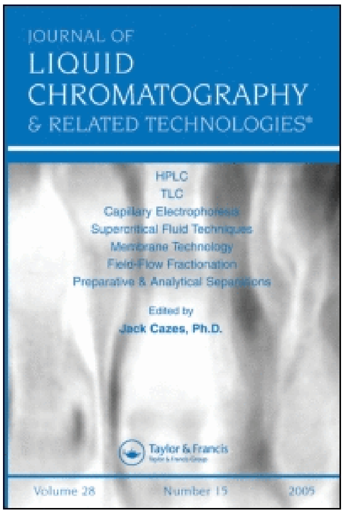

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THE USE OF COMPUTER AIDED CHEMISTRY TO PREDICT CHIRAL SEPARATION IN LIQUID CHROMATOGRAPHY

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ABSTRACT

A computational technique using a combination of molecular mechanics, MO and intermolecular interaction energy calculations has been developed that is capable of predicting the possibility of chiral separation in liquid chromatography, the most retained enantiomer and the orientations between the enantiomers and the chiral stationary phase.

INTRODUCTION

An increasing number of chiral stationary phases CSPs have been developed for separation by high performance liquid chromatography (1). For the successful resolution of optical isomers on such phases, it is desirable to have some insight into the underlying separation mechanism. Several models have been proposed to explain the resolution, where the number of attractive interactions between the solute and CSP have varied from none (environmental chirality) to three (2). Theoretically, however, there are as many origins of interactions as there are atoms in the solute-CSP complex.

In this paper, we wish to present a model based upon a combination of semiempirical molecular orbital (MO) calculations (CNDO/2), molecular mechanics (MM2PI) and intermolecular energy calculations.

METHOD OF CALCULATION

The molecular mechanics calculations were performed using MM2PI, which is similar to the MMPI-MM2 program by Lipkowitz et al. (3). MM2PI, which uses the pi-electron routines of MMPI together with the MM2 equations and parameters, gives geometries and energies close to those obtained with MMP2 (4). A subroutine of the MIMIC program (5) provided rigid rotations and spline interpolations. Charges and atomic dipole moments were calculated with the CNDO/2 method (6). A method similar to that of Caillet and Claverie was used for evaluating the interaction energies (7).

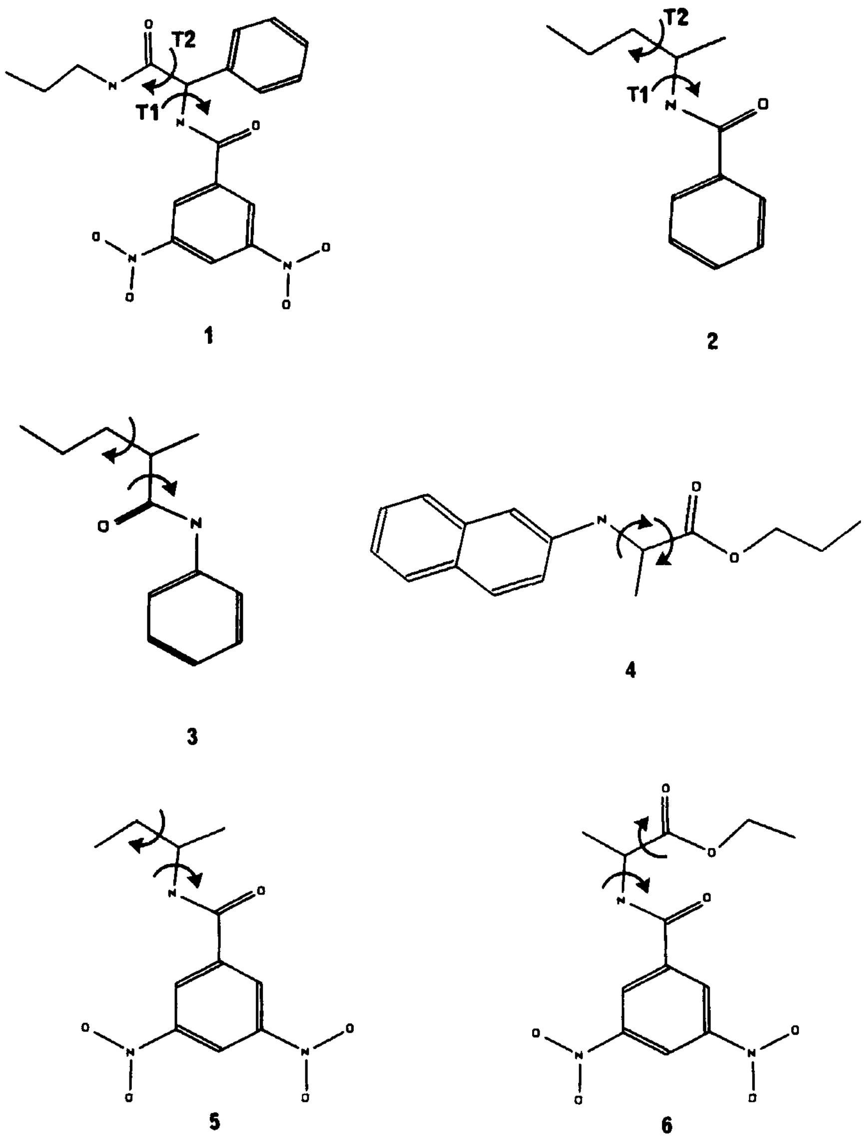
The total interaction energy (E_{TOT}) is the sum of contributions of potential (E_P) and electrostatic (E_{EL}) energies, where the latter consist of monopole-monopole (E_{QQ}), monopole-dipole (E_{QD}) and dipole-dipole (E_{DD}) interactions:

