Different Enantioselective Interaction Pathways Induced by Derivatized Quinines

Gloria Uccello-Barretta, Federica Balzano, Cristiana Quintavalli, and Piero Salvadori*

Centro di Studio del CNR per le Macromolecole Stereordinate ed Otticamente Attive, Dipartimento di Chimica e Chimica Industriale, via Risorgimento 35, 56126 Pisa, Italy

Received October 21, 1999

The stereochemistries in solution of the diastereoisomeric complexes formed by quinines modified at the hydroxyl site (9-*O*-acetylquinine; 9-*O*-(3,5-dimethoxyphenylcarbamate)quinine) or quinuclidine nitrogen (*N*-benzylquininium chloride) and each enantiomer of 2-(3′,5′-dinitrobenzamido)-1-phenylethanol have been compared to those of the free compounds by ^{1}H NMR investigations. Completely different interaction models, also involving changes of the free state conformations, have been obtained.

Introduction

Chiral molecular recognition is currently the subject of increasing attention and intense research. In this field, Cinchona alkaloids have demonstrated widespread potentiality, being successfully employed as chiral resolving agents,[1] chiral auxiliaries, catalysts in asymmetric processes,[2,3] new chiral stationary phases for HPLC,[4] and as chiral solvating agents for NMR spectroscopy.[5]

The versatility of Cinchona alkaloids is commonly attributed to their ability to act as multisite receptors, by virtue of the presence of several functionalities. With the aim of understanding the molecular basis of their strong performances, accurate conformational investigations have been carried out on them using both computational and NMR methods.[6] The multifunctionality of Cinchona alkaloids has also given an important aim to be pursued: the modulation and optimization of interactions responsible for the chiral discrimination by selective modification of functional groups. Regarding this, successful modifications of Cinchona alkaloids have given efficient ligands for the catalytic asymmetric osmylation reaction[2] and new chiral selectors to be immobilized onto silica for preparing chiral HPLC stationary phases.[7] Cinchona alkaloids analogues containing 9,9′-spirobifluorene moiety, instead of the quinoline ring, have also been prepared.[8]

To define the stereochemical basis of enantiodiscrimination by quinine derivatives and to understand how derivatization can be used to enhance the enantioselectivity, we have compared by ^{1}H NMR spectroscopy the enantiodiscriminanting capabilities of 9-*O*-acetylquinine (**QuiOAc**), 9-*O*-(3,5-dimethoxyphenylcarbamate)quinine (**Quicarb**), and *N*-benzylquininium chloride (**Quibec**) toward the multifunctional chiral analyte 2-(3′,5′-dinitrobenzamido)-1-phenylethanol (**1**) (Chart 1). Since the conformational changes of chiral selectors upon substrate binding are fundamental in the understanding of mechanisms of chiral recognition, we have compared the

* Ph: +39-50-918203. Fax: +39-50-918409. E-mail: psalva@dcci.unipi.it.

(1) (a) Newman, P. *Optical Resolution Procedures for Chemical Compounds*; Riverdale: New York, 1981. (b) Duke, C. C.; Carter, S. R.; Hambley, T. W.; Holder, G. M.; Cutler, D. J. *Chirality* **1994**, *6*, 670−680. (c) Chung, J. Y. L.; Hughes, D. L.; Zhao, D.; Song, Z.; Mathre, D. J.; Ho, G. J.; McNamara, J. M.; Douglas, A. W.; Reamer, R. A.; Tsay, F. R.; Varsolona, R.; McCauley, J.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1996**, *61*, 215−222.

(2) (a) Nelson, D. W.; Gypser, A.; Tong Ho, P.; Kolb, H. C.; Kondo, T.; Kwong, H.-L.; McGrath, D. V.; Rubin, A. E.; Norrby, P.-O.; Gable, K. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 1840−1858. (b) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 11038−11053. (c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. (d) Ungváry, F. *Coord. Chem. Rev.* **1995**, *141*, 371−493. (e) Salvadori, P.; Superchi, S.; Minutolo, F. *J. Org. Chem.* **1996**, *61*, 4190−4191. (f) Superchi, S.; Minutolo, F.; Pini, D.; Salvadori, P. *J. Org. Chem.* **1996**, *61*, 3183−3186. (g) Petri, A.; Pini, D.; Salvadori, P. *Tetrahedron Lett.* **1995**, *36*, 1549−1552. (h) Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron* **1994**, *50*, 11321−11328. (i) Petri, A.; Pini, D.; Rapaccini, S.; Salvadori, P. *Chirality* **1995**, *7*, 580−585.

(3) (a) Faber, W. S.; Kok, J.; de Lange, B.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4775−4794. (b) Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87−129. (c) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, *56*, 872−875. (d) Gasparski, C. M.; Miller, M. J. *Tetrahedron* **1991**, *47*, 5367−5378. (e) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 541−544.

(4) (a) Rosini, C.; Bertucci, C.; Pini, D.; Altemura, P.; Salvadori, P. *Tetrahedron Lett.* **1985**, *26*, 3361−3364. (b) Rosini, C.; Altemura, P.; Pini, D.; Bertucci, C.; Zullino, G.; Salvadori, P. *J. Chromatogr.* **1985**, *348*, 79−87. (c) Pini, D.; Rosini, C.; Bertucci, C.; Altemura, P.; Salvadori, P. *Gazz. Chim. Ital.* **1986**, *116*, 603−606. (d) Salvadori, P.; Rosini, C.; Pini, D.; Bertucci, C.; Uccello-Barretta, G. *Chirality* **1989**, *1*, 161−166. (e) Karlsson, A.; Pettersson, C. *Chirality* **1992**, *4*, 323−332. (f) Nesterenko, P. N.; Krotov, V. V.; Storoverov, S. M. *J. Chromatogr., A* **1994**, *667*, 19−28.

(5) (a) Rosini, C.; Uccello-Barretta, G.; Pini, D.; Abete, C.; Salvadori, P. *J. Org. Chem.* **1988**, *53*, 4579−4581. (b) Van Oeveren, A.; Menge, W.; Feringa, B. L. *Tetrahedron Lett.* **1989**, *30*, 6427−6430. (c) Salvadori, P.; Pini, D.; Rosini, C.; Bertucci, C.; Uccello-Barretta, G. *Chirality* **1992**, *4*, 43−49. (d) Klein, J.; Borsdorf, R. *Fresenius J. Anal. Chem.* **1994**, *350*, 644−646. (e) Klein, J.; Hartenstein, H.; Sicker, D. *Magn. Reson. Chem.* **1994**, *32*, 727−731. (f) Uccello-Barretta, G.; Pini, D.; Mastantuono, A.; Salvadori, P. *Tetrahedron*: *Asymmetry* **1995**, *6*, 1965−1972. (g) Zymanczyk-Duda, E.; Skwarczynski, M.; Lejczak, B.; Kafarski, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1277−1280.

