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Stereochemical features of the stereoselective interaction between (*R*)- or (*S*)-7,7′-bis(1-propen-3-oxy)-2,2′-dihydroxy-1,1′-binaphthyl and quinine☆

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ABSTRACT

Quinine forms diastereoisomeric adducts with the enantiomers of 7,7′-bis(1-propen-3-oxy)-2,2′-dihydroxy-1,1′-binaphthyl. Their stereochemistry in solution was investigated by ^{1}H NMR spectroscopy at various temperatures and by analysis of the intermolecular ^{1}H{^{1}H} nuclear Overhauser effect enhancements. A hypothesis for the chiral discrimination mechanism involved in the HPLC separation of this binaphthyl compound on a quinine-based chiral stationary phase is given.

INTRODUCTION

The last 10–15 years have witnessed intense research activity in the preparation and use of chiral stationary phases (CSPs) for the LC resolution of racemates [1], so that the organic chemist is now able to separate easily many classes of chiral compounds. For the CSPs derived from low-molecular-mass optically active compounds chemically bound to a silica matrix, for which a 1:1 interaction between the chiral residue of the CSP and the enantiomer of the substrate is generally assumed (*i.e.*, the so-called independent CSPs), some efforts have also been made to formulate hypotheses on the mechanism by which the enantioselective retention takes place. Such investigations have been carried out using both computational [2,3] and spectroscopic methods [4–6] (nuclear magnetic resonance, absorption spectroscopy, etc.), determining and comparing the structures of the diastereoisomeric adducts arising from the free selector of the CSP and the enantiomers of a substance which are separated on the phase.

We have recently proposed [5] a mechanism for the enantioseparation of binaphthyl derivatives on a quinine-based CSP: the ^{1}H NMR analysis of the diastereoisomeric mixtures of quinine (Q), the soluble model of the CSP, and (*R*)- or (*S*)-2′-(2-propoxy)-1,1′-binaphthyl-2-ol (A), a binaphthyl compound well resolved on this CSP, afforded one possible chiral discrimination model, involving only two selector–selectand points of interaction. This kind of chiral recognition rationale is only seemingly different from the classical "three-point" interaction model of Dalglish [7,8], because other interactions could really be present, being too weak to be detected by NMR or UV spectroscopy.

In order to obtain more spectroscopic evidence for the factors responsible for HPLC separation of binaphthols, we investigated the interaction of quinine with 7,7′-bis(1-propen-3-oxy)-2,2′-dihydroxy-1,1′-binaphthyl (B), which is well resolved on the quinine-based CSP and has two free OH groups in the 2,2′-positions, instead of one as in A. The stereochemistry of

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the diastereoisomeric adducts formed by quinine and the two enantiomers of B was investigated by ^1H NMR analysis of quinine–(*R*)-B and quinine–(*S*)-B mixtures in C^2HCl_3 solutions and the results are discussed here.

EXPERIMENTAL

Preparation of the enantiomers of 7,7'-bis-(1-propen-3-oxy)-2,2'-dihydroxy-1,1'-binaphthyl (B)

Racemic 7,7'-bis(1-propen-3-oxy)-2,2'-dihydroxy-1,1'-binaphthyl (B) was obtained by a copper–benzylammine-catalysed coupling of the corresponding 2-hydroxy-7-(2-propenyloxy)-naphthalene according to Brussee and Jansen [9]. The compound obtained gave satisfactory elemental analysis and the NMR spectra of the product were consistent with the expected structure. The enantiomers of B were obtained by HPLC resolution on a Pirkle ionic (*R*)-N-(3,5-dinitrobenzoyl)phenylglycine column.

