Spectroscopic and Molecular Mechanics Calculations of Discrimination between Enantiomers Possessing an Electron Rich Aromatic Group Directly Attached to the Chiral Carbon Atom with Optically Pure Benzoyl Derivatives

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The discrimination between enantiomers that have a chiral centre directly attached to the electron rich aromatic ring by interactions with optically pure electron deficient aromatic compounds was studied by ^{1}H NMR and molecular mechanics calculations. The enantiomeric spectroscopic discrimination is due to formation of non-bonding interactions which lead to the formation of diastereoisomeric complexes. The calculated HOMO energy values for electron rich racemic compounds and LUMO values for electron poor resolving agents are in good agreement with the observed chemical shift differences between enantiomers by ^{1}H NMR. Exceptions to these observations are seen for compounds which possess groups that are in a position to sterically push apart the complexation components and thus decrease the binding energy and diminish the enantiomeric discrimination. The discrimination strongly depends on concentration of the components in the solution, their ratio, temperature and the polarity of the media. Polar racemic compounds show the smallest enantiomeric discrimination by increasing the polarity of the media. For good enantiomeric discrimination both chiral centres must be rigidly bound to the aromatic rings. If the chiral centre is separated from the aromatic ring by flexible bonds the enantiomeric recognition fails despite the formation of strong non-bonding interactions. The binding energies calculated by AMBER and MM+ force fields are relatively weak (~ 2 kcal mol^{-1}) * suggesting that only a small portion of the molecules in solution are incorporated into the complexes. Our attempt to provide evidence for selective binding of only one enantiomer to the template molecule was unsuccessful. Nevertheless our results support the formation of inter-exchangeable diastereoisomeric complexes. Although it might be argued that two sets of signals should also be obtained for the template molecule, all our ^{1}H NMR spectra show only one set of signals for the optically pure template and two sets of signals for the racemic component in their chloroform solutions. Despite low binding energies enantiomeric discrimination with strong electron accepting resolving agents can be achieved in as low as 0.01 mol dm^{-3} chloroform solution.

The non-bonding interactions between electron rich and electron poor aromatic compounds is a well established phenomenon in organic chemistry.[1,2] The important studies on simple aromatic compounds were performed in micellar media[3] and in cell membrane proteins.[4]

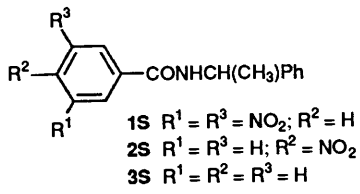
Enantiomeric discrimination in a chiral organic solvent is also a well known phenomenon in organic chemistry.[5] Pirkle first observed different ^{19}F NMR signals for the two enantiomers of 2,2,2-trifluoro-1-phenylethanol in (*R*)-1-phenylethylamine.[6] With (*R*)-2-naphthylethylamine, the size of the shift non-equivalence was greater. These amines have also been used in the analysis of chiral carboxylic acids as diastereoisomeric salts.[7] Few other chiral amines have been examined as solute–solute resolving agents in this manner, although quinine has been reported as a solute–solute resolving agent in the analysis of certain aryl alcohols and some binaphthyl derivatives.[8] In the analysis of 2-arylpropanoic acids (such as the drugs 'ibuprofen', and 'ketoprofen') 1,2-diphenyldiaminoethane has been used.[9] In our laboratory the enantiomeric discrimination between racemic amides and optically active amide templates has been studied in chloroform solution by ^{1}H and ^{19}F NMR spectroscopy[10–12] and in micelles.[13]

Results and Discussion

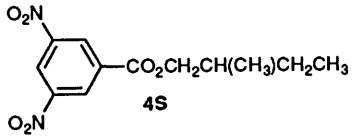
Here we address the chiral discrimination through non-bonding interactions between π-electron rich and π-electron poor aromatic compounds. Two classes of compounds are represented: one class is optically pure electron poor aromatic compounds (**1–5**), referred to in this study as template molecules or resolving agents; and the other class is electron rich aromatic compounds **6–19**. The resolving agents are amides **1–3** and esters **4** and **5**. The amides differ by their electron density on the aromatic ring while the esters differ by the size of their aliphatic parts. The electron rich aromatic racemic compounds are esters and alcohols with different electron densities on the aromatic ring. The majority of them are derived from 1-phenylethanol. According to GC all of the compounds studied here were of analytical purity.

The ^{1}H NMR spectra of all racemic electron rich compounds **6–19** show only one set of signals regardless of the polarity of the solvent (chloroform, methanol and dimethylsulfoxide), their concentration and temperature. A representative example of ^{1}H NMR spectroscopic discrimination in chloroform solution of the racemic electron rich compounds **6–19** with electron poor aromatic compounds **1–3** is presented in Fig. 2 for racemic **16** with template **1S**. Racemic **16** shows only one set of signals (a singlet for the aromatic protons, two singlets for the three methoxy groups, one singlet for the acetyl group, one quartet for the aliphatic methyl, and one quartet for their chiral hydrogen). In the presence of template **1S** all signals in the spectrum of racemic ester **16** are doubled in ratio according to the enantiomeric composition [Fig. 1(*a*)]. The differences in chemical shifts between enantiomers strongly depends on the global concentration of the compounds in the solution, their

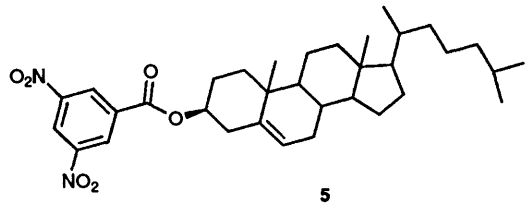
* 1 cal = 4.18 J.



1S $R^1 = R^3 = NO_2$; $R^2 = H$
2S $R^1 = R^3 = H$; $R^2 = NO_2$
3S $R^1 = R^2 = R^3 = H$



4S



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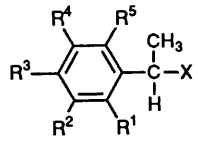
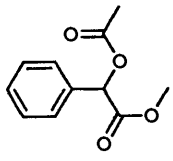


6 $R^1 = R^2 = R^3 = R^4 = R^5 = H$; X = OH
7 $R^1 = R^2 = R^3 = R^4 = R^5 = H$; $X = O_2CCH_3$
8 $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = CH_3$; X = OH
9 $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = CH_3$; $X = O_2CCH_3$
10 $R^1 = R^2 = R^5 = H$; $R^3 = R^4 = OCH_3$; X = OH
11 $R^1 = R^2 = R^5 = H$; $R^3 = R^4 = OCH_3$; $X = O_2CCH_3$
12 $R^1 = R^2 = R^5 = H$; $R^3 = R^4 = OCH_3$; $X = O_2CC(CH_3)_3$
13 $R^1 = R^3 = R^5 = CH_3$; $R^2 = R^4 = H$; X = OH
14 $R^1 = R^3 = R^5 = CH_3$; $R^2 = R^4 = H$; $X = O_2CCH_3$
15 $R^2 = R^3 = R^4 = OCH_3$; $R^1 = R^5 = H$; X = OH
16 $R^2 = R^3 = R^4 = OCH_3$; $R^1 = R^5 = H$; $X = O_2CCH_3$