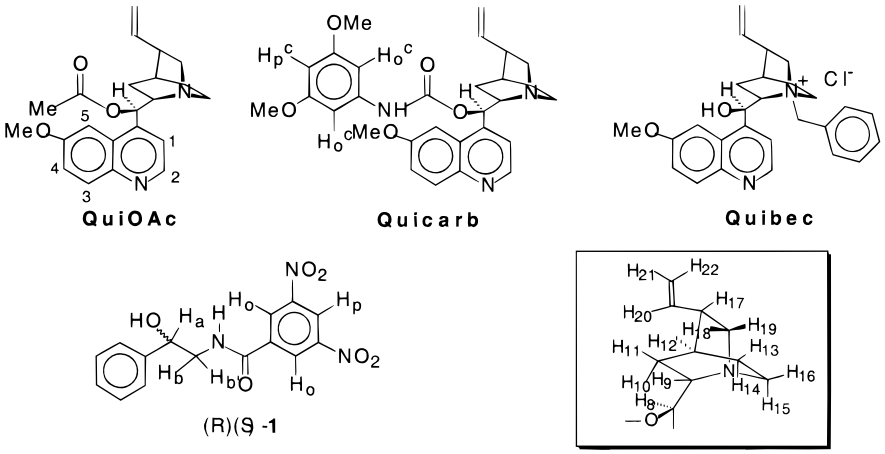
(6) (a) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *J. Org. Chem.* **1990**, *55*, 6121−6131. (b) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 195−204. (c) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069−8076. (d) Oleksyn, B. J.; Suszko-Purzycka, A.; Dive, G.; Lamotte-Brasseur, J. *J. Pharm. Sci.* **1992**, *81*, 122−127. (e) Berg, U.; Aune, M.; Matsson, O. *Tetrahedron Lett.* **1995**, *36*, 2137−2140. (f) Bürgi, T.; Baiker, A. *J. Am. Chem. Soc.* **1998**, *120*, 12920−12926.

(7) (a) Bertucci, C.; Rosini, C.; Pini, D.; Salvadori, P. *J. Pharm. Biomed. Anal.* **1987**, *5*, 171−176. (b) Rosini, C.; Bertucci, C.; Pini, D.; Altemura, P.; Salvadori, P. *Chromatographia* **1987**, *24*, 671−676. (c) Pettersson, C.; Gioeli, C. *J. Chromatogr.* **1987**, *398*, 247−254. (d) Pettersson, C.; Gioeli, C. *J. Chromatogr.* **1988**, *435*, 225−228. (e) Lämmerhofer, M.; Lindner, W. *J. Chromatogr., A* **1996**, *741*, 33−48. (f) Piette, V.; Lämmerhofer, M.; Bischoff, K.; Lindner, W. *Chirality* **1997**, *9*, 157−161. (g) Kellner, K.-H.; Blasch, A.; Chmiel, H.; Lämmerhofer, M.; Lindner, W. *Chirality* **1997**, *9*, 268−273. (h) Lämmerhofer, M.; Di Eugenio, P.; Molnar, I.; Lindner, W. *J. Chromatogr., B* **1997**, *689*, 123−135.

(8) Winter-Werner, B.; Diederich, F.; Gramlich, V. *Helv. Chim. Acta* **1996**, *79*, 1338−1360.

10.1021/jo991661l CCC: $19.00
Published on Web 05/23/2000

Chart 1



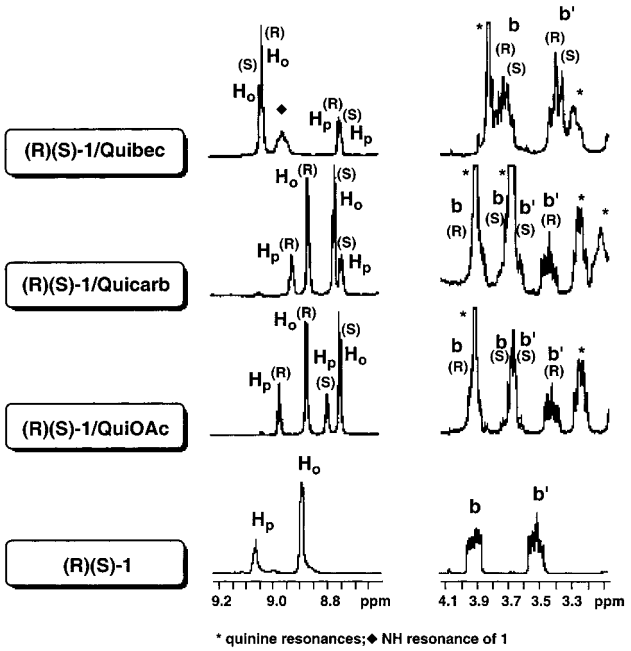


Figure 1. ^{1}H NMR (300 MHz, $CDCl_3$, ppm referred to TMS as external standard, 25 °C) spectral regions corresponding to the 3,5-dinitrobenzoyl (H_o and H_p) and methylene ($CH_bH_{b'}$) proton resonances of **1** (120 mM) in (a) free (*R*)(*S*)-**1**, (b) (*R*)(*S*)-**1**/**QuiOAc**, (c) (*R*)(*S*)-**1**/**Quicarb**, and (d) (*R*)(*S*)-**1**/**Quibec**.

conformations of the quinine derivatives **QuiOAc**, **Quicarb**, and **Quibec** and analyte **1** in the free state with the conformations of the diastereoisomeric adducts formed in solution by each quinine and the two enantiomers of **1**. This investigation has been carried out by analyzing the intra- and intermolecular dipolar interactions, in $CDCl_3$, by means of 1D NOE and 2D ROESY techniques.[9]

Results

Chemical Shift Nonequivalences Measured in Mixtures Containing Quinine Derivatives and 1. The comparison of the ^{1}H NMR spectra in $CDCl_3$ (Figure 1) of the pure chiral analyte (*R*,*S*)-**1** and its equimolar mixtures with each quinine derivative clearly shows that all three chiral auxiliaries produce a remarkable variation of the chemical shifts of **1** (Table 1). Only **QuiOAc** and **Quicarb** double the NMR signals of the two enantiomers of the analyte **1** remarkably. In these cases, the relative positions of the signals originated by the two enantiomers are different. Therefore all three quinines interact with the substrate **1**, but only **QuiOAc** and **Quicarb** display significant enantiodiscrimination, probably by means of different interaction mechanisms.

Interestingly, both the acetyl **QuiOAc** and carbamoyl **Quicarb** quinine derivatives produce a change in the coupling pattern of the methylene-methine fragment of (*S*)-**1** but not (*R*)-**1**. The *N*-benzyl quinine, **Quibec**, does not change this coupling pattern for (*S*)- or (*R*)-**1** (Figure 1). These results suggest that the two quinines modified at the hydroxyl site may change the conformation of the (*S*)-enantiomer.

Conformational Analysis by ^{1}H NMR. To understand why the three chiral auxiliaries behave in such a different way and to identify the interactions that stabilize the diastereoisomeric species in solution, we have determined the stereochemistries of the quinine derivatives and chiral analyte and compared these conformations to those of the diastereoisomeric species formed by each chiral auxiliary and (*R*)- or (*S*)-**1**.