NMR measurements

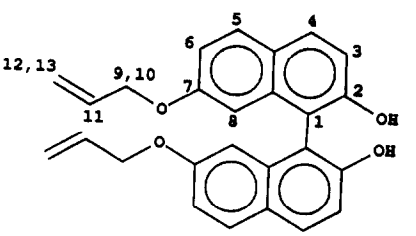
NMR measurements were performed on a Varian VXR-300 spectrometer. The temperature was controlled (accuracy ±1°C) by the Varian temperature control unit. The proton spin–lattice relaxation times (T_1) were measured by the conventional inversion–recovery (180°–τ–90°–T)$_n$ pulse sequence. Nuclear Overhauser effect (NOE) experiments were performed on carefully degassed samples (10%, w/v) in the difference mode. The decoupler was placed at the required frequency to saturate the proton in question. The decoupler power used was the minimum required to saturate the spin of interest. A waiting time varying from 10 to 30 s was used to allow the system to reach equilibrium. Each NOE experiment was repeated at least four times and results reproducible to within ±5% were obtained.

RESULTS AND DISCUSSION

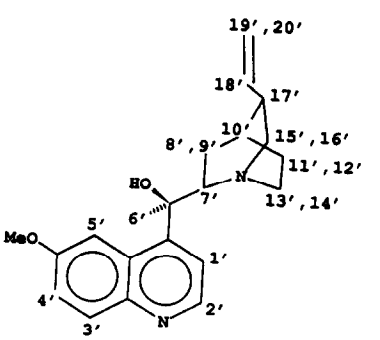
The usefulness of NMR spectroscopy in the detection of diastereoisomeric interactions has been extensively demonstrated [4–6]. An immediate test for their occurrence is the non-equivalence induced in the nuclei of two enantiomers in the presence of a chiral compound. In fact, in the ^1H NMR spectra of mixtures of quinine and (*R*,*S*)-2'-(2-propoxy)-1,1'-binaphthyl-2-ol (A), only non-equivalence of the alkoxyl protons of A was observed (the aromatic proton resonances being unaffected); subsequently, the alkoxy group of A was proved to be in different stereochemical environments in the two diastereoisomeric solvates.

With 7,7'-bis(1-propen-3-oxy)-2,2'-dihydroxy-1,1'-binaphthyl (B), quinine induced splitting of all resonances of B due to alkyl and aromatic protons. In Fig. 1a the portion of the ^1H NMR spectrum of (*R*,*S*)-B ($CDCl_3$, 25°C) corresponding to the resonances due to the aromatic protons is shown and compared with the spectrum in the presence of equimolar amounts of quinine in Fig. 1b: the latter presents two sets of resonances for each proton or equivalent protons of B. Thus, as a consequence of the interaction with quinine, the aromatic protons of B, originally enantiotopic, became diastereotopic.

The ^1H NMR analysis of equimolar Q–(*S*)-B



B



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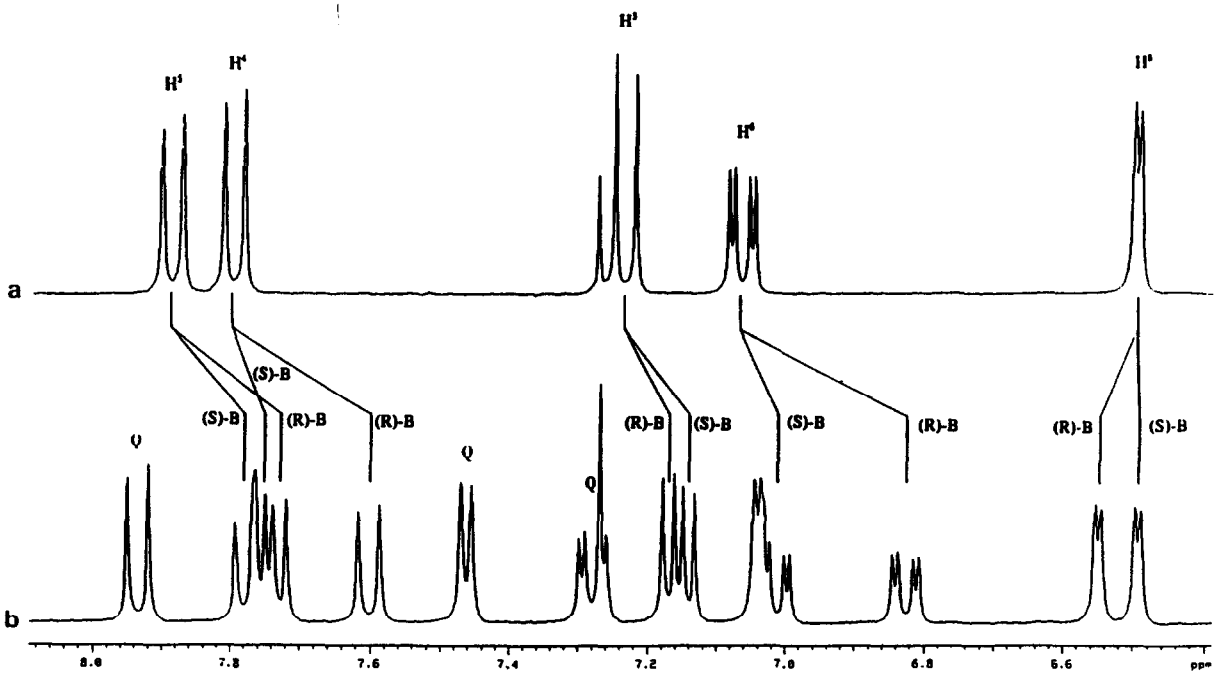

