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A NOVEL APPLICATION OF CINCHONA ALKALOIDS AS CHIRAL AUXILIARIES: PREPARATION AND USE OF A NEW FAMILY OF CHIRAL STATIONARY PHASES FOR THE CHROMATOGRAPHIC RESOLUTION OF RACEMATES.(#)

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ABSTRACT: The preparation of new chiral stationary phases derived from quinine, quinidine and cinchonidine and their application to resolution of racemic binaphthyl derivatives are described. From the comparison of the results achieved on the three phases, the knowledge of the elution orders, obtained by circular dichroism, and the analysis, by ^{1}H NMR spectroscopy, of the structures of the adducts between quinine and 2'-(2-propoxy)- 1,1'-binaphthyl-2-ol, it has been possible to provide an experimental basis to a chiral recognition mechanism.

The use of Cinchona alkaloids as chiral auxiliaries goes back to the birth of stereochemistry; the first resolution ever made, in fact, was carried out[1] by means of quinicine and cinchonicine, derivatives of quinine and cinchonine respectively, two of the most known of the above alkaloids. Later on these compounds have been largely employed[2] as resolving agents and about 25% of all resolutions uses these natural bases[3]. In addition, the Cinchona alkaloids have found many applications in asymmetric synthesis: H. Wynberg and coworkers used[3] them in several organic reactions such as Michael and 1,4-thiol additions, epoxidation of electron poor olefins and 2,2-cycloadditions. Other significant synthetic applications concern, for instance, the enantioselective phase transfer alkylation[4] of carbonyl compounds in the presence of N-(p-benzylsubstituted)benzylcinchoninium bromide (e.e. about 95%) and the use of Cinchona alkaloids as chiral complexing agents toward $LiAlH_4$ to carry out asymmetric reductions of prochiral ketones[5].

The large success of these substances as asymmetric catalysts has been very nicely accounted for by Wynberg[3] on the basis of different simultaneous interactions between the catalyst and the reactant. The possibility of multiple interactions between the alkaloid and different polifunctional organic compounds prompted us to use these substances as commercially available materials to modify silica supports and to obtain new chiral stationary phases (c.s.p.) for the resolution of racemates.

Quinine and some other Cinchona alkaloids have been already used[6] to prepare asymmetric sorbents but the hydroxy group or the quinuclidine nitrogen were employed to form the bond with the chromatographic support: of course in this way an important functional group was not available to interact with the enantiomers of

(#) This paper is dedicated to Prof. Dr. Hans Wynberg in occasion of his 65th birthday.

the substrate. For the first time quinine has been bonded covalently to a silica support by means of the olefinic double bond obtaining a new chiral phase (SiSQuin) efficient in separating racemic alkyl aryl carbinols and binaphthyl derivatives[7-9].

Aim of the present work is to have a better insight into the mechanism of the chiral recognition exerted by the above stationary phase. Therefore, the resolution of binaphthyl compounds has been examined here extending the investigation to a larger number of samples with respect to our previous work[7,8] and by comparing the performances of SiSQuin with the ones of similar phases, SiSQuind and SiSCincd, derived from quinidine and cinchonidine, respectively. However a particular effort has been made to get direct evidence for the interactions which account for the chiral discrimination process by spectroscopic techniques[10]. The family of binaphthyl derivatives has been chosen for this study, because they are quite well resolved by SiSQuin. In addition a detailed study on the resolution of these compounds could be relevant in consideration of their widespread use as ligands in asymmetric synthesis[11] and taking also into account that some substances with biaryl structure are known[12] to show interesting biological properties.

RESULTS AND DISCUSSION

Chromatographic separations. The anchoring of the alkaloid moiety to the silica support has been carried out by exploiting the recently reported[13] observation that alkyl mercaptans, in the presence of a radical source, give, in a good yield, anti-Markovnikov addition to the vinyl group of the alkaloids. Then, by reacting γ-mercaptopropyl silica, obtainable following a described procedure[14], with the suitable alkaloid in the presence of AIBN as radical source, the three chiral stationary phases SiSQuin, I, (from quinine), SiSQuind, II, (from quini-

