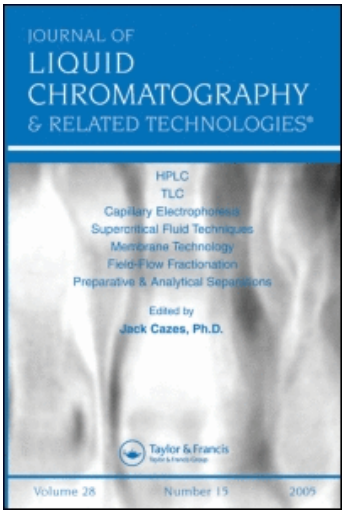

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Computational Chemical Analysis of the Separation of Derivatized R- and S-Amino Acid Enantiomers on N-(tert-Butylaminocarbonyl)-(S)-valylamino- propylsilica Gel and (R)-1-(α-Naphthyl)-ethylaminocarbonyl-glycylamino-propylsilica Gel by Liquid Chromatography

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COMPUTATIONAL CHEMICAL ANALYSIS OF THE SEPARATION OF DERIVATIZED R- AND S-AMINO ACID ENANTIOMERS ON N-(tert-BUTYLAMINOCARBONYL)-(S)-VALYLAMINO-PROPYLSILICA GEL AND (R)-1-(α-NAPHTHYL)-ETHYLAMINOCARBONYL-GLYCYLAMINO-PROPYLSILICA GEL BY LIQUID CHROMATOGRAPHY

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ABSTRACT

The chiral selectivities of N-(tert.-butylaminocarbonyl)-(S)-valylaminopropylsilica gel and (R)-1-(α-naphthyl)-ethyl-aminocarbonyl-glycylaminopropylsilica gel were studied using model compounds. The differences in the final energy values of molecular interactions between the model chiral phase and derivatized (R)- and (S)-amino acids, calculated by molecular

INTRODUCTION

Hydrogen bonds and steric effects are considered to be the major chiral recognition forces in normal-phase liquid chromatography. Indeed, analyses of chiral complexes by NMR and IR have indicated the presence of hydrogen bonds.[1] Furthermore, hydrogen bond formation has also been demonstrated by X-ray crystallography.[2] On the other hand, the development of computational chemical analysis has eased the study of molecular interaction, and some bonded phases for gas and liquid chromatography have been analyzed.[3-5] If a chiral center is defined, the energy of a chiral complex can easily be calculated and the probability of chiral separation can be estimated from the energy difference betw between chiral complexes. Several so-called Pirkle type chiral recognition phases have been synthesized and, therefore, the chiral recognition model was targeted for computational chemical analysis to understand the retention mechanism and predict enantiomer separation. The details of the conformation of model chiral phases were analyzed previously;[6-12] however, the relation between calculated energy values and the separation factor α values was not well presented. Only a limited number of such results have been reported.[13,14] The chiral recognition of N-butyrylvaline-tert-butylamide for (R)- and (S)-4-nitrobenzoyl amino acids was investigated using the CAChe™ molecular mechanics calculations, and the chiral recognition center was investigated from the geometry of the chiral phase and the energy difference between the complexes. Generation of a three-dimensional visual structure helped in studying the chiral recognition center; however, the energy values did not support the elution order.[15]

In this study, liquid chromatographic data reported by Oi[16] were analyzed using a model chiral phase and molecular mechanics calculation to understand the present limitations in both chromatographic environment and computational chemistry. The chiral phases were N-(tert.-butylamino-carbonyl)-(S)-valylaminopropylsilica gel and (R)-1-(α-naphthyl) ethylamino-carbonylglycylaminopropylsilica gel.