Fig. 1. ^{1}H NMR spectra (300 MHz, C^2HCl_3, 0.027 *M*, 25°C, δ in ppm referred to TMS as external standard) of (a) free B and (b) Q–(*R*, *S*)-B mixture (1:1 molar ratio).

and Q–(*R*)-B mixtures, at the same concentration and temperature, allowed the assignment of the resonances due to the *S*- and *R*-enantiomers, respectively (Table I).

TABLE I

^{1}H NMR (300 MHz, C^2HCl_3, 0.027 *M*, 25°C) CHEMICAL SHIFTS OF (*S*)-B AND (*R*)-B IN THE PRESENCE OF QUININE (1:1 MOLAR RATIO) AND IN THE FREE STATE

Chemical shifts in ppm referred to TMS as external standard.

H	Free B	(*S*)-B–Q	(*R*)-B–Q
3	7.236	7.147	7.164
4	7.800	7.751	7.602
5	7.890	7.778	7.734
6	7.066	7.012	6.826
8	6.498	6.494	6.550
9	4.326	4.278	4.237
10	4.263	4.220	4.156
11	5.874	5.840	5.848
12	5.161	5.128	5.158
13	5.115	5.081	5.112
OH	5.053	5.300	5.400

The analysis of the dependence of the chemical shifts of the free compound B on temperature variations showed (Table II) that no significant perturbation was observed between +50 and

TABLE II

^{1}H NMR (300 MHz, C^2HCl_3, 0.027 *M*) CHEMICAL SHIFTS OF FREE B IN THE TEMPERATURE RANGE −50 TO +50°C AND VARIATIONS ($\delta_{-50°C} - \delta_{+50°C}$) IN THIS RANGE

Chemical shifts in ppm referred to TMS as external standard.

H	−50°C	25°C	50°C	$\delta_{-50°C} - \delta_{+50°C}$
3	7.193	7.236	7.237	−0.044
4	7.787	7.800	7.793	−0.006
5	7.847	7.890	7.886	−0.039
6	7.065	7.066	7.066	−0.001
8	6.420	6.498	6.516	−0.096
9	4.277	4.326	4.332	−0.055
10	4.209	4.263	4.274	−0.065
11	5.919	5.874	5.866	+0.053
12	5.236	5.161	5.148	+0.088
13	5.172	5.115	5.102	+0.054
OH	5.190	5.053	5.017	+0.173

−50°C. The sole exceptions were the OH protons and the *peri* protons H-8: on going to lower temperatures, the former shifted downfield and latter upfield. By varying the overall concentration of the solutions of the free B in the concentration range $3.6 \cdot 10^{-2}$–$1.83 \cdot 10^{-1}$ *M*, no variation in the proton chemical shifts of B was observed, clearly indicating that B does not give rise to autoassociation phenomena. Therefore, the effect of temperature on the chemical shifts of B must be attributed to intramolecular effects: the progressive deshielding of the OH proton at lower temperatures indicates a strengthening of the OH···OH intramolecular hydrogen bond, the direct consequence of which could be a change in the dihedral angle between the two aromatic planes and, hence, a variation of the chemical shifts of the *peri* protons (H-8).