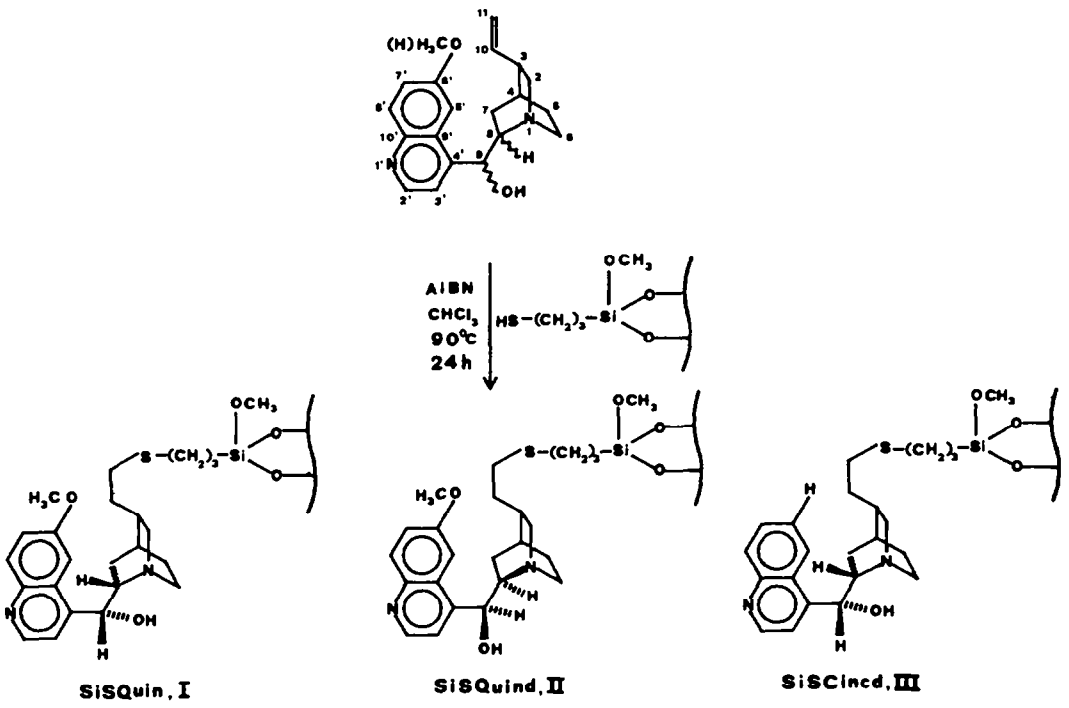
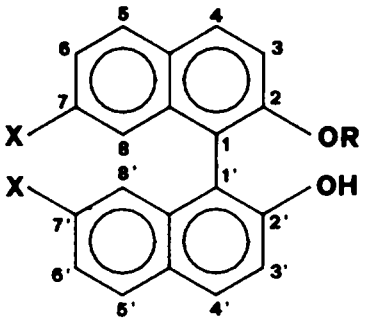


Fig. 1. The structures of the chiral stationary phases prepared.

dine) and SiSCincd, III, (from cinchonidine) have been prepared (Fig. 1). These phases have been slurry packed in 250x4.6 mm I.D. columns, using conventional techniques.

As it is well known[2] quinine and cinchonidine differ only for the substitution of the quinoline ring in the position 6' and possess the same absolute configuration of the four chiral centres. On the contrary, quinine and quinidine differ for the absolute configuration at C(8) and C(9) and, in practice, they are considered as a "quasi-enantiomeric" pair[1] (Fig.1). The binaphthyl derivatives



	R:	X:
1	H	H
2	CH_3	H
3	n-C_4H_9	H
4	n-$C_{12}H_{26}$	H
5	$CH_2CH{=}CH_2$	H
6	i-C_3H_7	H
7	$CH_2COOC_2H_5$	H
8	$COCH_3$	H
9	H	OCH_3
10	H	$OCH_2CH{=}CH_2$