$$E_{TOT} = E_P + E_{EL} \tag{1}$$

$$E_{EL} = E_{QQ} + E_{QD} + E_{DD} \tag{2}$$

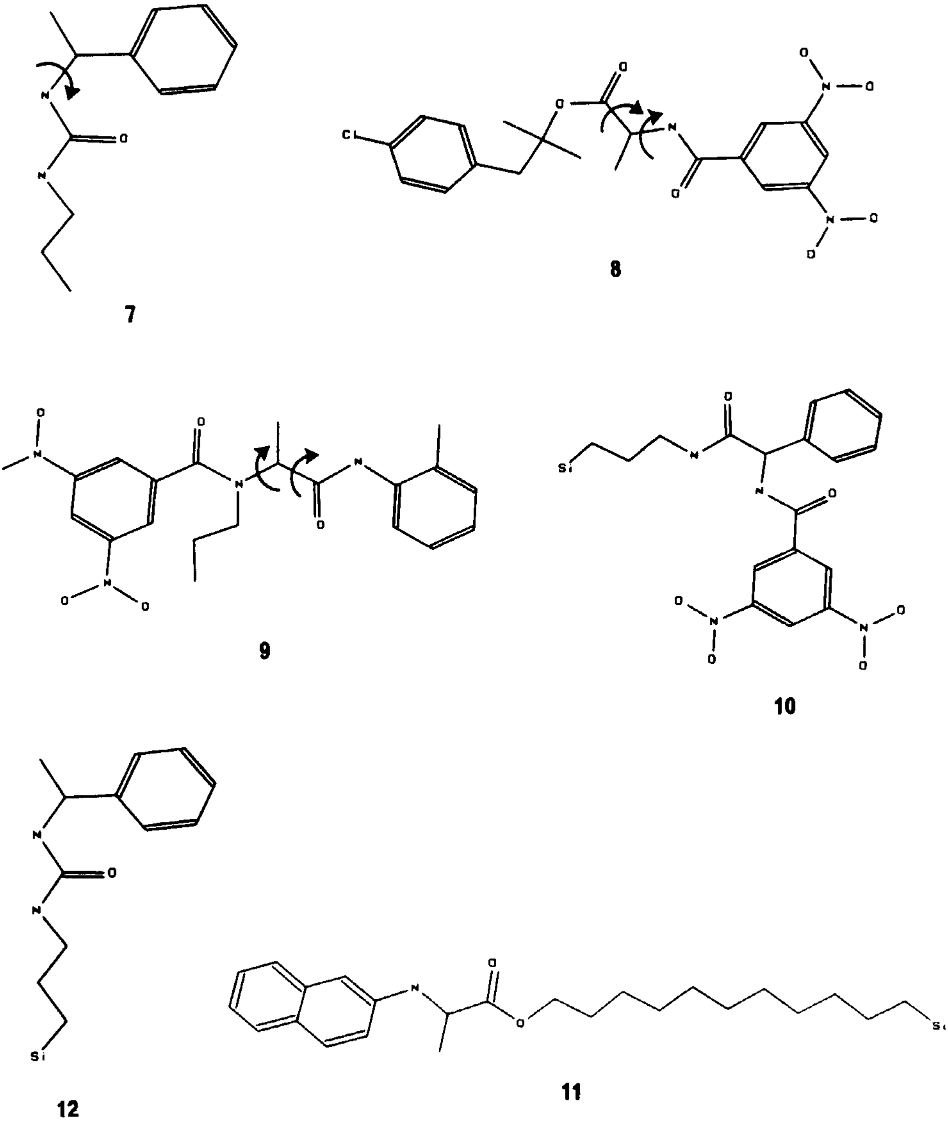
The electrostatic energies were calculated from the equations:

$$E_{QQ} = K \sum_{ij} \frac{Q_i Q_j}{r} \tag{3}$$



Scheme 1.