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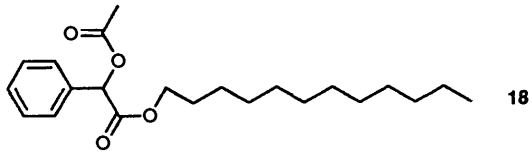

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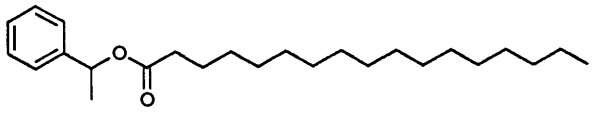

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ratio, polarity of the solvent, and temperature. The enantiomers' signals are very well separated with a tenfold excess of the template molecule **1S** in chloroform (for instance, the ^1H NMR spectrum of a chloroform solution of 0.1 mol dm^{-3} **1S** and 0.01 mol dm^{-3} racemic **16** shows separation of the aromatic signals by 25.3 Hz). Separation still exists in solution with a ten-fold excess of the racemic electron rich compound (the ^1H NMR spectra of 0.01 mol dm^{-3} **1S** and 0.1 mol dm^{-3} **16** shows 3.4 Hz aromatic signals' separation). The effect is much more pronounced in chloroform than in methanol and is completely absent in a polar solvent such as dimethylsulfoxide. Low temperature provides better separation of the signals. It was not possible to observe two sets of signals of the template molecule **1S** at 50 times higher concentration of **7** (chloroform solution of 0.01 mol dm^{-3} **1S** and 0.5 mol dm^{-3} **7**) but at the same time, enantiomeric discrimination of racemic **7**—even with a small molar ratio of the template—was observed (Fig. 2).

In all cases studied, the alcohols in the same concentration range as the corresponding esters have smaller differences between the enantiomeric signals. Perhaps alcohols increase the media polarity much more than the corresponding esters and in this way cause the decrease in signal separation. The nature of non-bonding interactions between the electron rich enantiomers and the optically pure template molecules is not clear. Hydrogen bonding[15] could be present, but is not crucial, otherwise better separation would be obtained for alcohols than for esters. Charge transfer complexes between two aromatic rings is present between template molecule **1S** and racemic compounds **6–19** as shown by UV spectroscopy. The formation of a new absorption band of relatively low intensity was observed around 400 nm. The formation of the complex can even be detected visually. For example, racemic **19** is an oil at room temperature whereas the template molecule **1S** is crystalline. Mixing them together without solvent results in the formation of an orange colour upon contact of the crystals with the oil. Every attempt to find two new UV absorption bands in chloroform solution of racemic **6–19** and **1S** for the two diastereoisomeric complexes was unsuccessful.

To get a better picture of the nature of the non-bonding interactions between racemic electron rich compounds **6–19** their IR spectra were recorded. The first reason why IR spectroscopy was chosen is that the spectra can be taken without solvent and in that way the formation of the complexes is enhanced (this is based on our observation of the ^1H NMR assay). The second reason is that the IR time-scale is significantly different to that of NMR and thus might give different species. It is also known that enantiomers without intramolecular interactions possess identical IR spectra in all possible mixed ratios.[14] All our electron rich compounds **6–19** are oils and their IR spectra do not differ by varying the enantiomeric composition. The equivalent mixtures of the racemic compounds and template **1S** were prepared in chloroform and the solution was placed on the NaCl plate where the solvent was left to evaporate at room temperature. The IR spectra of the equimolar mixtures show many new signals which are very similar to the signals of the uncomplexed components. For example, a very strong CO vibration of the ester group of racemic **16** in the equimolar mixture with **1S** shows two new poorly resolved signals as a shoulder to the CO vibration of pure **16** [Fig. 3(*a*)]. In the mixture with only **16R** one shoulder exists. Computer subtraction of IR spectra of components **16R** and **1S** from the IR spectra of their mixture results in a new spectrum [Fig. 3(*b*)(ii)] which clearly does not have any resemblance to the components' spectrum. These

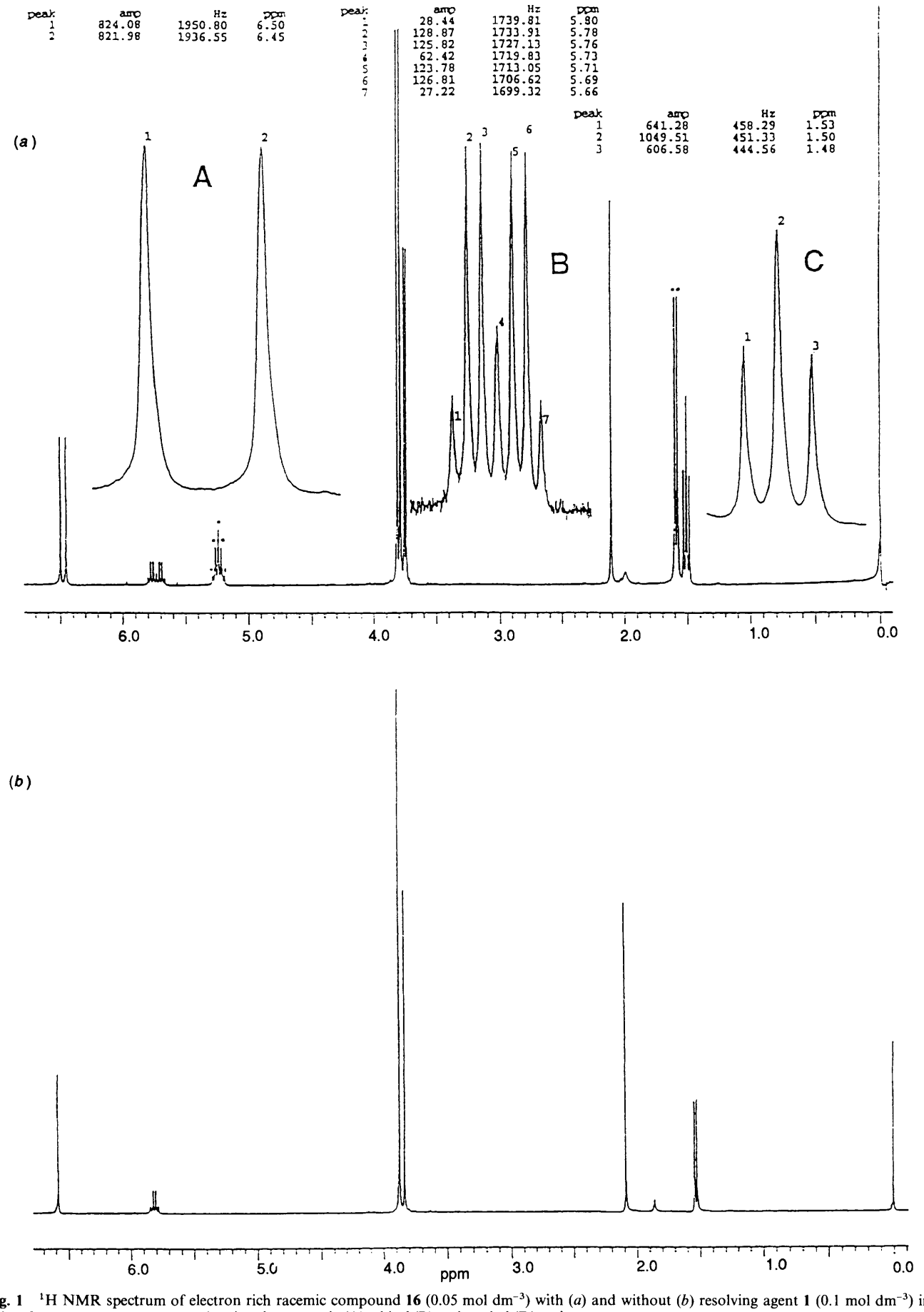

Fig. 1 ^{1}H NMR spectrum of electron rich racemic compound **16** (0.05 mol dm^{-3}) with (*a*) and without (*b*) resolving agent **1** (0.1 mol dm^{-3}) in chloroform at room temperature showing the aromatic (A), chiral (B) and methyl (D) regions