Chart

	SiSQuin, I[a]				SiSQuind, II				SiSCincd, III			
Compound	k_1[b]	α	CD[c] sign	Abs. Conf.	k_1[b]	α	CD[c] sign	Abs. Conf.	k_1[b]	α	CD[c] sign	Abs. Conf.
1	3.87	1.10	+	S	3.88	1.0	-	R	3.73	1.05	+	S
2	1.03	1.08	+	S	1.37	1.07	-	R	0.97	1.	+	S
3	0.9	1.11	+	S	0.91	1.07	-	R	1.03	1.	+	S
4	1.27	1.10	+	S	1.32	1.09	-	R	1.30	1.	+	S
5	0.85	1.09	+	S	0.88	1.12	-	R	0.87	1.	+	S
6	0.72	1.16	+	S	0.78	1.17	-	R	0.94	1.	+	S
7	0.89	1.	+	S	1.09	1.	-	R	1.	1.	+	S
8	1.05	1.	+	S	1.17	1.08	-	R	1.5	1.	+	S
9	3.19	1.11	+[d]	S	4.	1.05	-[d]	R	4.5	1.	+[d]	S
10	3.47	1.09	+[d]	S	4.44	1.	-[d]	R	4.9	1.	+[d]	S

(a): Resolutions of 1-6 from ref. 8.
(b): In all the experiments described the eluent was CH_3CN at 1 ml/min.
(c): The CD detection was done at 235 nm.
(d): The CD detection was done at 242 nm.

TABLE - Chromatographic separations of binaphthyl derivatives 1-10

having the structures shown in the Chart and prepared as reported in the literature[15] have been separated on the c.s.p. I, II and III. The values of the capacity factor[16] of the first eluted enantiomer k_1 together with the values of the separability factors[16] α are presented in the Table, whilst the resolution of 6 on II is reported in Fig. 2a.

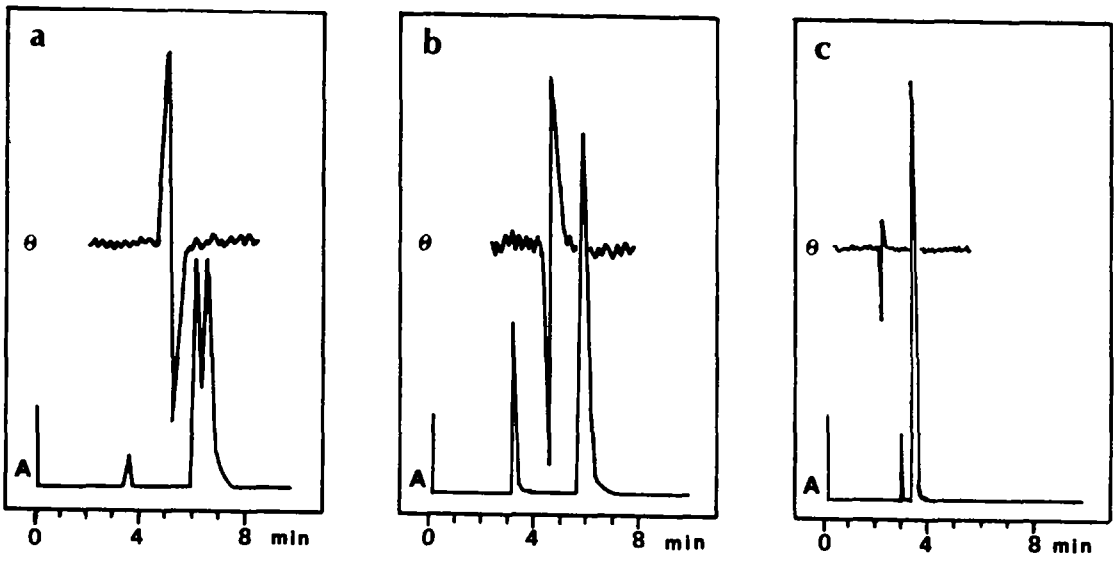


Fig. 2. a) Resolution of 6 on the phase II; b) resolution of 4 on the phase SiSQuinac; c) resolution of 2,2'-dimethoxy-1,1'-binaphthyl on the phase I. In all cases the eluent was acetonitrile at a flow rate of 1 ml/min. The detection was carried out at 230 nm for absorbance (A) and 235 nm for circular dichroism (θ). The u.v. and c.d. traces have been obtained by means of a two-pen recorder. Because the c.d. pen is displaced with respect to the u.v. one, a shifting results between the two traces. Then real retention times can be obtained only from the absorption data.