Stereochemistries of Free Compounds. The conformation of **1**, as represented in Figure 2, has been established on the basis of the relative intensities of the H_a-H_b and $H_a-H_{b'}$ NOEs, indicating that the CH_a proton is nearer proton H_b and further from proton $H_{b'}$. By using the Altona equation,[10] the values of 14° and 113° have been calculated for the dihedral angles $H_a-C-C-H_b$ and $H_a-C-C-H_{b'}$ from the vicinal coupling constants (J_{ab} = 8.5 Hz, $J_{ab'}$ = 3.4 Hz). The lack of significant NOEs between the hydroxyl proton and both methylene protons indicates that the OH group is directed toward the N−H proton, probably as a result of the formation of an intramolecular hydrogen bond NH−OH. Accordingly, no concentration dependence (100−1 mM) of proton chemical shifts of **1** has been found.

The conformations of the three quinine derivatives have been determined on the basis of NOEs, indicated in Figure 3, and on the basis of the dihedral angle $H_8-C_9-C_8-H_9$, obtained from the vicinal coupling constant[10] between the protons H_8 and H_9 (J_{89} is 7.3, 7.3, and 2 Hz for **QuiOAc**, **Quicarb**, and **Quibec**, respectively).

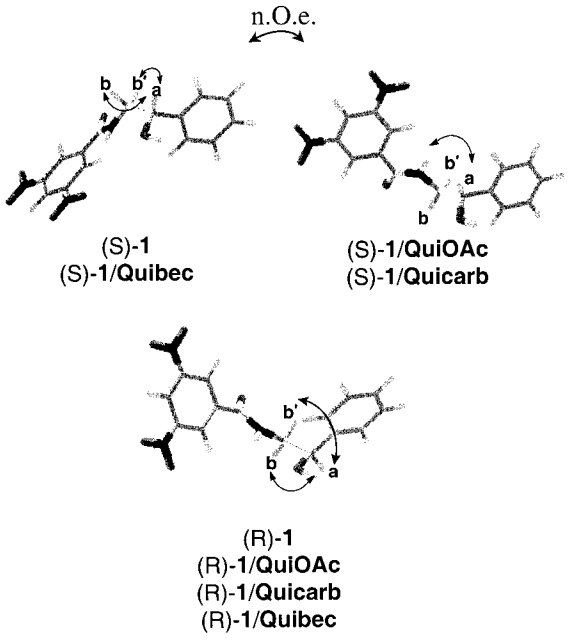
(9) Neuhaus, D.; Willianson, M. *The Nuclear Overhauser Effect*; WCH Publishers: New York, 1989.

(10) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792.

Table 1. Nonequivalences ($\Delta\Delta\delta$,[a] 300 MHz, $CDCl_3$) and Complexation Shifts ($\Delta\delta$,[b] 300 MHz, $CDCl_3$) Induced in the Protons of 1 (120 mM) by Equimolar Amounts of Quinines

				$\Delta\delta^b$ (Hz)					
	$\Delta\Delta\delta^a$ (Hz)			**QuiOAc**		**Quicarb**		**Quibec**	
proton	**QuiOAc**	**Quicarb**	**Quibec**	(S)−**1**	(R)−**1**	(S)−**1**	(R)−**1**	(S)−**1**	(R)−**1**
H_o	29.2	23.6	6.9	−42.0	−12.8	−37.1	−13.5	41.2	34.3
H_p	45.5	49.1	3.0	−75.7	−30.2	−91.5	−42.4	−93.6	−90.6
NH	24.0	28.5	12.5	145.4	121.4	186.4	157.9	527.8	515.3
CH_a	8.5	9.3	3.9	−30.7	−22.2	−9.0	−18.3	−17.4	−21.3
C**H**−H	66.2	49.6	4.1	−69.0	−2.8	−63.8	−14.2	−54.2	−50.1
C$\overline{\text{H}}$−$\underline{\text{H}}$	80.4	82.8		50.6	−29.8	55.8	−27.0	−38.4	

[a] $\Delta\delta\delta = |\delta_S - \delta_R|$, Hz: δ_S, chemical shift of the (*S*)-enantiomer of **1** in the presence of the chiral auxiliary; δ_R, chemical shift of the (*R*)-enantiomer of **1** in the presence of the chiral auxiliary. [b] $\Delta\delta = \delta_{mixture} - \delta_{free}$, Hz: $\delta_{mixture}$, chemical shift measured for each enantiomer of **1** in the presence of the chiral auxiliary; δ_{free}, chemical shift measured for free **1**.



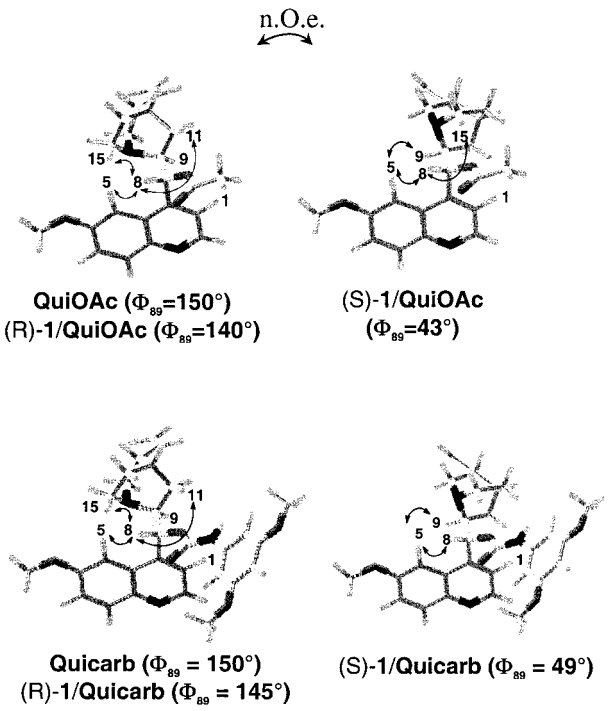


Figure 2. Conformations from NMR data of (*R*)- and (*S*)-**1** in the free states and in the complexes formed with **QuiOAc**, **Quicarb**, and **Quibec**.

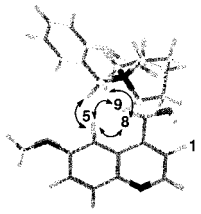


Figure 3. Conformations from NMR data of quinine derivatives in the free states and in the complexes formed with (*S*)-**1** and (*R*)-**1**.

For the two chiral auxiliaries derivatized at the hydroxyl group, **QuiOAc** and **Quicarb**, we have found *closed* conformations for the free state (NOE $H_9-H_5 \cong H_9-H_1$, Figure 4a), with the *N*-quinuclidine nitrogen pointed toward the quinoline ring. On the other hand, **Quibec**, with the OH group underivatized, has an *open* conformation (NOE $H_9-H_5 > H_9-H_1$) (Figure 3), in which the quinuclidine nitrogen is oriented away from the quinoline ring. In all cases the proton H_8 is mainly directed toward the quinoline proton H_5 (NOE $H_8-H_5 \gg H_8-H_1$, Figure 4a).