The lack of intermolecular autoassociation phenomena in solutions of free B, at least in the solvent used, reasonably allows us to interpret all the variations observed in the chemical shifts of B in the presence of quinine as a direct consequence of the interaction with the alkaloid. The analysis of the magnitude of the non-equivalence, *i.e.*, the difference between the chemical shifts of (*S*)-B and (*R*)-B in the presence of quinine, and the evaluation of the complexation shifts for each enantiomer (*i.e.*, the difference between the chemical shifts of the protons of B in the presence of Q and those in absence of Q) allowed to draw some qualitative conclusions about the strength of the diastereoisomeric interaction and about their origin (Table III).

For each proton of B, quinine produced a greater chemical shift variation in (*R*)-B than in (*S*)-B. This could indicate a tighter interaction in the pair (*R*)-B–Q with respect to the pair (*S*)-B–Q. Accordingly, the *R*-enantiomer of B is the most retained on the quinine-based CSP [5].

The strong downfield shift of the OH groups of (*R*)- and (*S*)-B in the two mixtures relative to the free state is a clear indication of the formation of an intermolecular hydrogen bond. In addition, for both enantiomers, the interaction with quinine gave rise to a large upfield shift of the "external" aromatic protons H-3, -4, -5 and -6. The most relevant difference for the two enantiomers lies in the behaviour of the proton H-8, which is unaffected in the *S*-enantiomer and downfield shifted in the *R*-enantiomer. All these observations can be interpreted as follows: for both enantiomers, the upfield shift of the external aromatic protons in the presence of quinine could be simply attributed to the proximity of shielding groups of quinine, such as the aromatic quinoline nucleus or the quinuclidine nitrogen atom. Two interpretations can be invoked to explain the behaviour of the aromatic proton H-8 in the (*R*)-B–Q mixture: its deshielding in the presence of quinine could be due either to proximity to groups of quinine having a deshielding effect or, more reasonably, to a variation of the dihedral angle between the aromatic planes of (*R*)-B as a consequence of the interaction with Q. A decrease in the above dihedral angle could lead the protons H-8 to be more proximate to the deshielding cone of the aromatic moiety of B.

The effect of temperature variations between +50 and −50°C on the chemical shift of B for (*S*)-B–Q and (*R*)-B–Q mixtures was also investigated and the results are summarized in Table IV. Lowering the temperature produced a pro-

TABLE III

^{1}H NMR (300 MHz, C^2HCl_3, 25°C) COMPLEXATION SHIFTS ($\Delta\delta_S$, $\Delta\delta_R$) AND NON-EQUIVALENCE ($\delta_S - \delta_R$) IN THE (*S*)-B–Q AND (*R*)-B–Q MIXTURES (0.027 *M*, 1:1 MOLAR RATIO)

H	$\Delta\delta_S$ [a,b]	$\Delta\delta_R$ [a,b]	$\delta_S - \delta_R$ [a,c]
3	−0.089	−0.072	−0.017
4	−0.049	−0.198	+0.149
5	−0.112	−0.156	+0.044
6	−0.054	−0.240	+0.186
8	−0.004	+0.052	−0.056
9	−0.048	−0.089	+0.041
10	−0.043	−0.107	+0.064
11	−0.007	−0.026	−0.008
12	−0.033	−0.003	−0.030
13	−0.034	−0.003	−0.031
OH	+0.247	+0.347	−0.100

[a] Chemical shifts in ppm referred to TMS as external standard.

[b] $\Delta\delta_S = \delta_{Scompl} - \delta_{Sfree}$; $\Delta\delta_R = \delta_{Rcompl} - \delta_{Rfree}$.

[c] δ_S is the chemical shift of B in the (*S*)-B–Q mixture and δ_R is the chemical shift of B in the (*R*)-B–Q mixture.

TABLE IV

^{1}H NMR (300 MHz, C^2HCl_3, 0.042 *M*) CHEMICAL SHIFTS OF B IN THE (*R*)-B–Q AND (*S*)-B–Q MIXTURES (MOLAR RATIO 1:1) IN THE TEMPERATURE RANGE −50 TO +50°C

Chemical shifts in ppm referred to TMS as external standard.