EXPERIMENTAL

The computer used for the calculations was a Macintosh IIfx, and the software for the computational chemical calculations was CAChe™ from Sony-Tektronix (Tokyo, Japan). The computational chemical calculation was performed without modification of the programs. The geometry of a molecule, created using CAChe™ molecular editor, was first optimized using molecular mechanics calculation. The properties used for the calculation were bond stretch, bond angle, dihedral angle, improper torsion, van der Waals,

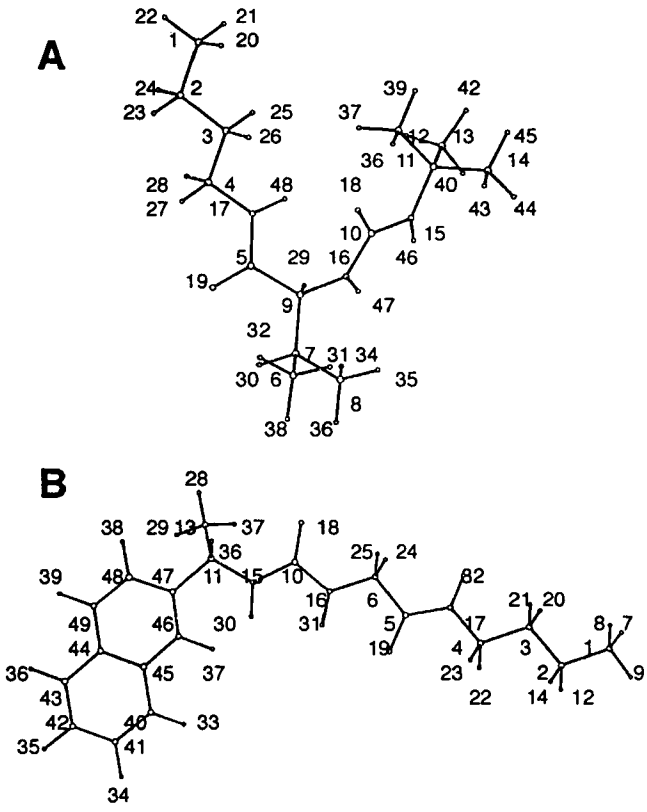

Figure 1. Structure of model compounds of Chiral Phase I (A) and II (B) with atomic numbers. A: N-(tert.-butylaminocarbonyl)-(S)-valylaminobutane, B: (R)-1-(α-naphtyl)ethylaminocarbonylglycylaminobutane. See the detail of atoms in Table 1.

electrostatic (MM2 bond dipoles) and hydrogen bond. The cut-off distance for van der Waals interaction was 9Å.[17] The electronic properties of the molecule were obtained using extended Hückel where all molecular orbitals were used for the calculation.[17] The electron density was visualized through the CAChe™ tabulator, and the hydrogen bond center was estimated from the electron density. The optimized energy values of a complex made through hydrogen bond between a chiral phase model and an analyte were used to study the chiral selectivity.

Table 1

Net Atomic Charge (au) of Model Chiral Phases I and II Calculated Using Extended Huckel