Analysis of the chemical shift dependence on total concentration has demonstrated that the acetylated quinine, **QuiOAc**, is monomeric in solution, whereas the two quinines having a C_9 hydrogen bond donor, **Quicarb** and **Quibec**, exist as dimers in equilibrium with monomers, with signals that are in fast exchange on the NMR time scale ($K_{autoassociation} = 1.8\ M^{-1}$ for **Quicarb** and 7.7 M^{-1} for **Quibec** as calculated by fitting dilution NMR data).

The stereochemistries of the dimers (Figure 5) have been determined by 2D ROESY analyses in highly concentrated solutions (80−200 mM). The H_3-H_5 NOEs for both quinine derivatives, as well as additional NH−H_2 and NH−H_3 NOEs for **Quicarb** or H_2−OH and H_3−OH NOEs for **Quibec**, including the absence of H_1−OMe NOEs, confirmed a head-to-tail autoassociation of the quinoline rings. The quinuclidine moieties are external to the dimers, as the H_2 and H_3 protons have not produced any NOEs with the quinuclidine nuclei. The monomeric quinine derivatives have retained the same conformation that has been found in highly diluted solution, where the monomer prevails.

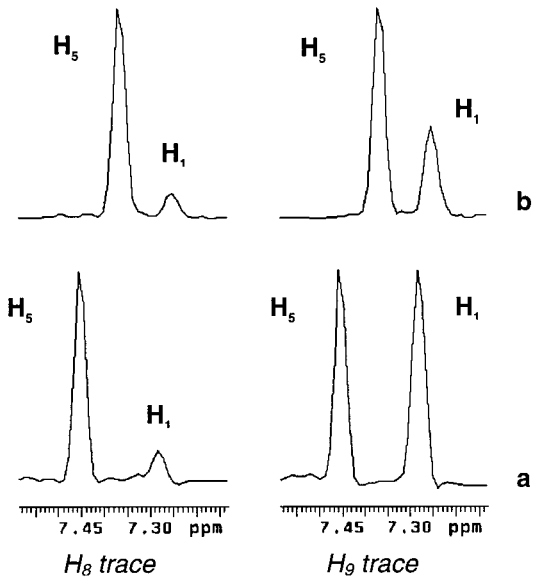


Figure 4. 2D ROESY analysis (300 MHz, $CDCl_3$, 25 °C, τ_m = 0.6 s) of (a) pure **QuiOAc**, (b) mixture (*S*)-**1**/**QuiOAc**, traces of H_8 and H_9 protons.

Stereochemistries of the Diastereoisomeric Complexes Formed by (*R*)- or (*S*)-1 and Quinine Derivatives. Some very interesting conformational features have been observed in the mixtures containing each quinine derivative and the (*S*)- or (*R*)-enantiomer of **1**.

In the mixture containing **QuiOAc** and (*S*)-**1**, both components change their conformation relative to the free state. For (*S*)-**1**, the methine proton has become equidistant from the two methylene protons (Figure 2). The two diastereotopic methylene protons of (*S*)-**1** have equivalent coupling constants in the **QuiOAc**/**1** mixture, $J_{ab} = J_{ab'} = 6.1$ Hz, corresponding to the same dihedral angles $H_a-C-C-H_b$ and $H_a-C-C-H_{b'}$ (about 130°). The NH group is also close to the methine and far away from the phenyl group given that only a NH-methine NOE has been detected. Therefore, the intramolecular NH−OH hydrogen bond present in the free state must be broken in the complex **QuiOAc**/**1**. The acetylated quinine, **QuiOAc**, assumes an *open* conformation (Figure 3) in which the quinuclidine nitrogen undergoes a clockwise rotation, withdrawing it from the quinoline plane, according to changes of the relative intensities of the H_9-H_5 and H_9-H_1 NOEs (Figure 4b).

In the diastereomeric mixture containing **QuiOAc** and the (*R*)-**1** both species have retained their free state conformations (Figures 2 and 3).

The origin of the different spectra for the diastereomeric complexes **QuiOAc**/(*S*)-**1** and **QuiOAc**/(*R*)-**1** is understandable on the basis of the different intermolecular NOEs (Figure 6). The (*S*)-enantiomer acts as a bidentate ligand interacting by means of its NH group with the quinuclidine nitrogen and by its OH group with the acetyl function of **QuiOAc**. These interactions are indicated by the NOEs NH−H_8, CH_a-H_8, CH_a-H_{15}, 3,5-dinitrobenzoyl−OMe. The two intermolecular H-bond interactions probably allow (*S*)-**1** to change its conformation and to break the intramolecular hydrogen bond present in its free state. The hydrogen bond between the NH group of (*S*)-**1** and the quinuclidine nitrogen also justifies the "opening" of the conformation of quinine.

In the other diastereoisomeric adduct, **QuiOAc**/(*R*)-**1** (see Figure 6), the 3,5-dinitrobenzoyl and NH protons produce small but detectable NOEs with H_2 and H_3 adjacent to the quinoline nitrogen. Similar dipolar interactions are also generated by one methylene proton. Finally, an intermolecular NOE between the NH proton of (*R*)-**1** and the H_8 proton of **QuiOAc** has also been detected. No NOEs between (*R*)-**1** and quinuclidine protons have been observed. Therefore, the **QuiOAc**−(*R*)-**1** interaction takes place at the quinoline plane at the opposite side of the quinuclidine nitrogen. The (*R*)-enantiomer of the analyte maintains its intramolecular hydrogen bond NH−OH and probably interacts with the quinoline nitrogen or acetyl function. These interactions can be assisted by the $\pi-\pi$ attraction between the aromatic moieties of the analyte and the quinoline plane.

The different type and strength of the interactions for the two diastereoisomeric complexes, each having 1:1 stoichiometry (see Experimental Section), are well reflected in their respective association constants, which are $K = 41.2\ M^{-1}$ for (*S*)-**1**/**QuiOAc** and $K = 13.4\ M^{-1}$ for (*R*)-**1**/**QuiOAc**.