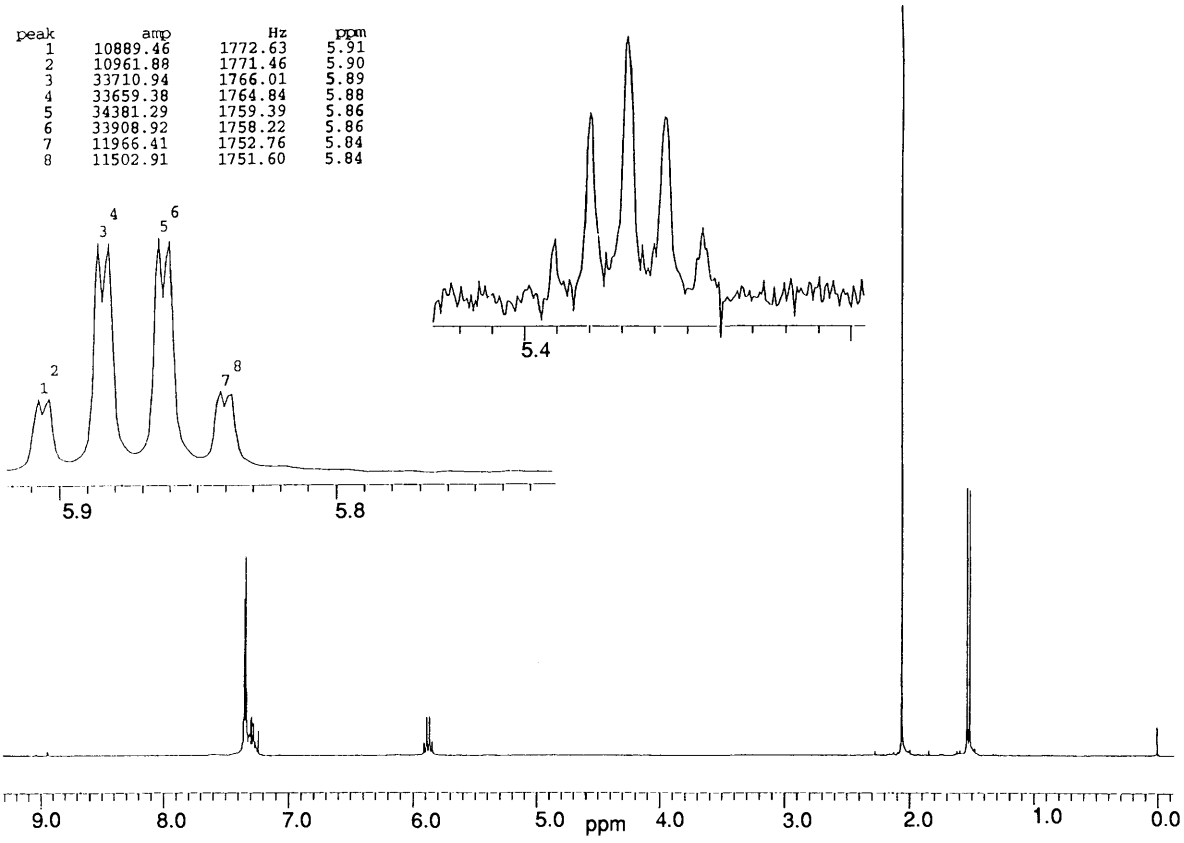

Fig. 2 ^{1}H NMR spectrum of chiral hydrogen region for **7** (0.5 mol dm^{-3}) and **1S** (0.01 mol dm^{-3}) in chloroform at room temperature

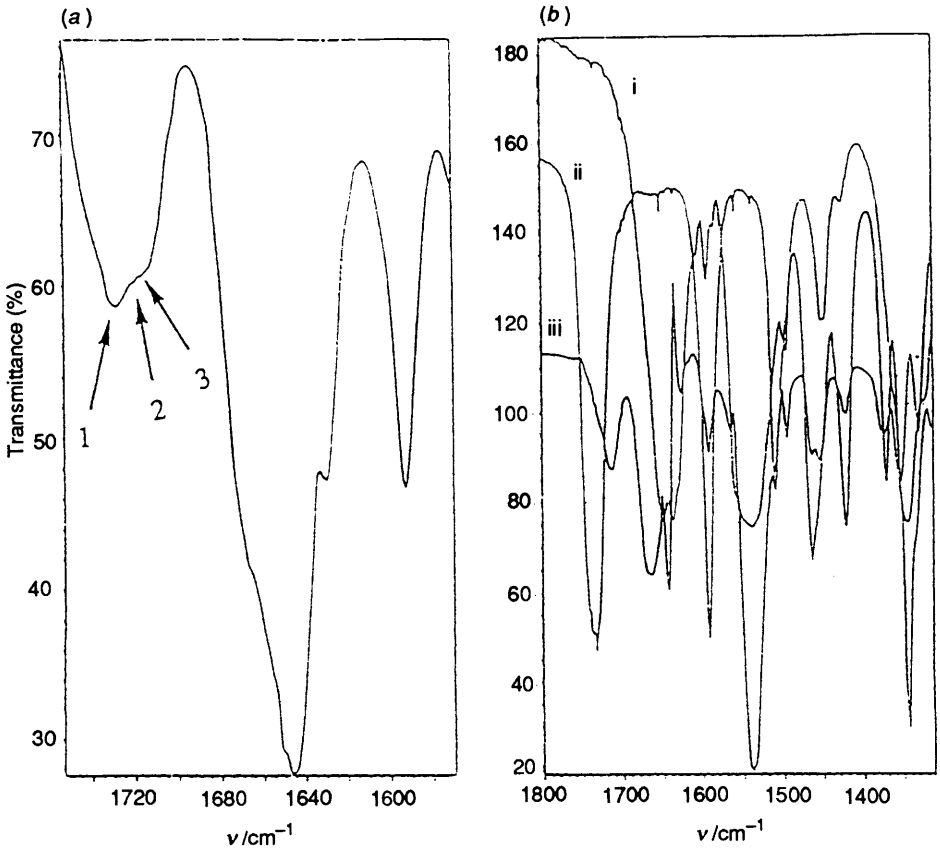

Fig. 3 IR spectra of the neat mixture of **1S** and racemic **16**(*a*), pure **16R**(*b*)(i), pure template **1S**(*b*)(iii) and spectrum left after subtraction of **16R** and **1S** from their equimolar mixture (*b*)(iii)

observations support the formation of diastereoisomeric non-bonding interactions between the electron rich and the electron poor compound.