The results in the Table show clearly that the c.s.p. I and II provide separability factors which are similar, whilst the c.s.p. III looks less effective in the separation of the same compounds. As it has been previously discussed[8,9,17], it is possible to establish in a fully reliable way the elution order of binaphthyl enantiomers from a c.s.p., by recording the circular dichroism (c.d.) at a suitable wavelength and applying the exciton model. By means of the low-energy coupling mode of the long-axis polarized electrically allowed ^1B transition of the β-naphthol chromophores of 1, it is possible to correlate a positive c.d. for the above coupling mode (for which 235 nm could be a representative wavelenght and then used to follow the chromatographic separation) to the S absolute configuration of 1. Considering that in the case of 1, a positive c.d. is measured at 235 nm for the first eluted peak on the c.s.p. I, it can be concluded that the less retained enantiomer has S absolute configuration. This result can be safely extended to compounds 2-8 taking into account that a simple substitution on one of the hydroxyl groups should not change to a large extent the spectroscopic properties of the interacting chromophores. As far as compounds 9 and 10 are concerned, the introduction of two further alkoxy groups in position 7 and 7' affects the absorption spectrum: a significant red shift of the ^1B transition of about 5 nm occours, on passing from 1 to 9. The main consequence of this fact is that 235 nm can no longer be considered as a good wavelength for the low energy component of the couplet, so another, more red shifted wavelength (240-245 nm), must be chosen. By recording the c.d. at 242 nm a positive sign is measured for the first eluted

enantiomer, on the c.s.p. I, confirming the S configuration also in the case of 9 and 10.

For all the compounds studied in the present investigation, we have an inversion of the elution order on passing from phase I to II. This fact is in agreement with what already known[1b] in the classical resolution procedures by diastereoisomeric salt formation and in asymmetric synthesis[3]: quinine and quinidine behave as an enantiomeric pair. The present data show that this is also true when these compounds act as derivatizing agents for silica to form chiral stationary phases. Considering that the two phases I and II differ only for the absolute configuration of the two atoms C(8) and C(9), certainly one must conclude that this fragment plays a key role in the chiral recognition.

An important aspect of the present investigation concerns the role played by the hydroxyl group at C(9) of the alkaloid moiety. If the c.s.p. SiSQuinac, in which the above -OH function is blocked by an acetyl group, is employed[8] to separate the compounds 1-10 only poor resolutions can be obtained: a broad peak is observed in the absorption, whilst only the c.d. detector is able to indicate that a resolution has been obtained. An example of these results is reported in Fig. 2b where the resolution of 4 on the phase SiSQuinac is presented. These results clearly point out that the C(9) hydroxyl group is active in the chiral discrimination process. It is also noteworthy that at least one -OH group must be present on the binaphthyl derivatives. As a matter of fact, when both at the 2 and 2' positions on the substrate, as in 2,2'-dimethoxy-1,1'-binaphthyl, -OR functions are present, no separation is observable in absorption, and again only the c.d. detector indicates a small resolution (Fig. 2c).

As mentioned at the beginning of this paragraph, the separation factors α for the compounds 1-10 obtained on the phase III are reduced with respect to the corresponding values obtained on I (Table). Taking into account that the only structural difference between I and III is due to the presence in I of a methoxy group at the 6' position of the heteroaromatic ring (Fig. 1), one has to conclude that even the above group plays an important role in the chiral discrimination.