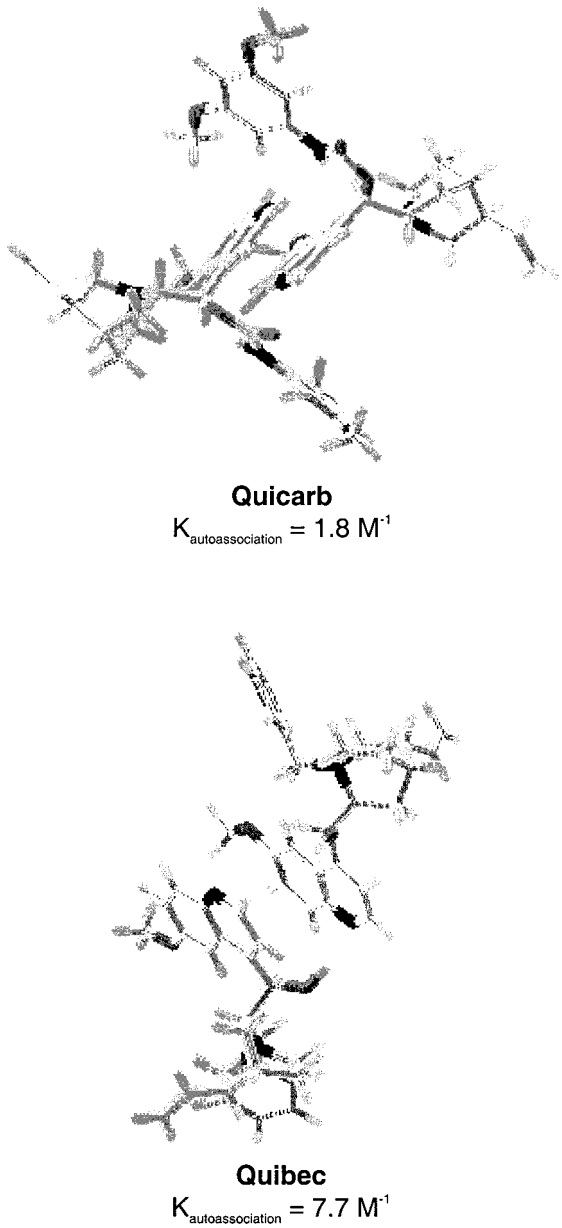


Figure 5. Conformations of the dimers of **Quicarb** and **Quibec** from NMR data.

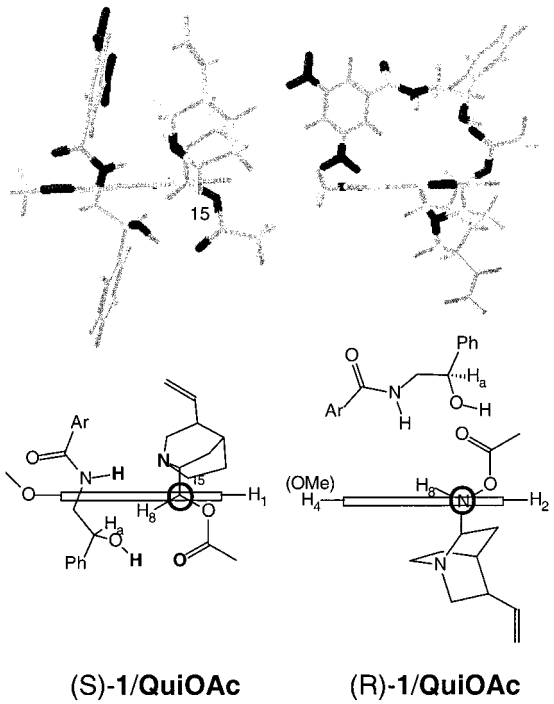


Figure 6. Representation of the diastereoisomeric complexes formed by **QuiOAc** and (*S*)- or (*R*)-**1**.

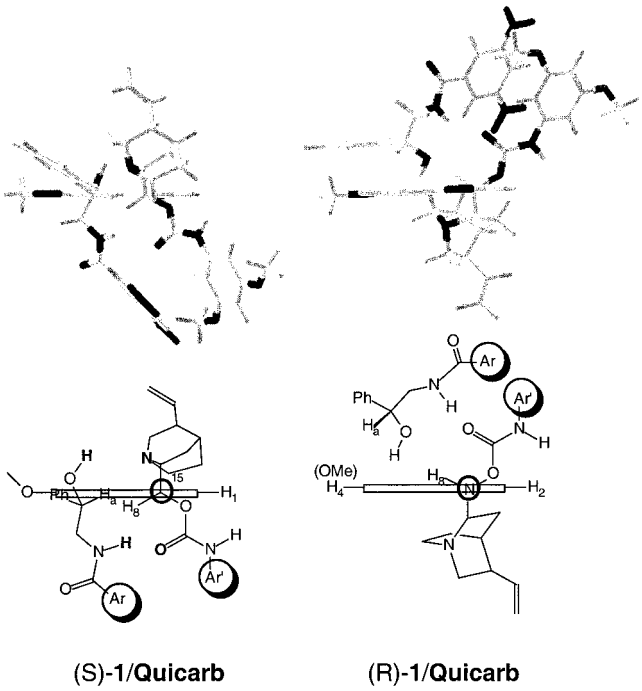


Figure 7. Representation of the diastereoisomeric complexes formed by **Quicarb** and (*S*)- or (*R*)-**1**.

In the case of the carbamoyl derivative of quinine, **Quicarb**, a similar behavior for the two diastereoisomeric adducts has been found. The interaction between (*S*)-**1** and **Quicarb** causes a change in the conformation of both components (Figures 2 and 3), analogous to that observed for **QuiOAc**/(*S*)-**1**, whereas there is little interaction of **Quicarb** with (*R*)-**1**, as the conformations of both compounds remain unchanged from the free state.

However, the intermolecular interactions involved in the formation of the diastereoisomeric adducts are rather different (Figure 7). For the **Quicarb**/(*S*)-**1** pair, one of the quinine sites interacting with the chiral analyte is once again the quinuclidine nitrogen. This explains why the quinine derivative changes its conformation to *open*. However, it is the hydroxyl of (*S*)-**1** that interacts with the **Quicarb** quinuclidine nitrogen and not the NH group, as has been found for the acetyl quinine, **QuiOAc**. In fact, the NOE determinations indicate a proximity between the 3,5-dimethoxyphenyl group of **Quicarb** and the 3,5-dinitrophenyl group of the analyte. Moreover, the protons NH, CH_a, H_o, and H_p of (*S*)-**1** all produce NOEs with the proton H_8. It is noteworthy that we have measured a reproducible CH_a-H_{15} NOE that indicates the proximity of proton CH_a to the quinuclidine moiety.

