, J_{vic}=4.4Hz, 1H, CH), δ 7.24 (d, J_{vic}=7.9Hz, 2H, Ph), δ 7.13 (d, J_{vic}=7.9Hz, 2H, Ph).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.18; H, 8.47. Found: C, 71.20; H, 8.47.

3-(p-trifluorphenyl)-3-hydroxy-tert-butylpropanoate, **c.** ^{1} H NMR δ 1.43 (s, 9H, 3 CH_3), δ 2.58 (dd,

J_{gem}=18.6Hz, J_{vic}=8.6Hz, 1H, CH_2), δ 2.66 (dd, J_{gem}=18.6 Hz, J_{vic}=2.1Hz, 1H, CH_2), δ 3.65 (bs, 1H, OH), δ 5.11 (dd, J_{vic}=8.6Hz, J_{vic}=2.1Hz, 1H, CH), δ 7.48 (d, J_{vic}=8.5, 2H, Ph), δ 7.59 (d, J_{vic}=8.5, 2H, Ph)

Anal. Calcd for $C_{14}H_{17}F_3O_3$: C, 57.93; H, 5.86. Found: C, 58.05; H, 5.78.

3-(p-phenylphenyl)-3-hydroxy-tert-butylpropanoate, **d.** ^{1} H NMR δ 1.45 (s, 9H, 3 CH_3), δ 2.66 (dd, J_{gem}=16.2Hz, J_{vic}=7.7Hz, 1H, CH_2), δ 2.72 (dd, J_{gem}=16.2Hz, J_{vic}=5.4Hz, 1H, CH_2), δ 3.46 (bs, 1H, OH), δ 5.12 (dd, J_{vic}=7.7Hz, J_{vic}=5.4Hz, 1H, CH), δ 7.28-7.60 (m, 9H, pPh-Ph).

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.51; H, 7.38. Found: C, 76.50; H, 7.25.

3-(cynnamil)-3-hydroxy-tert-butylpropanoate, **e.** ^{1} H NMR δ 1.45 (s, 9H, 3 CH_3), δ 2.51 (dd, J_{gem}=16.2Hz, J_{vic}=7.6Hz, 1H, CH_2), δ 2.58 (dd, J_{gem}=16.2Hz, J_{vic}=4.5Hz, 1H, CH_2), δ 3.20 (bs, 1H, OH), δ 4.66 (m, J_{vic}=7.6Hz, J_{vic}=4.5Hz, J_{vic}=5.7Hz, J_{allyl}=1.2Hz, 1H, CH), δ 6.19 (dd, J_{vic}=15.7Hz, J_{vic}=5.7Hz, 1H, =CH-), δ 6.63 (dd, J_{vic}=15.7Hz, J_{allyl}=1.2Hz, 1H, =CH-), , δ 7.15-7.39 (m, 5H, Ph).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.58; H, 8.06. Found: C, 73.01; H, 8.15.

3-(β-naphthyl)-3-hydroxy-tert-butylpropanoate, **f.** ^{1} H NMR δ 1.44 (s, 9H, 3 CH_3), δ 2.70 (dd, J_{gem}=16.4Hz, J_{vic}=5.4Hz, 1H, CH_2), δ 2.76 (dd, J_{gem}=16.4 Hz, J_{vic}=7.5Hz, 1H, CH_2), δ 3.56 (bs, 1H, OH), δ 5.24 (dd, J_{vic}=7.5Hz, J_{vic}=5.4Hz, 1H, CH), δ 7.42-7.86 (m, 7H, Napht)

Anal. Calcd for $C_{17}H_{20}O_3$: C, 75.00; H, 7.35. Found: C, 74.95; H, 7.31.

3-(α-naphthyl)-3-hydroxy-tert-butylpropanoate, **g.** ^{1} H NMR δ 1.47 (s, 9H, 3 CH_3), δ 2.75 (dd, J_{gem}=15.8Hz, J_{vic}=9.2Hz, 1H, CH_2), δ 2.84 (dd, J_{gem}=15.8Hz, J_{vic}=3.8Hz, 1H, CH_2), δ 3.59 (bs, 1H, OH), δ 5.86 (dd, J_{vic}=9.2Hz, J_{vic}=3.8Hz, 1H, CH), δ 7.42-8.12 (m, 7H, Napht.)

Anal. Calcd for $C_{17}H_{20}O_3$: C, 75.00; H, 7.35. Found: C, 75.63; H, 7.29.

3-(cyclohexyl)-3-hydroxy-tert-butylpropanoate, **h.** ^{1} H NMR δ 0.8-2 (m, 11H, cyclo), δ 1.43 (s, 9H, 3 CH_3), δ 2.29 (dd, J_{gem}=16.2Hz, J_{vic}=9.3Hz, 1H, CH_2), δ 2.40 (dd, J_{gem}=16.2 Hz, J_{vic}=3.0Hz, 1H, CH_2), δ 2.99 (bs, 1H, OH), δ 3.69 (dq, J_{vic}=9.3Hz, J_{vic}=3.0Hz, J_{vic}=6.2Hz, 1H, CH).

Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.42; H, 10.52. Found: C, 68.48; H, 10.56.

3-phenyl-3-hydroxy-ethylpropanoate, **i.** ^{1} H NMR δ 1.23 (t, J_{vic}=7.1Hz, 3H, CH_3), δ 2.66 (dd, J_{gem}=16.2Hz, J_{vic}=6.7Hz, 1H, CH_2), δ 2.74 (dd, J_{gem}=16.2 Hz, J_{vic}=8.4Hz, 1H, CH_2), δ 3.37 (bs, 1H, OH), δ 4.15 (q, J_{vic}=7.1Hz, 2H, CH2), 5.10 (dd, J_{vic}=6.7Hz, J_{vic}=8.4Hz, 1H, CH) δ 7.17-7.42 (m, 5H, Ph)

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.04; H, 7.21. Found: C, 68.00; H, 7.30.

3-Phenyl-3-hydroxy-methylpropanoate, **l.** ^{1} H NMR 2.67 (dd, J_{gem}=16.1 Hz, J_{vic}=4.2Hz, 1H, CH_2), δ 2.78 (dd, J_{gem}=16.1Hz, J_{vic}=7.9Hz, 1H, CH_2), δ 3.42 (bs, 1H, OH), δ 3.69 (s, 3H, CH_3), δ 5.11 (dd, J_{vic}=4.2Hz, J_{vic}=7.9Hz, 1H, CH), δ 7.22-7.40 (m, 5H, Ph).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67. Found: C, 67.01; H, 6.80.

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