H	(*R*)-B–Q			(*S*)-B–Q		
	−50°C	+50°C	Δδ [a]	−50°C	+50°C	Δδ [a]
3	7.094	7.188	−0.094	6.950	7.183	−0.133
4	7.398	7.675	−0.277	7.580	7.751	−0.171
5	7.644	7.791	−0.147	7.653	7.813	−0.160
6	6.409	6.932	−0.523	6.922	7.032	−0.110
8	6.626	6.542	0.084	6.490	6.516	−0.026
9	4.066	4.286	−0.220	4.087	4.305	−0.218
10	3.869	4.216	−0.347	4.087	4.224	−0.137
11	5.846	5.849	−0.003	5.823	5.846	−0.023
12	5.218	5.139	0.079	5.135	5.128	0.007
13	5.174	5.094	0.080	5.099	5.081	0.018
OH	−[b]	4.800	–	–	4.620	–

[a] $\Delta\delta = \delta_{-50°C} - \delta_{+50°C}$.

[b] The signal of the OH proton at −50°C is not well recognized because of its superimposition on the aromatic proton at chemical shifts greater than 7 ppm.

gressive deshielding of the OH protons and a progressive shielding of the external aromatic protons of B. These effects can both be attributed to the tightening of the quinine–B intermolecular interactions caused by the temperature decrease. The temperature dependence of the H-8 proton is different in the two diastereoisomeric adducts: a progressive deshielding on going to lower temperatures in the (*R*)-B–Q mixture and an opposite effect in the (*S*)-B–Q mixture is observed. It is noteworthy that the temperature response of the H-8 proton in the (*S*)-B–Q pair is analogous to that found in free B. As already discussed, these variations could be reasonably attributed to conformational variations in the binaphthyl compound.

The relaxation parameters of the two enantiomers are also affected by the presence of quinine. In the fast exchange limit, the observed proton relaxation rates ($R_{obs} = 1/T_1$) in the (*R*)-B–Q and (*S*)-B–Q mixtures are the weighted mean of the proton relaxation rates in the bound (R_b) and free (R_f) states:

$$R_{obs} = x_b R_b + x_f R_f$$

where x_b and x_f are the molar fractions in the bound and free states, respectively.

As shown in Table V, the interaction with quinine produced an increase in the proton relaxation rates ($R = 1/T_1$) of both enantiomers and the effect was larger for the *R*- than for the *S*-enantiomer. This effect may be the result of the different degree of association to quinine for the two enantiomers [difference in the x_b values of (*R*)-B and (*S*)-B] or of the different intermolecular dipolar contributions to the relaxation due to quinine protons (difference in the R_b values of the two enantiomers), assuming that the reorientational correlation time for the two enantiomers in the bound state is the same and equal to that of quinine.

A more precise picture of the stereochemical features of the two diasteroisomeric adducts Q–(*S*)-B and Q–(*R*)-B was obtained by careful measurements of the inter- and intramolecular $^1H\{^1H\}$ NOE enhancements.

As far as the (*R*)-B–Q mixture is concerned, the most interesting and informative results were obtained on irradiation of the H-6′ and OMe protons of quinine and on irradiation of the protons H-3 and H-8 of (*R*)-B. As shown in Fig. 2, the saturation of the proton H-6′ of the quinine CHOH group produced the expected intramolecular enhancements of the absorptions

TABLE V

PROTON RELAXATION RATES ($R = 1/T_1$, s^{-1}) OF B IN THE FREE STATE AND IN THE (*S*)-B–Q AND (*R*)-B–Q MIXTURE (300 MHz, C^2HCl_3, MOLAR RATIO 1:1) AT 25°C

H	$R_{free\ B}$	$R_{(S)\text{-B–Q}}$	$R_{(R)\text{-B–Q}}$
3	0.386	0.741	0.845
4	0.560	0.694	0.762
5	0.558	0.686	0.737
6	0.407	0.440	0.537
8	0.496	0.654	0.670
9	0.961	1.081	1.229
10	0.968	1.171	1.242
11	0.247	0.185	0.171
12	0.399	0.369	0.384
13	0.386	0.359	0.401