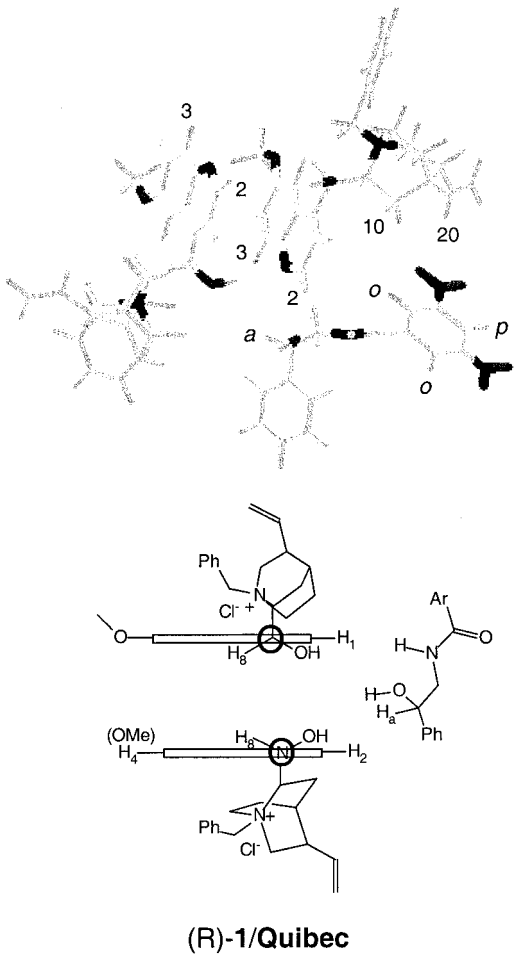
Therefore, it can be concluded that three interactions are important: (1) a hydrogen bond between the OH group of (*S*)-**1** and the quinuclidine nitrogen of **Quicarb**; (2) a hydrogen bond between the NH group of (*S*)-**1** and, probably, the C=O group of the **Quicarb** carbamate; (3) a $\pi-\pi$ interaction between the 3,5-dinitrophenyl and the 3,5-dimethoxyphenyl groups.

For the other enantiomer, (*R*)-**1**, the interaction with **Quicarb** takes place at the less hindered face of the quinine derivative. On the basis of the NOE data, the (*R*)-enantiomer, in its free state conformation, faces the quinoline plane at the side opposite to that of the quinuclidine nitrogen, with the 3,5-dinitrophenyl moiety bent at the 3,5-dimethoxyphenyl and with its NH−OH hydrogen bonded moiety directed toward the quinoline nitrogen (Figure 7).

It is noteworthy that, even if **Quicarb** is present in solution in a monomer−dimer equilibrium, the interaction with both enantiomers of the analyte only involves the monomer.

Finally, no conformational changes of both components are observed for mixtures containing the quinine derivatized at the quinuclidine nitrogen (**Quibec**) and either (*R*)-**1** or (*S*)-**1**. Very similar intermolecular NOEs have been detected between protons of **Quibec** and protons of (*R*)-**1** or (*S*)-**1**, so as to indicate that the stereochemistries of the two diastereoisomeric adducts must be very similar. This result is in keeping with the rather low extent of enantiodiscrimination found in the mixtures containing the chiral auxiliary and the racemate of the chiral analyte.

Furthermore, the protons H_o and H_p of the 3,5-dinitrobenzoyl group of (*R*)-**1** originate dipolar interactions with all of the quinoline protons H_1-H_5, but the ortho protons H_o have also given NOEs with H_{20} and H_{10} quinuclidine protons. Therefore, it seems reasonable to conclude that (*R*)-**1** faces the more hindered side of **Quibec**, the side containing the quinuclidine ring. However, an apparently incongruous NOE between the ortho protons of the 3,5-dinitrobenzoyl group of (*R*)-**1** and the OH proton of **Quibec** has also been detected, according to a structure in which the substrate approaches the opposite side of **Quibec**. Furthermore, the proton H_2 of **Quibec** gives remarkable NOEs to the CH, CH_2, and the phenyl protons of (*R*)-**1**. Conversely, the CH proton of (*R*)-**1** shows clear dipolar interactions only with the quinoline protons H_2 and H_3. Taking into account that it is quite difficult to explain why (*R*)-**1** should approach the more hindered quinoline side, it seems reasonable to suppose an interaction model as shown in Figure 8: (*R*)-**1** interacts directly with the dimer of **Quibec**. In this way (*R*)-**1** can bring its 3,5-dinitrobenzoyl moiety simul-



(R)-**1**/**Quibec**

Figure 8. Representation of the diastereoisomeric complex formed by **Quibec** and (*R*)-**1**.

taneously close to the quinuclidine ring of one **Quibec** monomer and to the OH group of the other **Quibec** monomer. This model also explains the proximity between the ethanolamine portion of **1** and the H_2 and H_3 protons of **Quibec**. It is noteworthy that the 2D ROESY map also reveals NOEs due to the presence of the **Quibec** dimer.

Conclusion

For the naturally occurring quinine and quinidine alkaloids an *open* conformation is preferred in solution. In NMR investigations regarding chiral recognition phenomena,[11] this *open* conformation is believed to be responsible for the enantiodiscriminating ability of the alkaloids, as the unhindered quinuclidine nitrogen is able to generate strong interactions with selectands, even if, in some cases, the quinuclidine nitrogen has not demonstrated involvement, probably because of the unnegligible bulkiness of the quinuclidine moiety.[12]

Therefore, not only is the relevance of quinuclidine nitrogen, the most basic site, clearly recognized in determining the strength of alkaloid interactions with acid-type substrates and in governing the enantiodiscriminating pathways, but also great importance seems to rely on the ground-state stereochemistry, as the free state *open* conformation can determine a greater accessibility to the same site.

Our results reveal two important findings. At least for the cases investigated, quinine derivatives having an available quinuclidine nitrogen result in the highest extent of enantiodiscrimination, even if these have a *closed* conformation in the free state (**QuiOAc** and **Quicarb**). The quaternarization of this quinuclidine site, as for **Quibec**, results in a completely different interaction mechanism with the chiral analyte, resulting in a lower degree of enantiodifferentiation but not labilization of the diastereoisomeric species. Finally, both the strength and the nature of the interactions with the analyte are greatly affected by *monomer*−*dimer* self-assemby of the quinines.[13]

The latter point gets to the root of chiral recognition mechanisms, not only for quinines but also for other classes of chiral selectors. The frequent hypothesis that the free state conformation of a ligand is retained in the diastereoisomeric adduct with a chiral selectand may be misleading. In fact, in our cases the formation of the most stable diastereoisomeric adducts (*S*)-**1**/**QuiOAc** and (*S*)-**1**/**Quicarb** involves significant conformational changes for the adducts relative to the free compounds. Similarly, misleading chiral discrimination mechanisms may also originate from the hypothesis that the knowledge of the stereochemistry for the components of only one diastereoisomeric species, the most stable one, can be assumed as a basis for extrapolating the stereochemistry of the less stable diastereoisomer. In fact, completely different interaction pathways have been found for the two enantiomers of **1** in the presence of the same chiral selectand.

Experimental Section

All spectra were recorded using a spectrometer operating at 300 MHz for ^{1}H, and the temperature was controlled to ±0.1 °C.

The 2D NMR spectra were obtained by using standard sequences. The double-quantum-filtered (DQF) COSY experiments were recorded with a spectral width of 3300 Hz; 512 increments of 8 scans and 2K data points were acquired. The relaxation delay was 5 s. The data were zero-filled to 2K × 1K, and a Gaussian function was applied for processing in both dimension. The phase-sensitive ROESY[9] spectra were acquired with a spectral width of 3300 Hz in 2K data points using 8 scans for each of the 512 t_1 increments, with a mixing time of 600 or 300 ms. A Gaussian function was applied for processing in both dimension.