	Phase I		Phase II		NAcAl		DNBAl	
No	Atom	Charge	Atom	Charge	Atom	Charge	Atom	Charge
1	C	0.9400	C	0.0707	C	0.0351	C	0.0480
2	C	0.1250	C	0.1125	C	1.1055	C	1.0569
3	C	0.1088	C	0.0949	C	0.3493	C	0.3489
4	C	0.3898	C	0.3748	C	0.0969	C	0.1190
5	C	1.0850	C	1.1059	C	1.2298	C	1.2349
6	C	0.3302	C	0.3147	C	0.5377	C	0.5386
7	C	0.1311	H	-0.0304	N	-0.4858	N	-0.5220
8	C	0.0831	H	-0.0305	O	-1.0795	O	-1.1205
9	C	0.0862	H	-0.0330	O	-1.0241	O	-1.0283
10	C	1.2930	C	1.2922	O	-0.5986	O	-0.6061
11	C	0.4389	C	0.3847	H	-0.0119	C	0.1220
12	C	0.0687	H	-0.0451	H	-0.0120	C	0.2726
13	C	0.0729	C	0.0668	H	-0.0326	C	0.1159
14	C	0.0792	H	-0.0452	H	-0.0338	C	0.2728
15	N	-0.5629	N	-0.5832	H	-0.0392	C	0.1242
16	N	-0.5425	N	-0.5378	H	-0.0385	N	1.1000
17	N	-0.5128	N	-0.4860	H	-0.0425	O	-0.7285
18	O	-1.1307	O	-1.1346	H	-0.0507	O	-0.7284
19	O	-1.0740	O	-1.0670	H	-0.0502	N	1.1002
20	H	-0.0379	H	-0.0451	H	-0.0532	O	-0.7283
21	H	-0.0379	H	-0.0451	H	0.1982	O	-0.7293
22	H	-0.0413	H	-0.0569	-	-	H	-0.0512
23	H	-0.0520	H	-0.0569	-	-	H	-0.0380
24	H	-0.0522	H	-0.0320	-	-	H	-0.0379
25	H	-0.0530	H	-0.0320	-	-	H	-0.0394
26	H	-0.0520	H	-0.0571	-	-	H	-0.0506
27	H	-0.0582	H	-0.0258	-	-	H	-0.0509
28	H	-0.0670	H	-0.0272	-	-	H	-0.0532
29	H	-0.0479	H	-0.0290	-	-	H	0.2031
30	H	-0.0636	H	0.2101	-	-	H	-0.0438
31	H	-0.0358	H	-0.1939	-	-	H	-0.0482
32	H	-0.0400	H	0.1919	-	-	H	-0.0528
33	H	-0.0413	H	-0.0567	-	-	-	-
34	H	-0.0422	H	-0.0530	-	-	-	-

Table 1 (continued)

Net Atomic Charge (au) of Model Chiral Phases I and II Calculated Using Extended Hückel

	Phase I		Phase II		NAcAl		DNBAl	
No	Atom	Charge	Atom	Charge	Atom	Charge	Atom	Charge
35	H	-0.0384	H	-0.0531	-	-	-	-
36	H	-0.0423	H	-0.0564	-	-	-	-
37	H	-0.0416	H	-0.0402	-	-	-	-
38	H	-0.0424	H	-0.0564	-	-	-	-
39	H	-0.0398	H	-0.0566	-	-	-	-
40	H	-0.0403	C	0.0169	-	-	-	-
41	H	-0.0402	C	0.0352	-	-	-	-
42	H	-0.0387	C	0.0250	-	-	-	-
43	H	-0.0440	C	0.0269	-	-	-	-
44	H	-0.0427	C	0.0756	-	-	-	-
45	H	-0.0420	C	0.0862	-	-	-	-
46	H	0.2007	C	-0.0429	-	-	-	-
47	H	0.2027	C	0.1016	-	-	-	-
48	H	0.2084	C	0.0120	-	-	-	-
49	-	-	C	0.0228	-	-	-	-

NAcAl and DNBAl are N-acetylalanine and 3,5-dinitrobenzoylalanine methyl esters, respectively; however, their structures are not given in the text. Above data indicate NH and CO groups are hydrogen bonding centers.

RESULTS AND DISCUSSION

The atomic distances within molecules and molecular shape are important for enantiomer separation. The model chiral phases of N-(tert.-butyl-aminocarbonyl)-(S)-valylaminopropylsilica gel and (R)-1-(α-naphthyl)-ethylaminocarbonylglycylaminopropyl silica gel were N-(tert.-butyl-aminocarbonyl)-L-valylaminobutane (Phase I) and (R)-l-(α-naphthyl)-ethylaminocarbonylglycylamino butane (Phase II), respectively.