Spectroscopic measurements. With the aim to obtain spectroscopic evidence on the nature of the interactions between the c.s.p. and the substrates, an investigation has been undertaken by means of ^{1}H NMR spectroscopy at 300 MHz on mixtures of 6 and quinine. Compound 6 has been chosen because it is well resolved on the phases I and II and so its enantiomers should afford the largest difference in the interaction with the phase, whilst quinine can be considered a suitable soluble model of the c.s.p. I. The results of the NMR analysis referred to the isopropyl group of 6 are reported in Fig. 3. The spectrum of free 6 shows: i) two doublets centered at 1.00 and 0.87 ppm, respectively, related to the resonances of the diastereotopic methyl groups, ii) a multiplet centered at 4.32 ppm due to the methine proton (Fig. 3 a,a'). The spectrum of an equimolar mixture of 6 and quinine shows a clear presence of four doublets (0.80, 0.84, 0.94 and 0.97 ppm) and two multiplets at 4.20 and 4.28 ppm (Fig. 3b, b'). This behaviour indicates the existence of the pair of diastereoisomeric complexes quinine /(R)-6 and quinine/(S)-6. If an enriched sample of 6 (e.e. of R ca. 20%) is used, signals having different intensities are obtained: in particular the resonances at 0.84, 0.97 and 4.28 ppm are the most intense ones (Fig. 3c, c') and are then assignable to the R enantiomer. This experiment provides really important information. In the diastereoisomer quinine/(R)-6 the chemical shifts of the isopropyl protons are very similar to the ones of free 6, whilst in the complex quinine/(S)-6 the same protons resonate at higher fields and then they are in a region of space closer to shielding groups. The following values of T_1 can be measured for the protons of the C_3H_7 groups in the two diastereoisomers: for quinine/(S)-6 we find CH_3 (0.80

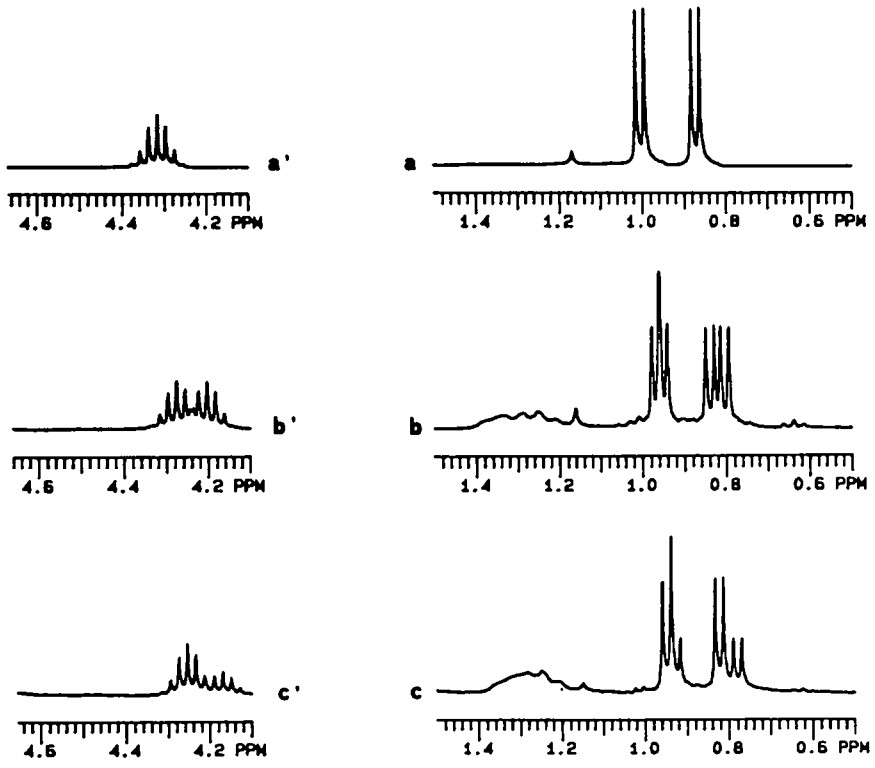


Fig. 3. The ^1H NMR spectra of free 6 in $CDCl_3$, in the region of the methyl groups (a) and methine proton (a'). The same in the presence of quinine, (b) and (b') respectively and using enriched 6 (e.e. of R 20%) (c) and (c').