With the assumption that non-bonding interactions are occurring through π–π stacking between the electron rich aromatic ring of the racemic compounds (**6–16**) and electron

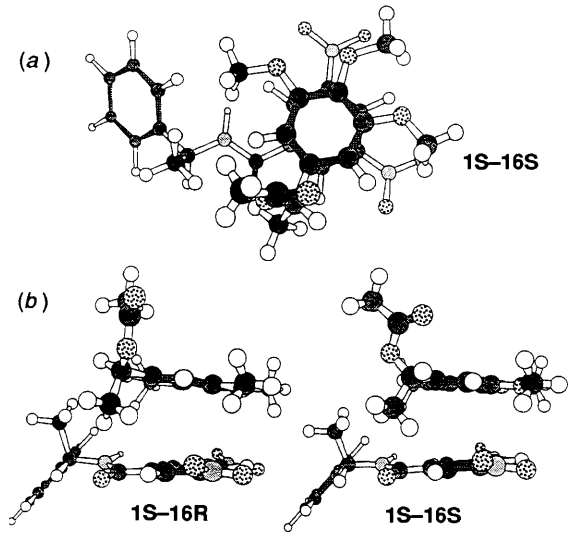

Fig. 4 Computer generated complexes through π–π stacking of racemic **16** and template **1S**

Table 1 HOMO and LUMO values calculated for racemic electron rich aromatic compounds by HyperChem and the ^{1}H NMR data obtained by enantiomeric differentiation of their chloroform solution with **1S**

Comp.	HOMO/eV	LUMO/eV	$\Delta\delta^a$/Hz
6	−9.552 999	0.323 450	0.9
7	−9.547 894	0.407 828	5.8 (5.7[b])
8	−9.376 440	0.317 283	1.0
9	−9.291 315	0.392 092	6.5
10	−9.030 024	0.193 514	0.4
11	−8.546 678	0.381 844	7.9
12	−8.544 975	0.393 979	7.4
13	−9.052 247	0.490 916	1.2
14	−9.191 100	0.345 333	4.9
15	−8.560 186	0.293 095	0.4
16	−8.466 936	0.358 279	7.0
17	−9.802 382	0.038 669	1.4[b]
18	−10.009 503	−0.166 129	0.9[b]
19	−9.662 046 1	0.310 044	5.1[b]

[a] Difference in chemical shift of methyl protons' two doublets. [b] Chemical shift differences for hydrogen bound on the chiral centre.

poor aromatic ring of the template molecule **1S**, molecular modelling calculations were performed in order to obtain the energy differences between the two diastereoisomeric complexes. The results obtained by calculation of the complexes of **16** and **1S** are presented here.

The isolated structure of compounds **1S**, **16R** and **16S** were built with a HyperChem computational program, and the molecular geometries were optimized by MM+ force field. These optimized structures were the base used for semi-empirical AM1 calculations of atomic charges. Optimized structures of **1S** and **16S** or **16R** are overlaid in such a way that the positive charge on the aromatic ring of **1S** overlaps with the negative charge of **16**. The component molecules of the complexes obtained were separated by distances of ~2 Å so the position of the aromatic rings were kept parallel. The complexes were optimized by AMBER force field and later with MM+ force field. The energy difference of about 2.3 kcal mol^{-1} is relatively small but sufficient for spectroscopic discrimination between the two enantiomers. The top view of the computer simulated structures of **1S–16S**, and side views for **1S–16R** and **1S–16S** are presented in Fig. 4. The electrostatic attraction holds the two aromatic rings together which are not absolutely parallel, because the steric repulsions between substituents 1 and 1′ are pushed away from the complex. The inclination angle between the two rings is 16° for **1S–16R**, and 10° for **1S–16S**.

If these structures are important for enantiomeric discrimination, certainly more stable complexes should be formed with the compounds that are electron rich. As a criterion for formation of the complexes we calculated the LUMO energies with AM1 semi-empirical force field. The values calculated together with the observed differences in the chemical shifts for methyl protons of the racemic electron donor molecules **6–19** (0.05 mol dm^{-3}) in their chloroform mixture with 0.1 mol dm^{-3} **1S** are presented in Table 1.

Comparison of the HOMO energies with differences in chemical shifts in the ^{1}H NMR spectra show that the same class of compounds have the same interesting features. Obviously the HOMO energies suggest the possibility that electron rich molecules form stronger non-bonding interactions with electron poor template molecules such as **1S**. In the series of esters **7**, **9** and **11** a clear pattern of increasing enantiomeric discrimination with increasing energy of HOMO was observed. The other series, **12**, **14** and **16**, deviates from this pattern. It is important to note that the energies of the complex formation are only 2–7 kcal mol^{-1} and small changes in the structure of the complex components will drastically change the energy of formation. Esters **11** and **12** differ only in the acid parts (acetyl group of **11** is substituted with pivaloyl in **12**). This change in structure does not cause significant differences in their HOMO and LUMO energies (Table 1). If anything, the enantiomeric discrimination should be slightly better with ester **12**. But because of the sterically more demanding **12**, the corresponding **1S–12** complex is less stable than the **1S–11** complex, which results in a discrepancy in their chemical shifts. A similar explanation can be offered for the lower enantiomeric discrimination in the complex with ester **14**. The ester group is locked between two methyl groups attached at the 2,6-aromatic position. This makes both methyl and ester groups on the chiral centre of the ester **14** obstruct complex formation with template **1S**. If the ester groups are replaced by a less space-demanding alcohol group, the corresponding alcohol (**13**) shows better enantiomeric discrimination than alcohols **6** and **8** and is now in agreement with their calculated HOMO energies. Ester **12** has one *tert*-butyl group which prevents the enantiomers from forming as strong a complex as would be predicted on the basis of the HOMO energy. The largest enantiomeric differentiation is observed with ester molecules, particularly racemic ester **11** in the chloroform solution with template molecule **1S**. Although our calculation of the HOMO energy for ester **16** shows that it is the most electron rich compound in the series studied here, the corresponding enantiomeric discrimination is less than that observed for esters **11** and **12**. The steric difference cannot be effectively employed in this case. Our MM+ calculation in the gas phase shows that the binding energy of **1S–16S** is higher than for both complexes of **1S** with **11** and **12**. The only reasonable explanation is that there are two consecutive effects with the introduction of one methoxy group in the 5-position of ester **11**. The first is that the energy of the HOMO is increased and in this way the formation of the complex is enhanced. The second is the change in polarity of the media which results in a decrease in the ^{1}H NMR enantiomeric discrimination. The second effect seems to predominate.