These model compounds were first constructed by the molecular editor of the CAChe™ program. These chiral stationary phases were shaped very differently as shown in Figure 1; Phase I was in the V-shape and Phase II was in the L-shape. The hydrogen bonding center, the electron delocalization of

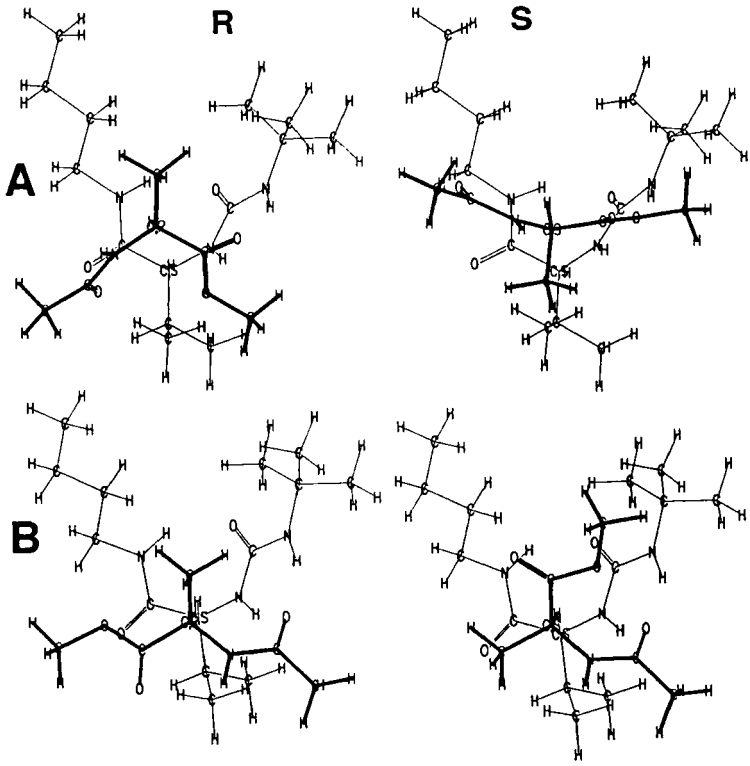

Figure 2. Chiral complex between Phase I and (R)- and (S)-N-acetylalanine methylesters. Molecules having cylinder bonds are analytes.

these phases, was studied using the Extended Huckel calculation of the CAChe™ program. The strongest electron acceptor group was the secondary amino group indicated by the atomic number 15-17 nitrogen and 46-48 hydrogen of Phase I in Fig. 1A, and the atomic number 15-17 nitrogen and 30-32 hydrogen of Phase II in Fig. 1B. The electron donor group of N-acetylamino acid methylesters was the carbonyl of the acetyl group and not that of the carboxyl group. The electron donor group of N-3,5-dinitrobenzoylamino acid methyl-esters was the carbonyl of the dinitrobenzoyl group.

The optimized complex forms of Phase I with (R)- and (S)-N-acetylalanine methyl esters are shown in Fig. 2, where the complexes of (R)- and (S)-amino acids are drawn using atomic symbols. The shadow molecule is

Table 2

Physical Properties and Separation Factor (α) of N-Acetylamino-Acid Methyl Esters Complexes with Chiral Phase I

Complex Form Compounds	α	R-form 1*[1]	e*[2]	FE*[3]	HE*[4]	VE*[5]	S-form FE*[3]	HE*[4]	VE*[5]
A Alanine	1.24	R	A	-62.71	-16.83	5.35	-56.21	-15.26	5.79
Leucine	1.99	R	B	-60.40	-16.34	4.34	-54.40	-14.53	6.46
Methionine	1.48	R	A	-65.63	-16.62	3.75	-57.06	-11.67	5.15
Phenylalanine	1.66	R	B	-69.67	-16.42	3.29	-68.90	-17.22	5.26
Phenylglycine	1.39	R	B	-72.82	-18.86	6.05	-65.95	-12.91	6.01
Valine	1.73	R	B	-56.79	-15.25	6.10	-55.01	-14.52	5.80
B Alanine	1.24	R	A	-58.81	-15.52	4.16	-60.09	-13.53	4.06
Leucine	1.99	R	B	-56.84	-14.80	4.65	-58.02	-13.91	4.18
Methionine	1.48	R	A	-63.01	-14.95	2.55	-63.86	-13.64	2.70
Phenylalanine	1.66	R	B	-71.01	-14.50	3.12	-72.12	-21.98	7.34
Phenylglycine	1.39	R	B	-72.33	-16.22	5.18	-76.79	-23.03	5.40
Valine	1.73	R	B	-59.09	-15.11	4.35	-59.28	-13.80	3.79

*Notes: [1]First eluted compound; [2]Eluent A: n-hexane / 1,2-dichloroethane / ethanol (40/10/1); Eluent B: n-hexane / 1,2-dichloroethane / ethanol (100/20/1); [3]Final energy (Kcal/mol); [4]Hydrogen bond energy; [5]van der Waals energy (Kcal/mol). Details of A and B: see in text.