ppm) 1.30s, CH_3 (0.94 ppm) 1.19s, CH 1.53s, for quinine/(R)-6 CH_3 (0.84 ppm) 1.19s, CH_3 (0.97 ppm) 1.19s, CH 1.53s. Reasonably the two methyl groups feel equivalent intra- and inter-molecular interactions in the latter, as shown by the same values of T_1, whilst in the former the relaxation times are significantly different, indicating different situations for the two methyl protons. The examination of the spectra provides further information: in fact the resonance relative to the -OH group occurs as a very broad singlet centered at 5.2 ppm, which moves downfield by further addition of quinine. By successive additions of methanol to the 1:1 quinine/6 mixture, the disappearance of the four doublets and the two multiplets due to the CH_3 and CH protons occurs and in excess of methanol, the spectrum strictly resembles that of the free 6. The added methanol competes with quinine in forming hydrogen bond with 6 and, in these last condition, the complex between quinine and 6 is not detectable. This provides a direct evidence of an intermolecular hydrogen bonding between quinine and 6. Interestingly, solutions in $CDCl_3$ of quinine/(R)-6 (1:1) and quinine/(S)-6 (1:1) mixtures, having the same concentration (10% w/v) and at the same temperature, show very different -OH signals: in the first pair the -OH resonance (5.70 ppm) is relatively sharp ($W_{1/2}$ = 40 Hz) with respect to the same resonance (5.45 ppm) in the second pair ($W_{1/2}$ = 60 Hz). The downfield shift of this signal in the first pair with respect to the second is a clear indication that in the former there is a stronger hydrogen bond than in the latter.

Further interesting information on the structure of the diastereoisomeric adducts between quinine and 6, can be obtained by means of nuclear Overhauser exper-

iments. The most important results can be summarized as follows. In the diastereoisomer quinine/(S)-6 the irradiation of the methyl protons of the isopropyl group which show the resonance at 0.8 ppm, produces in quinine a clear enhancement of the resonance due to the methoxy group (4%) together with a weaker effect on the methine proton at C(9) (2%). Also saturation of the CH proton of the isopropyl group of 6 enhances the $-OCH_3$ (4%). In addition, the saturation of the H(9) proton (5.38 ppm) gives rise to a weak but observable NOE effect at the H(3') binaphthol proton (7.20 ppm, 3%), adjacent to the -OH group. In the quinine/(S)-6 pair NOE effects cannot be observed at the aromatic protons of 6 by saturating the aromatic protons of quinine or vice-versa. In the diastereisomer quinine/(R)-6, the saturation of alkyl and aromatic protons of 6 causes no Overhauser effects at any proton of quinine. As well, the irradiation of the methoxy or aromatic protons of quinine produces no enhancements of any resonance of the binaphthol derivative.

Also the behaviour by saturating the -OH resonance is very different in the two pairs. In fact saturation of this resonance in the quinine/(R)-6 diastereoisomer produces clear enhancements of the resonances of the protons H(3') (7.20 ppm, 5%) and H(4') (7.70 ppm, 3%) of the binaphthol 6 and of the aromatic protons H(2) (8.35 ppm, 3%) and H(3) (7.32 ppm, 3%) of quinine. By contrast, irradiation of the -OH proton in the quinine/(S)-6 pair does not produce clear inter- or intra-molecular NOEs, either for partial overlap of this resonance with the resonance of H(10) vinyl proton (5.50 ppm) or for the considerable broadening of the -OH signal.

The intramolecular NOEs observed in both the diastereoisomers are in agreement with the conformation proposed in solution for quinine[18] and the cisoid conformation for the binaphthyl derivatives[19].

The results of the NMR investigations allow to provide an experimental and sound foundation for the structure of the diastereoisomeric pairs quinine/(S)-6 and quinine/(R)-6. As far as the first pair is concerned, the above described in-