As we have shown earlier the maximal spectroscopic discrimination was obtained in non-polar media—that was the reason to study esters containing long aliphatic chains, because they are of lower polarity. Although the polarity of the mixture is lower in comparison to similar shorter hydrocarbon length esters, the enantiomeric discrimination is diminished due to a decrease in the HOMO energy (Table 1 compounds **17–18** and **7–19**). It is also possible that the slow exchange between free

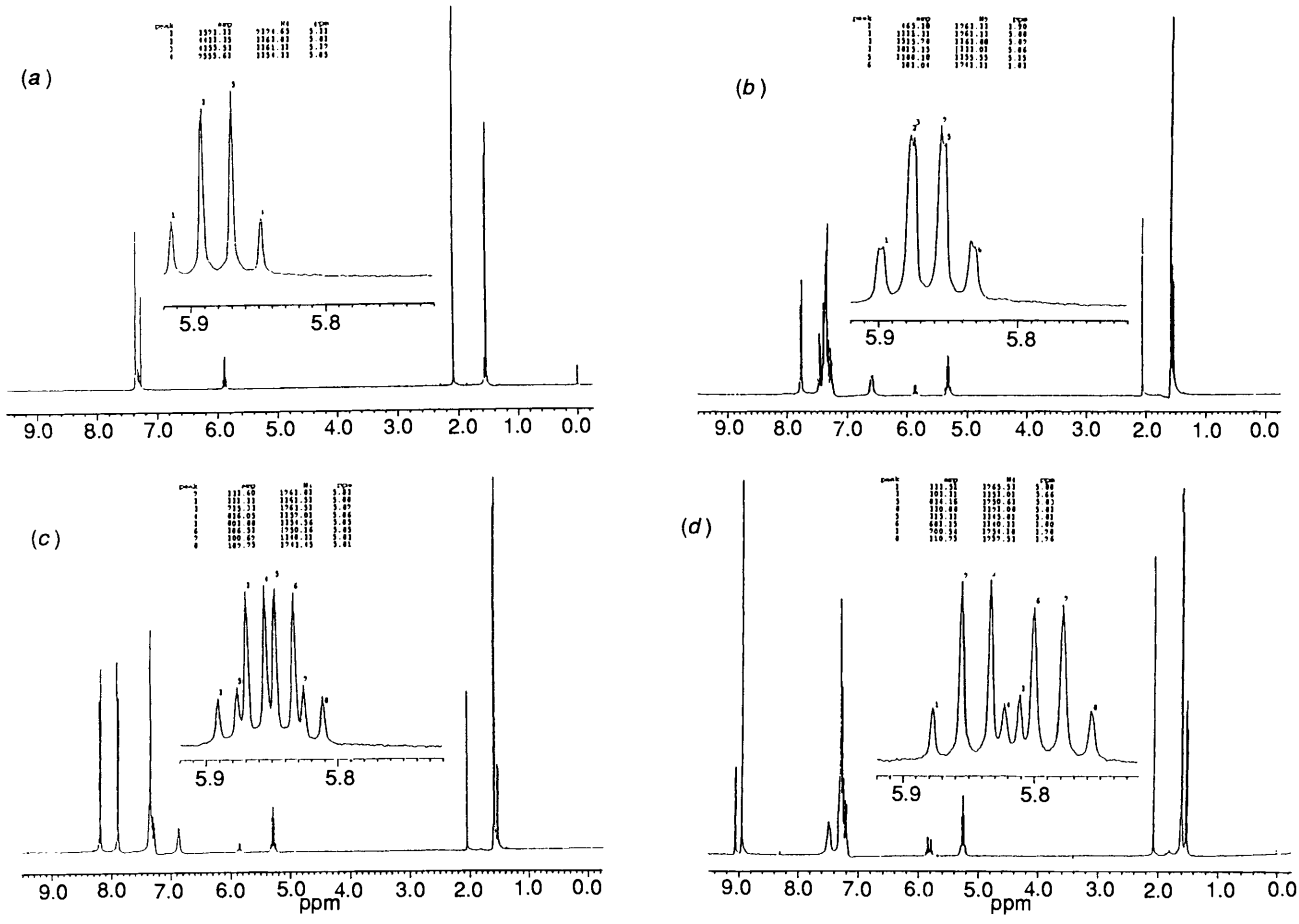

Fig. 5 ^{1}H NMR spectra of racemic **7** (*a*) with **3S** (*b*), **2S** (*c*) and **1S** (*d*) as resolving agents

Table 2 HOMO and LUMO values calculated for the optically pure electron poor template and their influence on enantiomeric discrimination in ^{1}H NMR spectra of their chloroform solution (0.1 mol dm^{-3}) of racemic **7** (0.05 mol dm^{-3})

Template	HOMO/eV	LUMO/eV	$\Delta\delta^a$/Hz
1S	−9.985 664	−2.818 228	16.3
2S	−9.822 14	−1.665 442	4.2
3S	−9.598 799	−0.327 372	1.0
4S	−11.548 005	−2.261 874	0
5	−7.688 411	−3.607 357	0

[a] Difference of chemical shift for hydrogen attached to the chiral centre of **7**.

ester and ester in the complex can broaden the signals and decrease the discrimination. This conclusion should be taken with caution because only two examples have been studied.

One of our targets in this study was to determine the enantiomeric recognition between enantiomeric electron rich molecules and an optically pure template molecule **1S**. The observed ^{1}H NMR discrimination can be explained in two ways. One explanation is that the optically pure acceptor molecule **1S** forms a selective complex with one of the enantiomers (enantiomer recognition) while the other remains uncomplexed in the solution, equilibrium (1). Alternatively, the

$$\mathbf{1S}\cdots\mathbf{11R} \rightleftharpoons \mathbf{1S} + \mathbf{11R} \quad \text{or} \quad \mathbf{1S}\cdots\mathbf{11S} \rightleftharpoons \mathbf{1S} + \mathbf{11S} \quad (1)$$

resolving agent can unselectively form complexes with both enantiomers, equilibrium (2). In both cases the ^{1}H NMR

$$\mathbf{1S}\cdots\mathbf{11R} \underset{-\mathbf{11R}}{\overset{\mathbf{11R}}{\rightleftharpoons}} \mathbf{1S} \underset{-\mathbf{11S}}{\overset{\mathbf{11S}}{\rightleftharpoons}} \mathbf{1S}\cdots\mathbf{11S} \quad (2)$$

spectra should present the average state because of the time-scale and cannot be used to support either of the two explanations. The time-scale of IR is relatively short and shows that in the liquid state only a small portion of the complexation components are in the complex. Because the IR signals of complexed aromatic rich compounds are very close to the signals of the free aromatic compound, it is impossible to determine their ratio by IR spectroscopy. Certainly their position depends on symmetry and the binding energy of the complex. On the evidence of the IR and ^{1}H NMR spectra the only satisfactory conclusion is that there is no selective binding of one electron rich enantiomer over the other with template molecule **1S** and that all species of these complexes are exchangeable [equilibrium (2)].

Enantiomeric discrimination studies were also performed with other electron poor optically pure template molecules **2S**, **3S**, **4S** and **5S**. Considerably smaller enantiomeric discrimination of electron rich racemic compounds **6**–**19** with template **2S** and **3S** in comparison with template **1S** was observed. For example, in the ^{1}H NMR discrimination studies with **3S** 1.0 Hz, with **2S** 4.2 Hz and with **1S** 16.3 Hz, differences for hydrogen atom attached to the chiral centre of the racemic molecule **7** were observed (Fig. 5). These results are in very good agreement with the LUMO energies of the acceptor templates (Table 2). This finding certainly supports the contention that non-bonding interactions between aromatic electron donor racemic molecules **6**–**19** and aromatic electron acceptor template molecules **1S**, **2S** and **3S** should be of the π–π stacking nature. With a higher HOMO energy for a racemic electron rich molecule and a lower LUMO energy for an electron poor

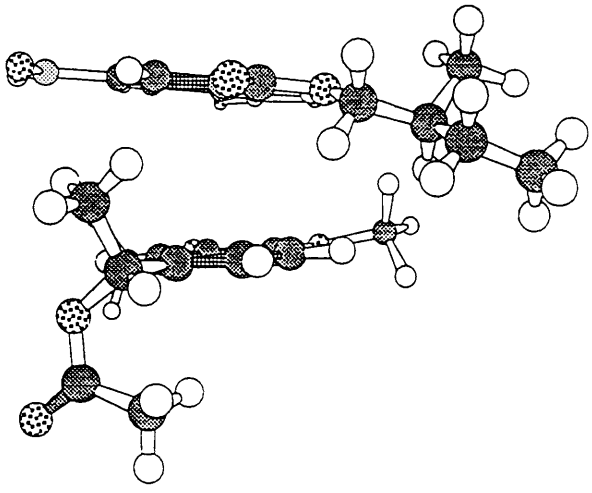

Fig. 6 Computer simulated π–π stacking between template **4S** and enantiomer **11R**

optical active template molecule better enantiomeric discrimination can be achieved.