Phase I and the clear molecules having cylinder bonds are (R)- and (S)-N-acetylalanine methyl esters. The final energy value of complexes with the (R)-N-acetylalanine methylester shown in Fig. 2A was -62.71 Kcal/mol and that with the (S)-N-acetylalanine methyl ester was -56.21 Kcal/mol. The calculated final hydrogen bonding and van der Waals energy values of other amino acid complexes are summarized in Table 2, Part A. The final energy values of all complexes with (R)-form amino acids were lower than those with (S)-form amino acids in Phase I. These complexes were constructed to form two hydrogen bonds. However, this result did not support the elution order where (R)-N-acetylalanine methylester which formed a complex with (S)-form Phase I was eluted before (S)-N-acetylalanine methylester. Therefore, we searched for an alternative location for complex formation to support the elution order. The complex form shown in Fig. 2B seemed to be an ideal complex form occurring in liquid chromatography, even though the energy value of

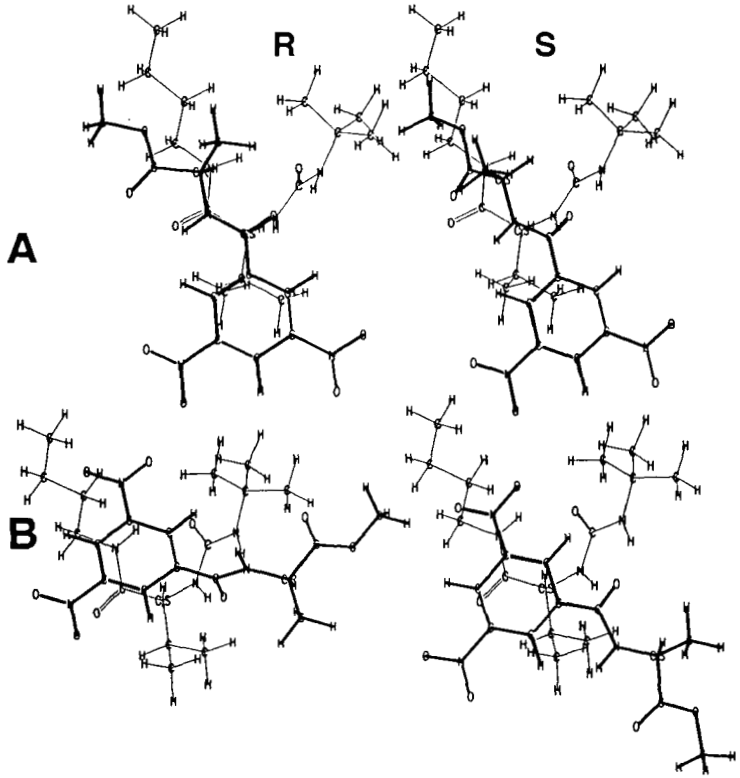

Figure 3. Chiral complex between Phase I and (R) and (S)-N-3,5-dinitrobenzoylalanine methylesters. Molecules having cylinder bonds are analytes.

(R)-N-acetylalanine methylester was 3.9 Kcal/mol higher and the hydrogen bonding energy value was 1.3 Kcal/mol lower than those of the complexes in Fig. 2A. The final energy values of complexes with the (R)- and (S)-N-acetylalanine methyl-esters were -58.81 and -60.09 Kcal/mol, respectively. The van der Waals energy values of the complex form in Fig. 2B were lower than those in Fig. 2A except (S)-N-acetylphenylalanine methylester and (R)-N-acetylleucine methylester. The calculated energy values of the complex form in Fig. 2B are summarized in Table 2, Part B. The energy values of all complex of S-form analyses were lower than those of R-form analyses. These results supported the elution order.