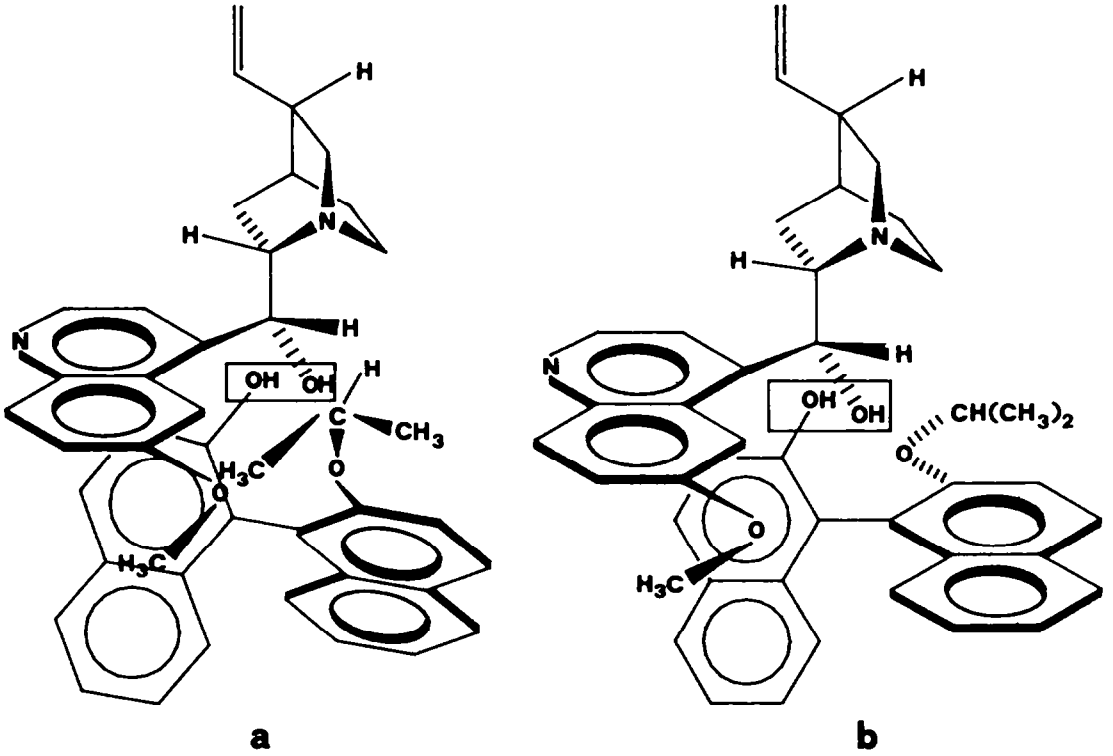


Fig. 4. A trial model of the diastereoisomeric adducts quinine/(S)-6 (a) and quinine/(R)-6 (b).

termolecular NOE effects strongly indicate that the methyl group (0.80 ppm) of the isopropyl substituent of 6 is in proximity of both the methoxy group and the methine proton at C(9) of quinine and this last proton is also close to H(3') of 6. In summary, all these facts can be accommodated by means of a structure, for the present diastereoisomer, as that reported in Fig. 4a. As far as the other pair is concerned, the clear NOE effect observed when the -OH resonance is saturated, points out that the aromatic protons H(3') and H(4') of 6 and H(2') and H(3') of quinine are close each other. This is in agreement with the existence of an intermolecular hydrogen bond between the two moieties. Taking into account the above discussed results, a reasonable picture of the structure of the quinine/(R)-6 pair is reported in Fig. 4b. The structure assigned to the above diastereoisomeric pair shows that they should have quite different energy contents: in the quinine/(R)-6 couple a definite hydrogen bond can be formed without giving rise to strong repulsive steric interactions which, on the contrary, can be present in the other adduct (i.e. closeness of the methoxy and isopropyl groups of quinine and 6, respectively). Therefore in our case indications of proximity (NOE) and hindered motion (T_1) should correspond to an unfavourable interaction for the quinine/(S)-6 pair leading to a shorter retention time for the (S)-6 antipode.

Mechanistic considerations. The formation of a pair of diastereoisomeric adducts between quinine and the enantiomeric forms of 6 is assumed as a model to interpret the results obtained and their structure is the key to understand the chiral recognition mechanism. First of all, it has been found that the S enantiomer of the compounds studied is eluted first on the c.s.p. I. This is perfectly in keeping with the reduced stability of the quinine/(S)-6 adduct with respect to the quinine/(R)-6 one. The C(9) hydroxyl group is the responsible of the existence of the diastereoisomeric pair. Its absence, as in the acetylated derivative of I, results into a very poor resolution. The inversion of the elution order on passing from phase I (quinine) to the quasi-enantiomeric phase II (quinidine) is still a consequence of the importance of the C(9) hydroxyl function. The increase of resolution with the increase of the bulkyness of the R substituent in compounds 2-6 can also be explained with the above model: a larger R group determines a larger difference in the extent of steric interaction between substrate and c.s.p.. This increases the difference in stability between the two diastereoisomeric adducts and hence increases the resolution. At the same time the importance of the $-OCH_3$ residue for resolution emerges. This group in fact determines the steric interaction which is responsible of the chiral discrimination as discussed above: as a matter of fact, c.s.p. III (cinchonidine), devoided of this group, provides only poor resolutions. In summary, the picture of the structure of the two diastereoisomeric adducts presented in Fig. 4 (a and b) fits very well the results obtained in the present investigation.