(continued)



Scheme 1. (continued)

$$E_{QD} = K' \sum_{ij} \frac{Q_i \underline{\mu}_j \underline{r}}{r^3} \qquad (4)$$

$$E_{DD} = K'' \sum_{ij} \left(\underline{\mu}_i \underline{\mu}_j - 3\left(\underline{\mu}_i \frac{\underline{r}}{r}\right)\left(\underline{\mu}_j \frac{\underline{r}}{r}\right)\right) \qquad (5)$$

where Q_i, $\underline{\mu}_i$ and Q_j, $\underline{\mu}_j$ are the atomic charges and atomic dipoles on atoms i and j, respectively, r is the interatomic distance, K, K' and K'' are conversion factors.

The potential energies were calculated using the equation:

$$E_p = \sum_{ij} \left(\frac{-A}{r^6} + \frac{BE^{-Cr}}{r^D}\right) \qquad (6)$$

where A, B, C and D are atomic parameters (8).

Compounds 1, 4 and 7 (Scheme 1) were used as model compounds for the commercially available chiral stationary phases 10 (9), 11 (10) and 12 (11), respectively.

Chromatographic data were taken from the literature (9, 10), except for compounds 8 and 9. These 3,5-dinitrobenzoyl (DNB) amides were synthesized from alaproclate and prilocaine by well-known methods. The chromatographic conditions for the separations on stationary phase 12 will be published elsewhere (12).

Amide moieties were assumed to be in the Z configuration. The conformational analysis (rigid rotations and molecular mechanics calculations) were performed on structures with the nitro-groups removed because force field parameters for such functionalities do not exist. This condition does not, however, affect the conclusions drawn from the analysis. In each compound, the torsion angles (indicated in Scheme 1) were changed by rigid rotations (10 deg. increments) in trial structures obtained from MM2PI. The final energy surfaces were calculated from the grid using spline-interpolation. Each minimum found was then subjected to full MM2PI relaxation. The energy surfaces, final energies and torsional angles of compounds 1 and 2 are depicted in Fig. 1 and 2 and Table 1, respectively. Contours are in units of 1 kcal/mol. Contour lines above 10 kcal/mol are not shown. Local maxima in Fig. 2 are depicted with M.

The global minimum of each compound was then selected as the input structure for the interaction (intermolecular interaction energy) calculations. The interaction energy minimizations were carried out using the method of Rosenbrock (13). Each molecule was assumed to be a rigid body. Both molecules were then rotated and translated with respect to a fixed coordinate system. Several orientations were chosen as starting points for the minimization process. The final interaction energies and orientations are presented in Table 2 and Fig. 3 - 9, respectively. Input structures were generated and molecular modelling was performed using Chem-X (14).

The computations were carried out either on a VAX 11/785 or on a VAX 8650.

RESULTS AND DISCUSSION

It should be emphasized that several approximations are involved in the use of computational chemistry and must be kept in mind when discussing the results. All calculations are performed in gas-phase at room temperature with only one pair of molecules involved. Also, the possible influence of the silica surface or the solvent is disregarded.

Conformational Analysis

Several local minima were found for each compound. The energy surfaces of 1 and 2 only are presented here (Fig. 1 and 2) and will be further discussed (15).