Two electron poor aromatic compounds **4S** and **5** do not cause ^{1}H NMR enantiomeric discrimination with electron rich compounds **6–19**. Although by comparison with their LUMO energies they should show similar enantiomeric discrimination as **1S** if not much better for the steroid template **5**. For example, on the basis of the calculated LUMO energy (−3.607 eV) for template **5**, which is quite a bit lower than the LUMO energy (−2.818 eV) for the best enantiomer discrimination agent **1S** presented here, one can expect that the steroid template will be the enantiomer discrimination agent of choice. Its chloroform solutions with electron rich aromatic enantiomers show the formation of a new absorption band indicating that the formation of the non-bonding complexes occurs, although there is no evidence of enantiomer discrimination in the ^{1}H NMR spectra with **6–19**.

A close examination of the non-bonding complexes of **1S** with enantiomers **6–19** shows that the differences in the diastereoisomeric complexes are mainly steric in nature. So the failure in the differentiation with **4S** and **5** should be caused by the flexibility of substituent in the 1-position of 3,5-dinitrobenzene of the template molecules **4S** and **5**. The different behaviour of amide analogues **1–3** from esters **4S** and **5** should be caused by differences of the rotational energies around O=C–N–H and O=C–O–C bonds respectively. If the rotational barrier around the O=C–O–C bond is relatively low, in the complexes between esters **4S** and **5** with enantiomers **6–19** the ester group will adopt the space orientation toward the substituent in the electron rich aromatic enantiomer in such a way that diastereomer complexes will have negligible energy differences. In other words the substituents with different size on the chiral centre of the electron rich compounds will cause orientation of the flexible ester group of the template molecule so that the same distances will be obtained with both diastereoisomeric complexes. That was supported by the computational study of the rotation barrier of the amide and the ester groups. For example the MM+ calculated energy barrier for the rotation around CO–N bond of amide **1S** is 22.8 kcal mol^{-1} while the rotational barrier of CO–O rotation of ester **5** is only 10.4 kcal mol^{-1}. This finding is not surprising because there are a large number of crystallographic data for small amides and peptides which show that the amide bond is firmly in the '*trans*' conformation. These are in complete agreement with our ^{1}H NMR enantiomeric discrimination results.

The computer simulated π–π stacking between optically pure electron poor template molecule **4S** and electron rich aromatic enantiomers **11R** is presented in Fig. 6. The calculated energy differences between the diastereoisomeric complexes are almost identical (0.3 kcal mol^{-1}) and are in the range of computational error. Not only can the flexible chain of the ester group adopt many conformations, but also the two chiral centres in the computer simulated complexes are relatively far away. Similar results are obtained with all the other complexes between template molecules **4S** and **5**.

Conclusions

Results presented here show that enantiomeric discrimination between electron rich aromatic racemic compounds with electron poor optically pure aromatic templates describe some interesting features regarding the nature of non-bonding interactions. Obviously, the enantiomeric discrimination is due to formation of non-bonding diastereoisomeric complexes. To obtain additional information about the nature of the racemic donor molecules, aromatic compounds derived from racemic 1-phenylethanol with two kinds of electron donating substituents, methyl and methoxy, were studied. Generally better enantiomeric discrimination was observed with racemic compounds that have higher electron donor ability (the electron donor abilities were judged on the basis of calculated HOMO energies). Better enantiomeric discrimination was achieved with stronger electron acceptors resolving aromatic compounds. All spectroscopic data obtained, as well as computer simulation, inevitably suggest that π–π stacking should be the major interaction between electron rich racemic compounds and electron poor resolving agents. The exceptions can be explained by steric hindrance of the substituents on the electron rich aromatic that push apart the complexation components. In that way the diastereoisomeric complexes are much weaker and the discrimination is considerably smaller than expected. To provide the enantiomeric discrimination, chiral centres in both resolving agents and racemic compounds must be 'rigidly' bound to the aromatic rings. If the chiral centre is separated from the aromatic rings by 'flexible' bonds, the diastereoisomeric complexes have small energy differences due to low rotational barriers that allow the chiral group to adopt positions with negligible interaction with the other chiral centre. The best examples are chiral amides and esters. Because of the low energy barrier in rotation around the O=C–O–C bond the ester template with similar acceptor ability as the amide does not produce the enantiomeric discrimination.

The experimental conditions strongly influence the ^{1}H NMR enantiomeric discrimination. Enantiomeric discrimination is increased with increasing concentration of the resolving agent. Less polar solvents are preferable for better spectroscopic separation of enantiomer signals, as is lower temperature.

Although the discrimination between enantiomers was observed in many cases, there is no preferable binding of optically pure resolving agents with one of the enantiomers. It seems that the diastereoisomeric complexes are in equilibrium in solution.

Experimental

Computer Methodology.—Calculations were performed with the HyperChem program[16] executed on IBM compatible 486 (66 MHz and 50 MHz) computers. A Macintosh IIfx computer was used to generate and view the structures included in this paper. Energy minimizations were carried out with the HyperChem default values. All molecular mechanical studies were first performed with the AMBER[17] force field and then with the MM+[18] force field until the root mean square of the gradient vectors was less than 0.001 kcal Å^{-1}. The molecules

studied were minimized separately and the atomic charge was calculated by the semi-empirical AM1[19] method. Atomic charges do not have a clear relation to experimental values. There are various ways to define atomic charges. HyperChem uses Mulliken atomic charges, which are commonly used in Molecular Orbital theory. These quantities have only an approximate relationship to experiment; their values are sensitive to the basis set and to the method of calculation. Here AM1 generated atomic charges were used to obtain, by AMBER force field, non-bonding intramolecular interactions. The complexes between template molecules **1–5** and enantiomers **6–19** were built in such a way that aromatic atoms with negative atomic charges of electronic rich aromatic compounds **6–19** and aromatic atoms with a positive atomic charge on the benzoate ring of templates **1–5** were overlaid. The aromatic rings were then separated to a distance of 2 Å holding the two rings parallel and eclipsed. The resulting structures were then minimized to gradients of less than 0.01 kcal $Å^{-1}$ using Polak–Ribiere conjugate gradients, the electrostatic interactions were scaled to 0.5. Of course in optimized complexes the two aromatic rings are not eclipsed and parallel anymore. The angle between the two plain vectors is 155–170°. This was caused by steric repulsion between the substituents on the two aromatic rings.