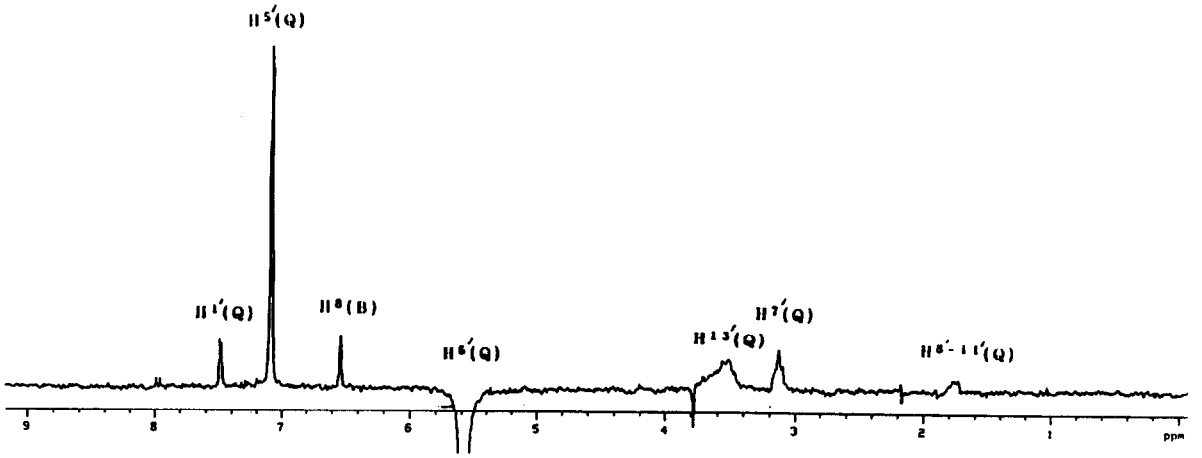

Fig. 2. $^1H\{^1H\}$ NOE difference spectrum of the (*R*)-B–Q mixture (0.167 *M*, 1:1 molar ratio, C^2HCl_3, 25°C) obtained by irradiation of the proton H-6′ of Q.

of the protons H-5′ and H-1′, but a significant intermolecular NOE on the *peri* proton H-8 of (*R*)-B was also observed. Conversely, on irradiation of the proton H-8 of (*R*)-B a small but significant enhancement of the resonance of H-6′ of Q in the same diastereoisomer was observed. The irradiation at the frequency of the OMe protons of quinine produced an intermolecular NOE on the proton H-8 of (*R*)-B, in addition to the intramolecular NOEs on the protons H-5′ and H-4′ of quinine. Another source of information on the stereochemistry of the (*R*)-B–Q adduct was the saturation of the proton H-3 of (*R*)-B: it produces NOEs both on the aromatic proton H-2′ of quinine and on the quinuclidine proton adjacent to the nitrogen atom (H-13′).

These results well fit with the picture in Fig. 3: in the (*R*)-B–Q adduct, the two naphthalene nuclei of (*R*)-B are close to the quinoline ring of quinine and to its quinuclidine moiety. Such a representation takes into account the proximity of the proton H-6′ of Q to the proton(s) H-8 of (*R*)-B and the proximity of the "two" H-3 protons of (*R*)-B to the proton H-2′ of quinine and to its quinuclidine ring.