The optimized complex forms of Phase I with (R)- and (S)-N-3,5-dinitrobenzoylalanine methyl esters are shown in Figs. 3 and 4. The final

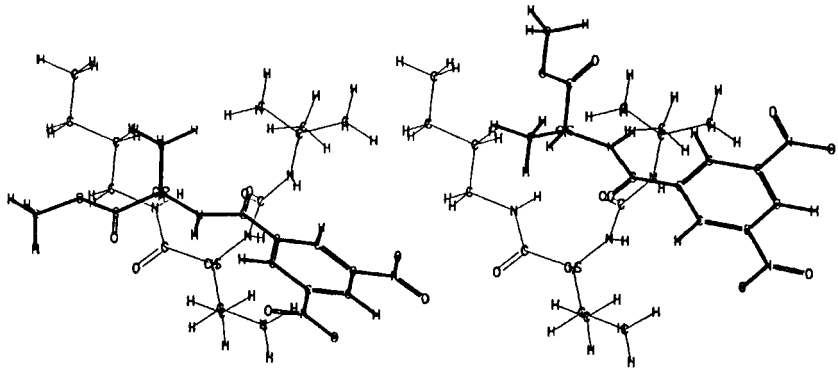

Figure 4. Chiral complex between Phase I and (R) and (S)-N-3,5-dinitrobenzoylalanine methylesters. Molecules having cylinder bonds are analytes.

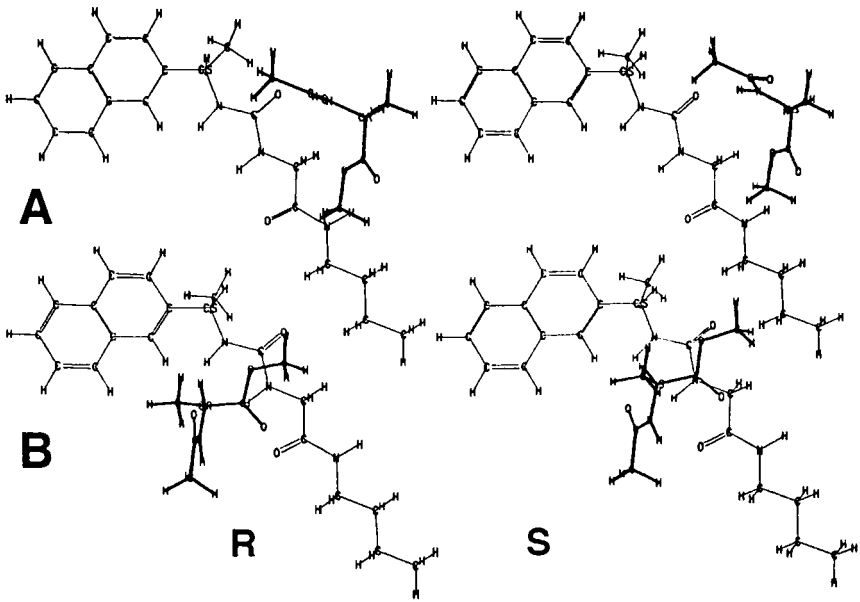

Figure 5. Chiral complex between Phase 11 and (R)- and (S)-N-acetylalanine methylesters. Molecules having cylinder bonds are analytes.