The limitations of the accuracy of our computational structures must be mentioned. The calculations were performed for systems in the gas phase, neglecting the fact that the complexes were formed in chloroform solutions. Ignoring solvents in the complex formation probably gives much higher differences in energies than is real. This is because complexion is driven by electrostatic forces that are much stronger in the gas phase than in any organic solvent. The rotation barriers of the esters and amide groups are obtained by single point calculation for different torsion angles and they tend to be a little higher than the experimental values. The treatment of nitro compounds is inaccurate because the energy is too positive and the atomic charges are too high.

General.—NMR spectra were recorded on a Varian Gemini 300 instrument with the deuterium signal of the solvents ($CDCl_3$) as the lock, and tetramethylsilane was used as the internal reference (*J*-values in Hz). IR spectra were recorded on Nicolet 550 FT-IR instrument with resolution of 2 cm^{-1}. UV studies were performed on a Perkin-Elmer Lambda 6 spectrometer. GCMS data were recorded on a Hewlett Packard 5890 gas chromatograph with a Hewlett Packard 5971 mass selective detector. All starting materials and reagents were purchased from Aldrich and were used without further purification. Template molecule (*S*)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine (**1S**) was obtained from Aldrich. The preparation and characterization of (*S*)-*N*-(4-nitrobenzoyl)-α-methylbenzylamine (**2S**) has been published elsewhere.[10] Although amide **3S** was synthesized previously, we describe here a simpler method of preparation.

(*S*)-α-*Benzamido*-α-*methyltoluene* (**3S**).—To a mixture of (*S*)-α-methylbenzylamine (1.21 g; 0.01 mol) and sodium hydroxide (0.4 g; 0.01 mol) in tetrahydrofuran–water mixture (10:1 v/v; 220 cm^3) benzoyl chloride (1.41 g; 0.01 mol) was added. The mixture was stirred at room temperature for 5 min and solvent was evaporated. The solid residue was partitioned between chloroform (300 cm^3) and water (100 cm^3). The chloroform layer was separated, washed with 10% sodium hydroxide (3 × 100 cm^3), 10% hydrochloric acid (3 × 100 cm^3), water (3 × 100 cm^3), and dried ($MgSO_4$). The solvent was evaporated and the solid residue was crystallized from chloroform–light petroleum (b.p. 30–50 °C); yield 90% (2.2 g); ν(KBr)/cm^{-1} 3332, 3061, 3030, 2969, 1630, 1520, 1490, 1318, 1277, 758, 701, 668 and 554; $\delta_H(CDCl_3)$ 7.74 (d, *J* 7.1, 1 H), 7.39–7.16 (m, 10 H), 5.24 (quint, *J* 7.1, 1 H) and 1.47 (d, *J* 7.1, 3 H); $\delta_C(CDCl_3)$ 167, 143, 134, 131, 128, 128, 127, 126, 49 and 22; *m*/*z* (%) 77 (95), 78 (14), 103 (7), 104 (38), 105 (100), 106 (10), 120 (10), 134 (3), 148 (2), 165 (3), 178 (3), 181 (3), 210 (7), 225 (M^+, 36) and 226 ($M + 1^+$, 6).

(*S*)-2-*Methylbutyl* 3,5-*Dinitrobenzoate* (**4S**).—A pyridine solution (200 cm^3) of (*S*)-2-methylbutanol (1.76 g; 0.01 mol) and 3,5-dinitrobenzoyl chloride (4.6 g; 0.02 mol) was stirred at room temperature overnight. The solvent was evaporated and solid residue was dissolved in chloroform (300 cm^3). The chloroform solution was washed with water (100 cm^3) and 10% sodium hydroxide (3 × 100 cm^3). The solvent was evaporated after drying over $MgSO_4$, and the residue crystallized from light petroleum; yield 85% (5.1 g); ν(KBr)/cm^{-1} 3108, 2870, 2879, 1720, 1633, 1542, 1540, 1451, 1340, 1297, 1176, 1167, 924, 776 and 731; $\delta_H(CDCl_3)$ 9.22 (d, *J* 2.2, 1 H), 9.16 (d, *J* 2.2, 2 H), 4.38 (dd, J_1 10.8, J_2 6, 1 H), 4.29 (dd, J_1 10.8, J_2 6, 1 H), 1.98 (oct, 6.7, 1 H), 1.59 (m, 1 H), 1.40 (m, 1 H), 1.09 (d, *J* 3.7, 3 H), 1.02 (t, *J* 7.4, 3 H); $\delta_C(CDCl_3)$ 162, 148, 134, 129, 122, 71, 34, 26, 16 and 11; *m*/*z* (%) 75 (100), 103 (35), 120 (4), 136 (2), 149 (42), 166 (4), 179 (10), 195 [3,5-$(NO_2)_2C_6H_3CO^+$, 68], 196 (25), 213 (4), 237 (2), 253 (3), 266 (2), 282 (M^+, 2) and 283 ($M + 1^+$, 3).

Cholesteryl 3,5-*Dinitrobenzoate* (**5**).—A pyridine solution (200 cm^3) of cholesterol (3.87 g; 0.01 mol) and 3,5-dinitrobenzoyl chloride (2.3 g; 0.01 mol) was stirred at room temperature for *ca.* 60 h. The solvent was evaporated and solid residue was partitioned between chloroform (400 cm^3) and water (100 cm^3). The chloroform layer was separated and washed with 10% sodium hydroxide (3 × 100 cm^3). The solvent was evaporated and the solid residue was crystallized from a small amount of chloroform; yield 2.65 g (47%); ν(KBr)/cm^{-1} 3108, 2936, 1727, 1556, 1462, 1340, 1331, 1286, 1173, 1074, 1027 and 996; $\delta_H(CDCl_3)$ 9.21 (t, *J* 2, 1 H), 9.15 (d, *J* 2, 2 H), 5.44 (m, 2 H), 4.98 (m, 1 H), 1.10 (s, 3 H), 0.93 (d, *J* 6.4, 3 H), 0.87 (d, *J* 6, 6 H), 0.70 (s, 3 H), 2.51–1.04 (remaining Hs); $\delta_C(CDCl_3)$ 162, 149, 139, 134, 129, 123, 122, 57, 56, 50, 42, 40, 39.5, 39.4, 38, 36.9, 36.8, 36.8, 36.6, 36.2, 35.7, 31.9, 31.8, 31.8, 31.8, 28.1, 28.0, 27.9, 27.7, 27.7, 24.2, 23.8, 23.7, 22, 19, 18 and 14; *m*/*z* (%), 91 (88), 105 (79), 133 (42), 144 (39), 145 (62), 146 (56), 173 (9), 191 (18), 193 (19), 207 (49), 213 (19), 255 (15), 281 (18), 353 (27) and 368 [(**4S**-3,5-dinitrobenzoic acid)$^+$, 100%].

Racemic Alcohols **8**, **10**, **13** and **15**.—Racemic 1-phenylethanol (**6**) and starting acetophenones for preparation of **8**, **10**, **13** and **15** were purchased from Aldrich. The corresponding acetophenones (0.02 mol) were dissolved in tetrahydrofuran (200 cm^3) and sodium borohydride (3.04 g; 0.08 mol) was added. The suspension was stirred at room temperature for three days. The excess of sodium borohydride was quenched with water, and solvent was evaporated. The residue was dissolved in chloroform, dried ($MgSO_4$) and evaporated leaving pure alcohol in 68–95% yield as oil.