In proposing the main mechanism active in the separation of the enantiomers by the above described c.s.p. one must consider the following fundamental aspects:

i. Formation of diastereoisomeric complexes between the substrate and c.s.p. through a single attractive interaction represented by the hydrogen bond involving the C(9) hydroxyl group.

ii. Steric interactions large enough to generate a significant difference in stability of the two diastereoisomeric pairs: such a difference being a function of the absolute configuration of the chiral residue in the c.s.p. and of the substrate.

In other words, at least for the substances investigated in the present work, the chiral discrimination originates from different steric fits into adducts formed by a single attractive interaction. This kind of chiral recognition rationale is then slightly different from the "three point" interaction model initially

proposed[20] by Dalglish and involving three attractive interactions between substrate and c.s.p.. A new class of chiral recognition mechanisms based on two or even a single interaction between the solute and the phase has recently emerged[21].

FINAL REMARKS

The most significant results of this work certainly concern the preparation of a new class of chiral stationary phases and a detailed study of the chiral recognition process. Such a knowledge is very important from both an immediate and fundamental point of view: the way of interaction, in fact, may help to a significant extent to decide how to modify the present phases to obtain better resolutions and a wider application. Furthermore an improvement of the present knowledge in the field of the chiral recognition may be useful to get information on the interactions between substrate and receptor in some fundamental biological process. In conclusion, the present study indicates that the Cinchona alkaloids can find new and interesting applications as chiral auxiliaries: these alkaloids can provide in fact a new family of efficient and cheap chiral stationary phases for the chromatographic resolutions of racemates. In addition, the n.m.r. investigation carried out in the present work suggests their use as chiral derivatizing agents for the determination of enantiomeric compositions of organic molecules: as a matter of fact, in the ^{1}H NMR spectrum of 6, well separated signals corresponding to the two enantiomers can be obtained, in the presence of quinine, allowing an accurate measurements of the relative concentrations of the antipodes of the above compound (e.e. about 20%), in good agreement with the known optical purity of the sample used.

EXPERIMENTAL

Chromatographic separations.

The chromatographic separations were carried out by means of a JASCO Twinkle apparatus connected to JASCO Uvidec-100V UV detector. The c.d. detection was provided by a JASCO J500C spectrometer equipped with a micro HPLC cell.

Preparation of the chiral stationary phases.

The chiral stationary phases have been prepared following a procedure already described[7-9]. The alkaloid content, evaluated as previously reported[8], was about 10% by weight.

Preparation of the racemic binaphthyl derivatives 1-10.

Binaphthol 1 was a commercial sample from Fluka (Buchs,CH) and used without further purification. Compounds 2-7 were prepared by alkylation of 1 with the suitable alkyl halide following a known procedure[15] or by acetylation with acetyl chloride (8). Compounds 9-10 have been obtained by a copper-benzylamine catalyzed coupling of the corresponding 2-hydroxy-7-alkyloxy-naphthalene, following Brussee and Jansen[22]. All the compounds gave satisfactory elemental analysis and the n.m.r. spectra of the products were consistent with the expected structures. The antipodes of 6 were obtained by alkylation of enantiomerically pure 2,2'-dihydroxyl,1'-binaphthyl, which was resolved following Jacques[23]. The enantiomeric composition of (R)-6 and (S)-6 so obtained, was cheked by HPLC on a Pirkle ionic (R)-N(3,5-dinitrobenzoyl)phenylglycine column.

N.M.R. Measurements.

The n.m.r. measurements were performed on a Varian VXR-300 spectrometer at temperature of 22°C in $CDCl_3$ as solvent. The temperature was controlled (accuracy ± 1°C) by the Varian temperature control unit. The proton spin-lattice relaxation times (T_1) were measured with the inversion recovery ($180°-\tau-90°-T$)$_n$ pulse sequence. The 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 the equilibrium. Each NOE experiment was repeated at least four times and results reproducible to ± 1% have been obtained.

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