The ^{1}H{^{1}H}-NOE experiments were performed in the difference mode. The decoupler power used was the minimum required to saturate the spin of interest. A waiting time of 5−10 s was used to allow the system to reach the equilibrium. Each NOE experiment was repeated at least four times. All of the solutions were accurately degassed by freeze−pump−thaw cycles for 1D and 2D NOE experiments.

The stoichiometries were determined[14] by measuring the chemical shift of quinine in solutions prepared by mixing different volumes of stock solutions of each component having

(11) Reeder, J.; Castro, P. P.; Knobler, C. B.; Martinborough, E.; Owens, L.; Diederich, F. *J. Org. Chem.* **1994**, *59*, 3151−3160.

(12) (a) Salvadori, P.; Rosini, C.; Pini, D.; Bertucci, C.; Altemura, P.; Uccello-Barretta, G.; Raffaelli, A. *Tetrahedron* **1987**, *43*, 4969−4978. (b) Uccello-Barretta, G.; Pini, D.; Rosini, C.; Salvadori, P. *J. Chromatogr., A* **1994**, *666*, 541−548.

(13) (a) Williams, T.; Pitcher, R. G.; Bommer, P.; Gutzwiller, J.; Uskokovic, M. *J. Am. Chem. Soc.* **1969**, *91*, 1871−1872. (b) Uccello-Barretta, G.; Di Bari, L.; Salvadori, P. *Magn. Reson. Chem.* **1992**, *30*, 1054−1063.

(14) (a) Job, P. *Ann. Chem.* **1928**, *9*, 113−134. (b) Homer, J.; Perry, M. C. *J. Chem. Soc., Faraday Trans. 1* **1986**, *82*, 533−543.

the same molar concentration *M* to obtain a prefixed volume *V* directly in the NMR tube. Owing to the solubility of **1**, the stoichiometry was determined on quite dilute solutions ($M = 0.015$).

The autoassociation constants were determined by analyzing the dependence of the chemical shifts from the total concentration in the range 200−2 mM for **Quicarb** and 120−4 mM for **Quibec**.[13b]

The heteroassociation constants for the two diastereoisomeric complexes (*S*)-**1**/**QuiOAc** and (*R*)-**1**/**QuiOAc** were determined by nonlinear fitting[15] of the experimental data (concentration vs chemical shift) obtained from the analysis of the proton NMR spectra acquired for two sets of solutions progressively diluted from 122.5 to 0.4 mM, containing equimolar amounts of **1** and **QuiOAc**.

Melting points were determined using a Koffler hot-stage apparatus. Optical rotations were measured using a Perkin-Elmer 142 polarimeter.

Materials. *N*-benzylquininium chloride (**Quibec**) was purchased from Fluka. L-(+)-and D-(−)-mandelic acid were obtained from Aldrich. All chemicals were purified prior to use by standard methods.[16] (*R*)- and (*S*)-2-(3′,5′-dinitrobenzamido)-1-phenylethanol [(*R*)- and (*S*)-**1**] have been prepared starting from (*R*)- and (*S*)-2-hydroxy-1-phenylethanol [(*R*)- and (*S*)-**2**], respectively, as previously reported.[17]

9-*O*-Acetylquinine (QuiOAc).[18] According to literature methods, **QuiOAc** was obtained starting from quinine in 92% yield: mp 116−117 °C (lit.[18] 115−117 °C); ^{1}H NMR ($CDCl_3$, 25 °C, 120 mM, ppm referred to TMS as external standard) 1.45 (1H, H_{11}, m), 1.49 (1H, H_{13}, m), 1.64 (1H, H_{14}, m), 1.80 (1H, H_{12}, m), 1.80 (1H, H_{10}, m), 2.07 (3H, OAc, s), 2.21 (1H, H_{17}, m), 2.55 (1H, H_{18}, m), 2.60 (1H, H_{16}, m), 2.98 (1H, H_{19}, m), 3.05 (1H, H_{15}, m), 3.32 (1H, H_9, m), 3.91 (3H, OMe, s), 4.96 (1H, H_{21}, dd, $J_{21-20} = 10.6$ Hz, $J_{21-22} = 1.6$ Hz), 4.97 (1H, H_{22}, dd, $J_{22-20} = 17.0$ Hz, $J_{22-21} = 1.6$ Hz), 5.80 (1H, H_{20}, ddd, $J_{20-22} = 17.0$ Hz, $J_{20-21} = 10.6$ Hz, $J_{20-17} = 7.7$ Hz), 6.44 (1H, H_8, d, $J_{8-9} = 7.3$ Hz), 7.30 (1H, H_1, d, $J_{1-2} = 4.5$ Hz), 7.32 (1H, H_4, dd, $J_{4-3} = 8.9$ Hz, $J_{4-5} = 2.9$ Hz), 7.40 (1H, H_5, d, $J_{5-4} = 2.9$ Hz), 7.96 (1H, H_3, d, $J_{3-4} = 8.9$ Hz), 8.69 (1H, H_2, d, $J_{2-1} = 4.5$ Hz).

Preparation of 9-*O*-(3,5-Dimethoxyphenylcarbamate)-quinine (Quicarb). 3,5-Dimethoxybenzoyl Azide. To a stirred suspension of 3,5-dimethoxybenzoic acid (50 mmol) in anhydrous toluene (60 mL) was added a solution of oxalyl chloride (70 mmol) in anhydrous acetone (40 mL). The reaction mixture, refluxed until no more gas development was observed, was allowed to warm to 50 °C, and the solvents were removed. Then to the crude residue, dissolved in anhydrous acetone (120 mL), was added a solution of sodium azide (184 mmol) in H_2O (50 mL), and the reaction mixture was stirred for 12 h. The organic materials were extracted with CH_2Cl_2. After the usual workup, 3,5-dimethoxybenzoyl azide was recovered (77% yield): ^{1}H NMR ($CDCl_3$, 25 °C, ppm referred to TMS as external standard) 3.81 (6H, s, 2 OMe), 6.65 (1H, H_p, t, $J_{p-o} = 2.0$ Hz), 7.22 (2H, H_o, d, $J_{o-p} = 2.0$ Hz). Anal. Calcd for $C_9H_9O_3N_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.19; H, 4.36; N, 20.32.