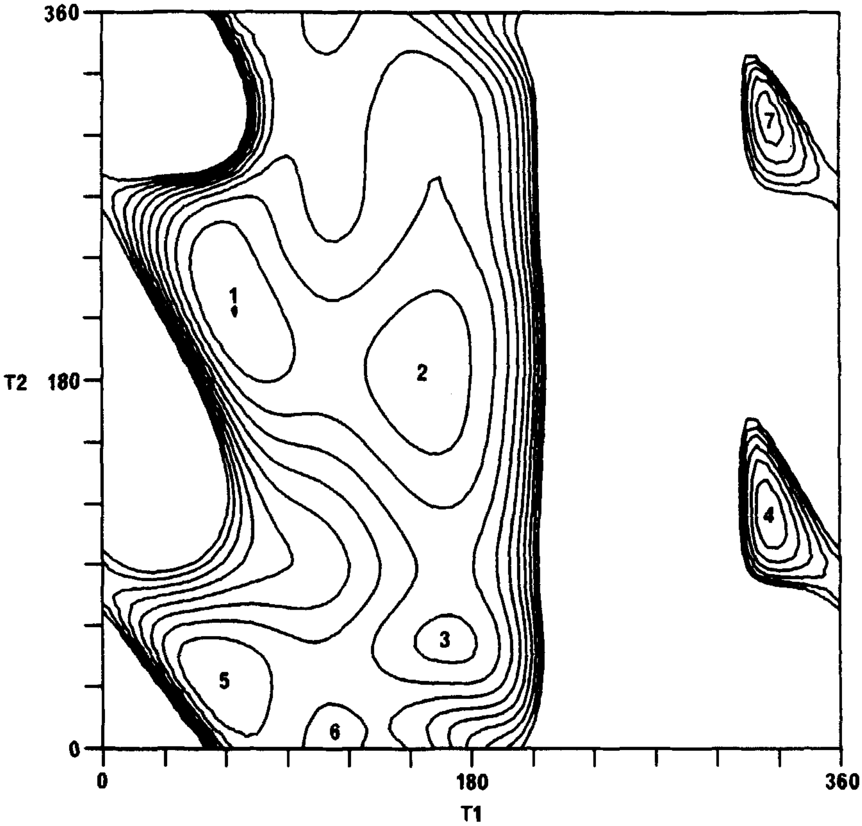


Fig. 1. Energy surface of 1 generated by rigid rotations.

Compound 1 displays seven local minima, all within 3 kcal/mol. The energy difference between the global minimum (#1) and the next higher minimum (#2) is 0.75 kcal/mol. At room temperature (298 K), the calculated population distribution of minima # 1 - 7, using the Boltzmann distribution, is 63.3 %, 17.8 %, 7.4 %, 5.8 %, 4.0 %, 1.2 % and 0.5 %, respectively.

Compound 2 shows six local minima (< 2 kcal/mol). The calculated distribution is 52.3 %, 17.9 %, 14.4 %, 8.0 %, 4.6 % and 3.0 %, respectively.

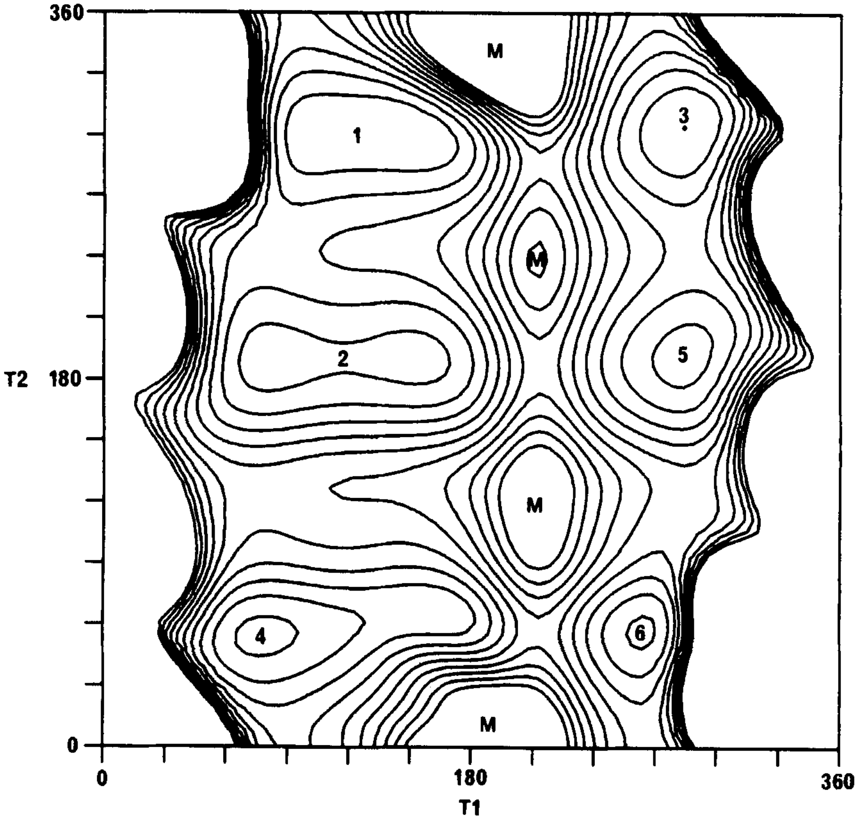


Fig. 2. Energy surface of 2 generated by rigid rotations.

Thus, several conformers may contribute to the structure of the solute-CSP complex. We have used the geometry of the global minimum for each compound in the interaction energy calculation although for a more thorough analysis one should take the whole population distribution into account.

TABLE 1

Energies and Torsional Angles of Compounds 1 and 2

Compound	minimum #	energy (kcal/mol)	T1 (deg.)	T2 (deg.)
1	1	0.00	63.5	-144.1
	2	0.75	159.3	-138.6
	3	1.27	163.9	82.5
	4	1.41	-50.9	105.5
	5	1.64	58.7	29.0
	6	2.33	98.1	-22.7
	7	2.88	-39.7	-43.8
2	1	0.00	113.9	-61.0
	2	0.64	94.6	-175.5
	3	0.76	-67.4	-54.6
	4	1.11	81.6	54.9
	5	1.44	-101.0	-171.9
	6	1.70	-112.9	59.8

TABLE 2

Interaction Energies of Compounds 1 - 9

Compound	R-form	S-form	CSP
2	-16.24	-16.50	1
3	-17.86	-17.37	1
5	-15.02	-14.75	4
6	-15.07	-15.67	4
8	-17.86	-17.35	7
9	-16.84	-16.81	7

Interaction-Calculations

Several relative orientations representing local minima were found for each complex studied. It is therefore of great importance to use a large number of different starting points in these calculations in order to cover the entire interaction energy surface. Calculated interaction energies are presented in Table 2.