Racemic Acetates **7**, **9**, **11**, **14** and **16**.—The corresponding alcohol (0.01 mol) was dissolved in pyridine (300 cm^3) and acetic anhydride (20 cm^3; 21.64 g; 0.21 mol) was added. The mixture was stirred at room temperature for *ca.* 60 h. The solvent was evaporated and the oily residue dissolved in chloroform (300 cm^3). The chloroform solution was extracted with 10% sodium hydroxide and evaporated after drying over $MgSO_4$. Esters **7**, **9**, **11** and **15** had satisfactory purity while the crude ester product **14** had a large amount of starting alcohol (~60%). The ester **14** was purified by flash chromatography on silica gel with ethyl acetate–light petroleum (1:4) as eluent. The yield for ester **14** was 27% and for the others 85–97%.

Racemic Dodecyl α-(Acetoxy)phenylacetate (**18**).—A pyridine (200 cm^3) solution of dodecanol (3.72 g; 0.02 mol) and *O*-acetylmandelic chloride (4.25 g; 0.02) was stirred at room temperature overnight. The solvent was evaporated and the residue was dissolved in ethyl acetate and filtered through a short column of silica gel. The filtrate was evaporated yielding pure oil product in 83% (6.3 g) yield; ν(neat)/cm^{-1} 3067, 3035, 2925, 2854, 1740, 1685, 1455, 1372, 1232, 1178, 1057, 754 and 696; $\delta_H(CDCl_3)$ 7.47 + 7.34 (m, 5 H), 11 (s, 1 H), 4.10 (t, *J* 6.8, 2 H), 2.16 (s, 3 H), 1.55 (m, 2 H), 1.23 (m, 18 H) and 0.80 (t, *J* 6.5, 3 H); $\delta_C(CDCl_3)$ 170, 169, 134, 129, 128, 127, 74, 65, 31, 29.5, 29.4, 29.3, 29.2, 29.0, 28.3, 25.5, 22.6, 20.5 and 14; *m*/*z* (%), 57 (18), 79 (13), 106 (11), 107 (100), 108 (13), 149 (48), 176 (22), 195 (2), 229 (2), 276 (2), 320 (6), 362 (M^+, 2).

Supplementary Material.—IR, MS, ^1H and ^{13}C NMR spectra for compounds **3S**, **4S**, **5** and **18** have been deposited.*

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* For details of the Supplementary Publications Scheme, see 'Instructions for Authors (1994)', *J. Chem. Soc., Perkin Trans. 2*, 1994, Issue 1 (Sup. Pub. No. 57004, 17 pp.).

References

1 R. Foster, *Organic Charge-Transfer Complexes*, Academic, New York, 1969; L. J. Andrews and R. M. Keefer, *Molecular Complexes in Organic Chemistry*, Holiden-Day, San Francisco, 1964.
2 J. K. Kochi, *Pure Appl. Chem.*, 1991, **63**, 255 and refs. therein.
3 F. M. Martens and J. W. Verhoeven, *J. Phys. Chem.*, 1981, **85**, 1773; M. D. Shin, K. S. Schanze, J. P. Otruba, P. E. Brown and G. D. Whitten, *Isr. J. Chem.*, 1987/88, **28**, 37.
4 For a recent review, see G. McLendon and R. Hake, *Chem. Rev.*, 1992, **92**, 481.
5 For NMR chiral resolving agents, see W. H. Pirkle and D. J. Hoover, in *Topics in Stereochemistry*, eds. N. L. Allinger, E. L. Eliel and S. H. Wilen, Wiley, New York, 1982, vol. 13, p. 263; E. Dunach and H. B. Kagan, *Tetrahedron Lett.*, 1985, **26**, 2649; W. H. Pirkle and A. Tsipouras, *Tetrahedron Lett.*, 1985, **26**, 2989; K. Rodgers, T. C. Pochapsky and S. G. Sligar, *Science*, 1988, **240**, 1657; W. H. Pirkle and T. C. Pochapsky, *Chem. Rev.*, 1989, **89**, 347.
6 W. H. Pirkle, *J. Am. Chem. Soc.*, 1966, **88**, 1837.
7 J. P. Guette, L. Lacombe and A. Horeau, *C. R. Acad. Sci., Ser. C*, 1968, **276**, 166; A. Horeau and J. P. Guette, *C. R. Acad. Sci., Ser. C*, 1968, **276**, 257; L. Mamiok, A. Marquet and L. Lacombe, *Tetrahedron Lett.*, 1971, **2**, 1093; C. A. Baxter and H. C. Richards, *Tetrahedron Lett.*, 1972, **3**, 3357; M. Mikolajczyk, A. Ejchart and J. Jurczak, *Bull. Acad. Pol. Sci.*, 1971, **19**, 721; A. Ejchart and J. Jurczak, *Bull. Acad. Pol. Sci.*, 1971, **19**, 725; A. Ejchart and J. Jurczak, *Bull. Acad. Pol. Sci.*, 1970, **18**, 455; M. Mikolajczyk, J. Ormelonczuk, M. Leitloff, J. Drabrawicz, A. Ejchart and J. Jurczak, *J. Am. Chem. Soc.*, 1978, **100**, 7003; R. A. Aitken and J. A. Gopal, *Tetrahedron Asymmetry*, 1990, **1**, 517.
8 C. Rosini, G. Uccello-Barretta, D. Pini, C. Abete and P. Salvadori, *J. Org. Chem.*, 1988, **53**, 4579.
9 The information for the unpublished results was taken from D. Parker, *Chem. Rev.*, 1991, **91**, 1441.
10 B. S. Jursic and S. I. Goldberg, *J. Org. Chem.*, 1992, **57**, 7172.
11 B. S. Jursic and S. I. Goldberg, *J. Org. Chem.*, 1992, **57**, 7370.
12 B. S. Jursic and Z. Zdravkovski, *J. Org. Chem.*, 1993, **58**, 5254.
13 B. S. Jursic, *Tetrahedron Lett.*, 1993, **34**, 963.
14 J. Jacques and A. Collet, *Enantiomers, Racemates, and Resolutions*, Wiley, New York, 1981, p. 17.
15 G. A. Jeffrey and W. Sanger, *Hydrogen Bonding in Biological Structures*, Springer-Verlag, New York, 1991.
16 HyperChem is a commercially available computation program from Autodesk, Inc., 2320 Marinship Way, Sausalito, California 94965, USA.
17 S. J. Weiner, P. A. Kollman, D. T. Nguyen and D. A. Case, *J. Comput. Chem.*, 1986, **7**, 230.
18 MM+ for HyperChem is derived from the public domain code developed by Professor Allinger, referred to as MM2 (1977), and distributed by the Quantum Chemistry Program Exchange (QCPE). Specifically, QCMP010 was used as a starting point for HyperChem MM+ code. HyperChem also includes the parameters generally referred to as the MM2(1991).
19 AM1 provided with HyperChem is based on the NDDO (Neglect of Diatomic Differential Overlap) approximation. The method is developed by the Dewar group at the University of Texas at Austin. The calculations were performed with PM3 parameter which is a variant of the AM1 method: J. J. P. Stewart, *J. Comput. Chem.*, 1989, **10**, 209; J. J. P. Stewart, *J. Comput. Chem.*, 1989, **10**, 221.

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