9-*O*-(3,5-Dimethoxyphenylcarbamate)quinine (Quicarb). A solution of 3,5-dimethoxybenzoyl azide (39 mmol) in anhydrous toluene (170 mL) was stirred at 110 °C until no more gas development was observed, and then quinine (33.2 mmol) was added. The reaction mixture was refluxed for a further 3 h. After the usual workup, **Quicarb** was recovered (69% yield) by recrystallization from THF/*n*-pentane: mp 119−121 °C; ^{1}H NMR ($CDCl_3$, 25 °C, 200 mM, ppm referred to TMS as external standard) 1.46 (1H, H_{13}, m), 1.51 (1H, H_{11}, m), 1.63 (1H, H_{14}, m), 1.79 (1H, H_{10}, m), 1.80 (1H, H_{12}, m), 2.21 (1H, H_{17}, m), 2.58 (1H, H_{18}, m), 2.58 (1H, H_{16}, m), 2.98 (1H, H_{19}, m), 3.06 (1H, H_{15}, m), 3.27 (1H, H_9, m), 3.66 (6H, 2 OMe^c, s), 3.89 (3H, OMe, s), 4.96 (1H, H_{22}, d, $J_{22-20} = 18.7$ Hz), 4.97 (1H, H_{21}, d, $J_{21-20} = 11.4$ Hz), 5.76 (1H, H_{20}, ddd, $J_{20-22} = 18.7$ Hz, $J_{20-21} = 11.4$ Hz, $J_{20-17} = 8.5$ Hz), 6.13 (1H, H_p^c, t, $J_{p-o} = 1.6$ Hz), 6.50 (1H, H_8, d, $J_{8-9} = 7.3$ Hz), 6.57 (2H, H_o^c, d, $J_{o-p} = 1.6$ Hz), 7.28 (1H, H_1, d, $J_{1-2} = 4.9$ Hz), 7.31 (1H, H_4, dd, $J_{4-3} = 9.4$ Hz, $J_{4-5} = 2.4$ Hz), 7.45 (1H, H_5, d, $J_{5-4} = 2.4$ Hz), 7.97 (1H, H_3, d, $J_{3-4} = 9.4$ Hz), 8.65 (1H, H_2, d, $J_{2-1} = 4.9$ Hz). Anal. Calcd for $C_{29}H_{33}O_5N_3$: C, 69.17; H, 6.61; N, 8.34. Found: C, 69.20; H, 6.58; N, 8.32.

***N*-Benzylquininium Chloride (Quibec).** ^{1}H NMR ($CDCl_3$, 25 °C, 80 mM, ppm referred to TMS as external standard) 1.46 (1H, H_{10}, m), 1.64 (1H, H_{13}, m), 1.93 (1H, H_{12}, m), 2.18 (1H, H_{11}, m), 2.24 (1H, H_{14}, m), 2.46 (1H, H_{17}, m), 2.98 (1H, H_{16}, m), 3.37 (1H, H_{19}, m), 3.53 (1H, H_{18}, m), 3.89 (1H, H_9, m), 3.93 (3H, OMe, s), 4.76 (1H, CH_2^{Bz}, d, $J = 12.2$ Hz), 4.88 (1H, H_{15}, m), 4.88 (1H, H_{21}, d, $J_{21-20} = 10.6$ Hz), 5.02 (1H, H_{22}, d, $J_{22-20} = 17.0$ Hz), 5.52 (1H, H_{20}, ddd, $J_{20-22} = 17.0$ Hz, $J_{20-21} = 10.6$ Hz, $J_{20-17} = 6.9$ Hz), 5.99 (1H, CH_2^{Bz}, d, $J = 12.2$ Hz), 6.56 (1H, H_8, d, $J_{8-OH} = 5.7$ Hz), 7.23 (1H, H_4, dd, $J_{4-3} = 8.9$ Hz, $J_{4-5} = 2.7$ Hz), 7.27 (1H, H_p, m), 7.27 (1H, H_5, d, $J_{5-4} = 2.7$ Hz), 7.29 (1H, d, $J_{OH-8} = 5.7$ Hz), 7.33 (2H, H_m, m), 7.66 (1H, H_1, d, $J_{1-2} = 4.9$ Hz), 7.69 (2H, H_o, d, $J_{o-m} = 6.9$ Hz), 7.92 (1H, H_3, d, $J_{3-4} = 8.9$ Hz), 8.62 (1H, H_2, d, $J_{2-1} = 4.9$ Hz).

(*R*)- and (*S*)-2-(3′,5′-Dinitrobenzamido)-1-phenylethanol [(*R*)- and (*S*)-1]. ^{1}H NMR ($CDCl_3$, 25 °C, ppm referred to TMS as external standard) 2.92 (1H), 3.56 (1H), 4.01 (1H), 5.00 (1H), 6.88 (1H), 7.30−7.50 (5H), 8.94 (2H), 9.16 (1H).

(*R*)- and (*S*)-2-Hydroxy-1-phenylethanol [(*R*)- and (*S*)-2].[19] To a stirred suspension of $LiAlH_4$ (66.0 mmol) in dry Et_2O (150 mL) was added D-(−)-mandelic acid (32.9 mmol). The reaction mixture was refluxed for 6 h, allowed to stir at room temperature for 2 h, treated with ice water, and then filtered. After the usual workup, (*R*)-**2** was recovered (70% yield) by recrystallization from Et_2O/pentane (1:2): mp 66 °C (lit.[19] 66−67 °C); $[\alpha]^{21}_D$ −39.3 (*c* 1.26, EtOH); ^{1}H NMR ($CDCl_3$, 25 °C, ppm referred to TMS as external standard) 2.30 (1H), 2.75 (1H), 3.60−3.80 (2H), 4.85 (1H), 7.20−7.50 (5H). Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found for (*R*)-**2**: C, 69.57; H, 7.24.

According to the above procedure, from L-(+)-mandelic acid was obtained (*S*)-**2**: 70% yield, $[\alpha]^{21}_D$ +39.3 (*c* 1.26, EtOH) according to literature.[19] Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found for (*S*)-**2**: C, 69.52; H, 7.25.

Acknowledgment. This work was supported by the Ministero della Ricerca Scientifica e Tecnologica (MURST) and CNR, Italy.

Supporting Information Available: Tables of vicinal coupling constants and calculated dihedral angles for (*S*)- or (*R*)-**1** and quinine in the free state and in equimolar mixtures. ^{1}H{^{1}H}-NOE difference spectra of **1** in $CDCl_3$. Traces of 300 MHz ROESY spectra of each quinine in the free state and in the equimolar mixtures containing (*R*)- or (*S*)-**1** in $CDCl_3$. Plot of concentration against chemical shifts for the determination of the autoassociation constants of **Quicarb** and **Quibec**. Job plot for the determination of the stoichiometry of (*S*)-**1**/**QuiOAc** and (*R*)-**1**/**QuiOAc**. Plot of concentration against chemical shifts for the determination of association constants of (*S*)-**1**/**QuiOAc** and (*R*)-**1**/**QuiOAc**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO991661L

(15) Uccello-Barretta, G.; Balzano, F.; Caporusso, A. M.; Iodice, A.; Salvadori, P. *J. Org. Chem.* **1995**, *60*, 2227−2231.

(16) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon Press: Toronto, 1983.

(17) Uccello-Barretta, G.; Cuzzola, A.; Balzano, F.; Menicagli, R.; Iuliano, A.; Salvadori, P. *J. Org. Chem.* **1997**, *62*, 827−835.

(18) Jaeger, F. M. *Verslag. Akad. Wetenschappen Amsterdam* **1926**, *35*, 61−74.

(19) King, R. B.; Bakos, J.; Hoff, C. D.; Markó, L. *J. Org. Chem.* **1979**, *44*, 1729−1731.