CSP(1) complexes

Compounds 2 and 3 bind to the CSP in very different orientations. This is not surprising since the dipole moment of the two compounds have opposite directions. The geometries of the global minimum orientations are results of a delicate balance between steric and electronic factors.

Both enantiomers of 2 have the phenylamide moiety almost perpendicular to the dinitrophenyl ring of the CSP (Fig. 3). This might seem a little puzzling at first. However, parallel orientations of the amide groups suffer from severe steric interactions between close-lying groups. The same is true for compound 3 (Fig. 4). In order to avoid such unfavorable interactions the molecules within each pair are rotated and translated with respect to one another. The distance between the center of the amide groups is 5.4 Å in the CSP-compound 2 complex and 3.7 Å in the CSP-compound 3 complex.

There also exists a local minimum orientation between compound 2 and the CSP which resembles the global minimum orientation between compound 3 and the CSP and vice versa. These orientations (Fig. 5) are, however, between 1.5 and 2.5 kcal/mol higher in energy compared with the corresponding global minimum.

The (S)-form of 2 (2S) and the (R)-form of 3 (3R) are predicted to interact stronger with the CSP compared with the corresponding enantiomers (see Table 2). This finding is in accordance with experimental results (9).

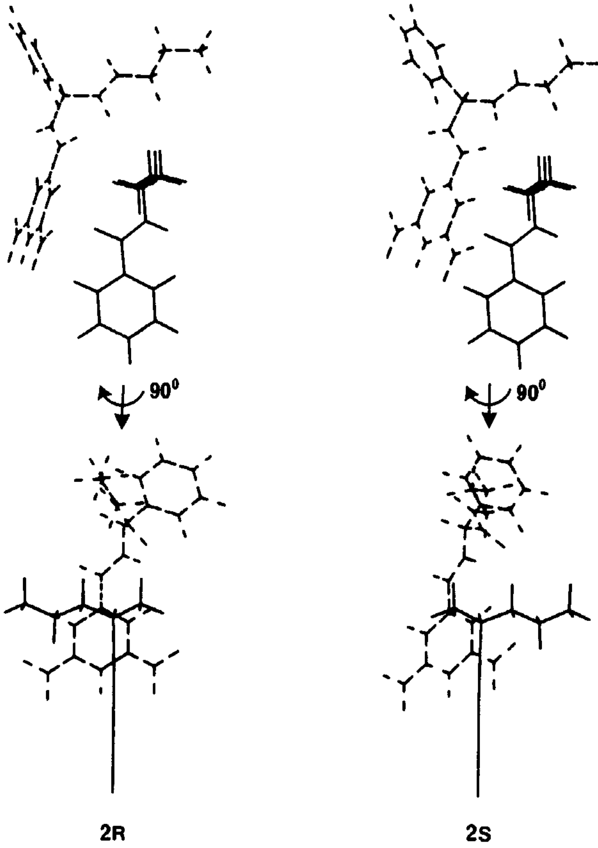


Fig. 3. Intermolecular orientations of the enentiomers of 2 and the CSP (1) (dashed)