NOE measurements indicated important differences in the stereochemistry of (*S*)-B–Q relative to that of (*R*)-B–Q. For the (*S*)-B–Q mixture the saturation of the OMe protons of quinine produced a small (<4%) but completely reproducible intermolecular NOE on the external aromatic protons H-4 and H-5 of (*S*)-B. This indicates that the OMe group of quinine is in proximity to the external aromatic protons H-3 and H-4 of (*S*)-B. Considering that also for the Q–(*S*)-B mixture there was evidence of OH···OH attractive intermolecular hydrogen bond interactions and taking into account the absolute configuration of B, one naphthalene ring of (*S*)-B must be assumed to be in proximity to the quinoline ring and the other external to it, as depicted in Fig. 4. Another important observation is that in the Q–(*S*)-B mixture the irradiation of the proton H-2′ of quinine produced an NOE on the proton H-3′ of another molecule of

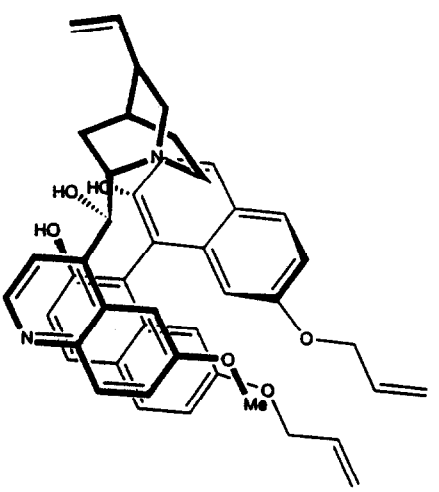

Fig. 3. Conformation of Q–(*R*)-B adduct from NMR results.

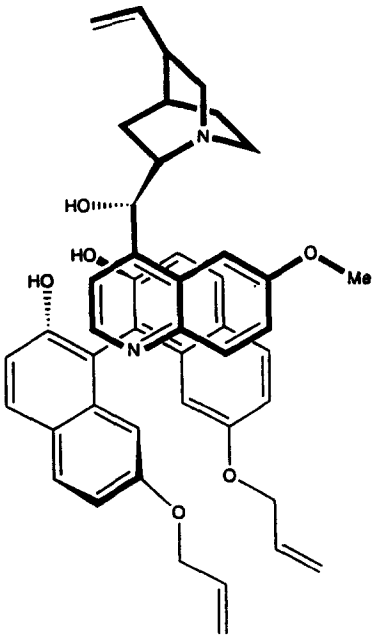

Fig. 4. Conformation of Q–(*S*)-B adduct from NMR results.

quinine. This enhancement is in keeping with the presence of autoassociation products of quinine, which have been extensively discussed in a recent paper [10]. Such an effect was not observed with the (*R*)-B–Q mixture.

CONCLUSION

Two diastereoisomeric adducts, (*R*)-B–Q and (*S*)-B–Q, in a prevalent conformation are present in solution. The formation of both pairs arises from the attractive intermolecular interaction due to the formation of the hydrogen bond between the OH groups of B and that of Q. In (*R*)-B–Q, the hydrogen bond formation could cooperate with the $\pi-\pi$ attractive interaction between the quinoline ring of Q and one aromatic nucleus of (*R*)-B to tighten the two components of the diastereoisomeric adduct. In (*S*)-B–Q, this cooperation is not allowed: one naphthalene ring of (*S*)-B, that external to the adduct, could originate a destabilizing steric repulsive interaction with the quinoline ring of Q, thus hindering a good fit between the other aromatic nucleus of B and the quinoline moiety, which is the required condition for $\pi-\pi$ interaction. The low stability of (*S*)-B–Q is also in agreement with the simultaneous presence of quinine autoassociation phenomena, which were not detected with (*R*)-B–Q.

The difference in stability between (*R*)-B–Q and (*S*)-B–Q fits well with the chromatographic result [5]: the *R*-enantiomer of B was the most retained on the CSP derived from quinine.

The interaction model discussed above is different from that proposed for the other binaphthyl compound A [5], where no $\pi-\pi$ attractive interaction was found for the most stable diastereoisomer or, at least, this interaction was too weak to be detected by NMR spectroscopy.

It is also important in the present instance that both diastereoisomers were detected, thus allowing the formulation of a hypothesis of a chiral discrimination mechanism. In addition, the ability of quinine to give rise to multiple interactions by using its different functional groups has been fully demonstrated: this is the basis of the versatility of this alkaloid as a chiral auxiliary in the chromatographic separation of chiral compounds by HPLC [5,11–15], as a chiral solvating agent [16] for the determination of enantiomeric purity by NMR spectroscopy and in asymmetric synthesis [17].

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