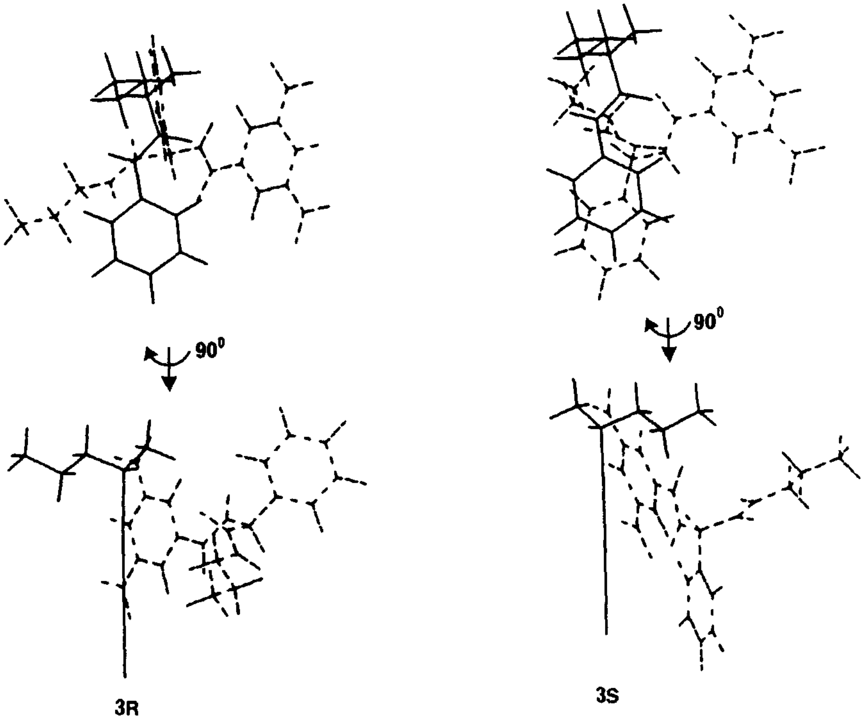


Fig. 4. Intermolecular orientations of the enentiomers of 3 and the CSP (1) (dashed)

CSP(4) complexes

All the complexes between the enantiomers of compounds 5 and 6 and the CSP have similar global minimum orientations (Fig. 6 and 7). The molecules in each complex are oriented in such a manner that the moieties containing the major dipoles, i.e. the dinitrophenylamide group in the solutes and the ester and nitrogen atom in the CSP, are in the vicinity of each other, keeping the steric interactions at a minimum.

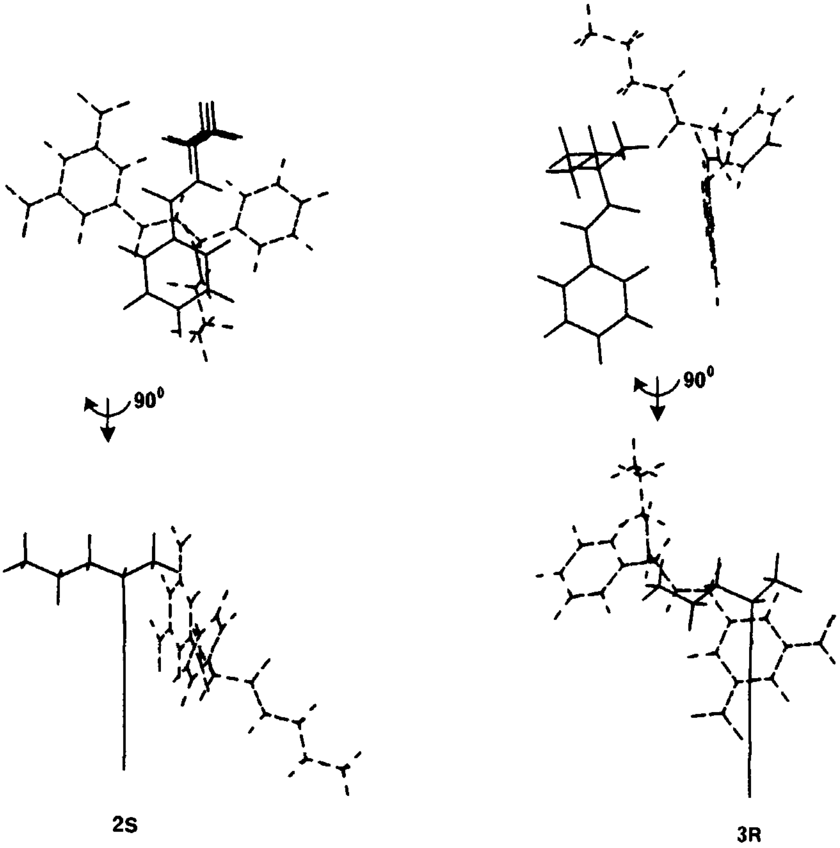


Fig. 5. Local minimum intermolecular orientations of the enentiomers 2S and 3R and the CSP (1) (dashed)

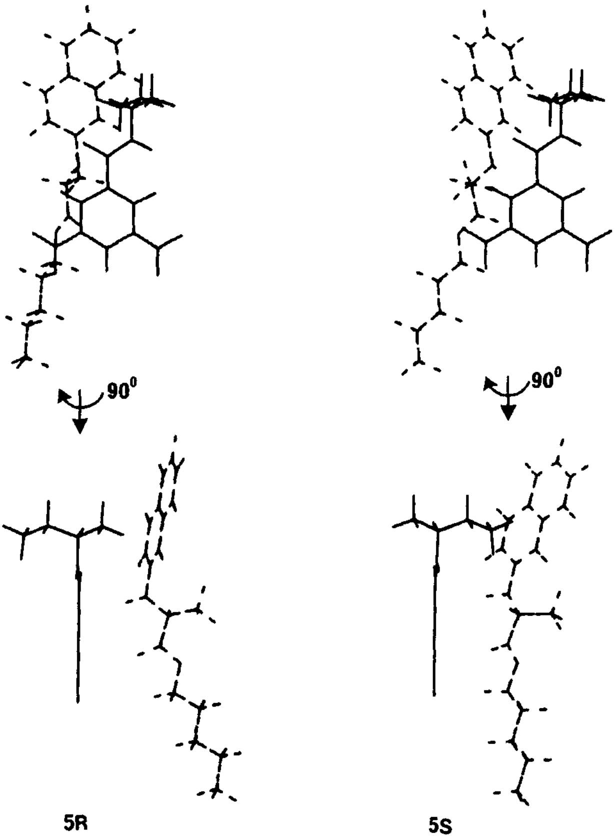


Fig. 6. Intermolecular orientations of the enentiomers of 5 and the CSP (1) (dashed)

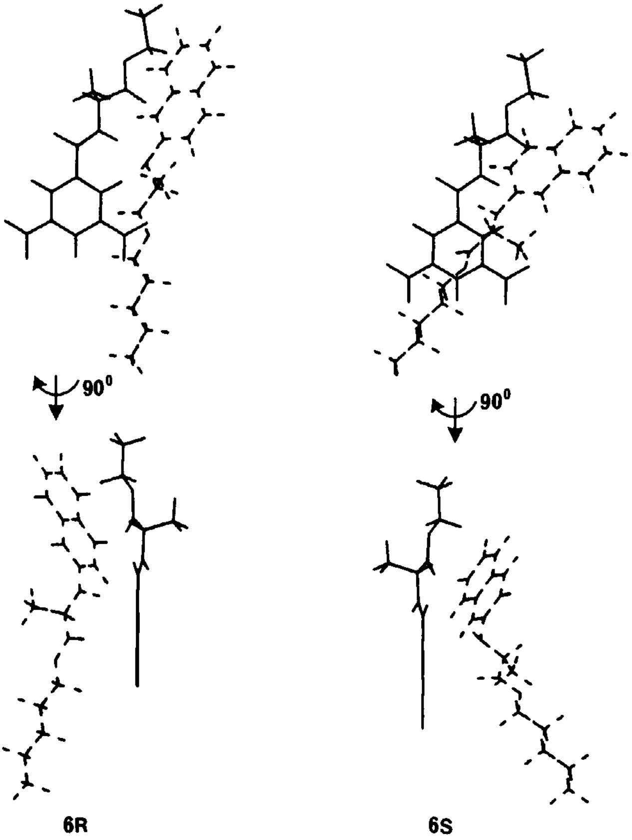


Fig. 7. Intermolecular orientations of the enentiomers of 6 and the CSP (4) (dashed)

According to the calculations 5R and 6S bind more strongly to the CSP compared with the corresponding enantiomer (see Table 2). Experimental results support this prediction (10).

CSP(7) complexes

Both enantiomers of the DNB-amides of alaproclate (8) and prilocaine (9) appear to bind to the CSP in a similar manner

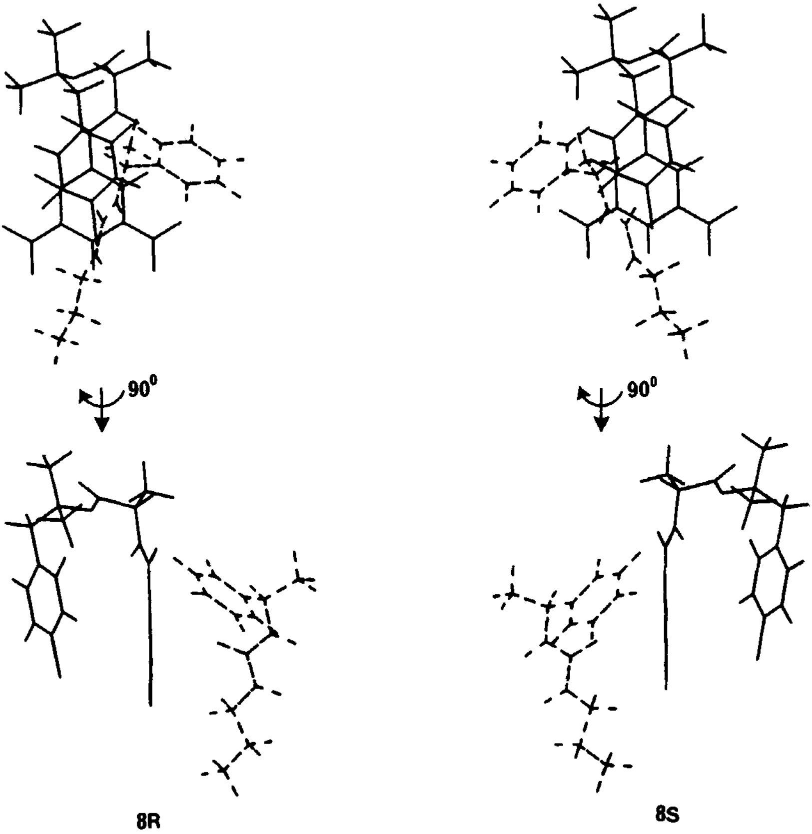
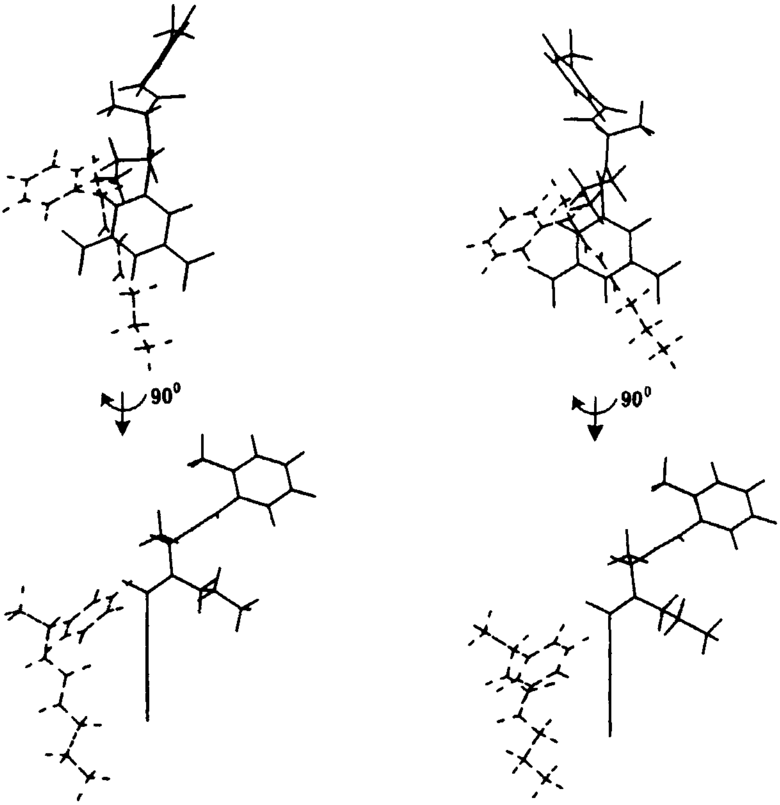


Fig. 8. Intermolecular orientations of the enentiomers of 8 and the CSP (7) (dashed)

(Fig. 8 and 9). The moieties containing the larges dipoles in each of the molecules constituting a pair are oriented close to each other.

The (R)-form of alaproclate (8R) interacts stronger with the CSP than the (S)-form (8S, see Table 2), which is in accordance with chromatographic data.



9R **9S**

Fig. 9. Intermolecular orientations of the enentiomers of 9 and the CSP (7) (dashed)

In prilocaine (9), the amide nitrogen is tertiary. The resultant bulkiness has a severe influence on the geometry of the low energy conformations of 9. The dinitrophenyl ring can no longer assume a planar arrangement with the amide moiety due to steric interactions between the ortho hydrogens on the phenyl ring and the propyl substituent on the amide nitrogen. Instead, the amide group is almost perpendicular to the phenyl ring (85.4 deg.).

This, in turn, has a severe impact on the chiral separation of 9. The interaction calculations predicts the interaction energy of the global minimum orientations of both 9R and 9S (Fig. 9) to be of equal magnitude. Thus, no chiral separation should be observed. This prediction is born out by experiments (12).

CONCLUSIONS

We have presented a computational technique (model) based upon a combination of molecular mechanics, MO and interaction energy calculations that seems capable of evaluating the possibility of chiral separation in liquid chromatography. If separation is predicted to occur, the model also calculates which enantiomer is eluted first and the orientation of the enantiomers with respect to the chiral stationary phase (CSP).

The absolute interaction energy values calculated by the model do not, however, seem to correlate in any predictable manner with chromatographic data. Thus, it is not possible to correlate the absolute values with capacity factors (k'-values). Nor do the obtained differences in interaction energies between different pairs of enantiomers separated on the same CSP seem to correlate with the separation factor (α). This is not a surprising fact keeping the approximations of the model in mind. A development of the model using a more rigorous treatment might resolve the above mentioned discrepancies.

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13. The optimizer is taken from the program CINMIN by Fraser, M., QCPE program no. 389, and adapted to our program.

14. Chem-X, developed and distributed by Chemical Design Ltd., Oxford, England.

15. Additional material on the conformational analysis is available from the authors.