Table 3

Physical Properties and Separation Factor (α) of N-3,5-Dinitro-Benzoylamino Acid Methyl Esters Complexes with Chiral Phase I

Complex Form		R-form					S-form			
	Compounds	α	1*[1]	e*[2]	FE*[3]	HE*[4]	VE*[5]	FE*[3]	HE*[4]	VE*[5]
A	Alanine	1.11	R	A	-67.43	-19.16	11.06	-66.46	-18.97	11.84
	Leucine	1.16	R	B	-68.03	-18.20	10.32	-65.22	-17.99	9.46
	Methionine	1.06	R	B	-73.06	-18.77	9.82	-70.84	-18.84	9.04
	Phenylalanine	1.08	R	B	-76.66	-18.82	9.43	-71.42	-15.45	11.36
	Phenylglycine	1.00	-	A	-83.94	-23.96	9.02	-79.51	-23.86	8.91
	Valine	1.11	R	A	-68.83	-18.88	10.23	-63.63	-19.27	9.49
B	Alanine	1.11	R	A	-68.28	-18.58	7.83	-67.55	-18.85	9.90
	Leucine	1.16	R	B	-67.90	-19.29	8.05	-67.78	-18.58	9.29
	Methionine	1.06	R	B	-73.02	-19.15	7.13	-72.11	-18.96	8.71
	Phenylalanine	1.08	R	B	-78.69	-19.54	9.40	-77.68	-19.24	8.50
	Phenylglycine	1.00	-	A	-84.34	-23.62	8.97	-81.19	-21.96	9.84
	Valine	1.11	R	A	-68.32	-19.61	8.42	-69.19	-18.89	9.15
C	Alanine	1.11	R	A	-68.79	-21.12	11.12	-68.47	-20.15	11.09
	Leucine	1.16	R	B	-67.39	-19.61	11.47	-68.54	-21.58	10.93
	Methionine	1.06	R	B	-72.01	-19.50	10.46	-72.75	-21.64	9.93
	Phenylalanine	1.08	R	B	-78.41	-21.86	11.71	-79.30	-21.47	11.19
	Phenylglycine	1.00	-	A	-81.25	-21.34	12.98	-83.26	-24.05	10.07
	Valine	1.11	R	A	-66.93	-19.85	13.06	-68.27	-21.40	11.71

Symbols: See Table 2; details of A~C: see in text.

energy values of Fig. 3A calculated by MM2 were -67.43 for (R)- and -66.46 Kcal/mol for (S)-form alanine, respectively. These complexes formed two hydrogen bonds. However, these results did not support the elusion order where (R)-N-3,5-dinitrobenzoylalanine methylester which formed a complex with S-form Phase I was eluted before (S)-N-dinitrobenzoylalanine methylester. The calculated energy values of other amino acid complexes are given in Table 3A. A different location for complex formation was, therefore, searched for to support the elution order. The complex form shown in Fig. 3B seemed to be the most stable form whose van der Waals energy values were the lowest as listed in Table 3B. However, this complex form did not support the elution order, too.

Table 4

Physical Properties and Separation Factor (α) of N-Acetyl Amino Acid Methyl Esters Complexes with Chiral Phase II

Complex Form			R-form				S-form			
	Compounds	α	1*[1]	e*[2]	FE*[3]	HE*[4]	VE*[5]	FE*[3]	HE*[4]	VE*[5]
A	Alanine	1.00	-	A	-66.99	-15.41	14.09	-67.51	-15.47	14.00
	Leucine	1.00	-	B	-64.98	-15.44	14.69	-65.28	-15.50	14.83
	Methionine	1.00	-	A	-68.79	-15.82	14.91	-69.66	-15.50	14.42
	Phenylalanine	1.00	-	B	-75.16	-16.04	16.21	-75.01	-16.09	16.45
	Phenylglycine	1.00	-	B	-78.60	-18.02	16.92	-78.71	-17.87	16.61
	Valine	1.02	R	B	-65.30	-15.51	14.39	-65.38	-15.61	14.33
B	Alanine	1.00	-	A	-64.87	-16.31	13.30	-64.43	-16.25	13.55
	Leucine	1.00	-	B	-66.34	-17.40	12.00	-65.63	-17.11	12.65
	Methionine	1.00	-	A	-71.88	-17.02	9.85	-71.16	-17.09	10.64
	Phenylalanine	1.00	-	B	-76.19	-16.73	12.13	-76.90	-16.69	11.48
	Phenylglycine	1.00	-	B	-79.03	-18.64	13.93	-78.56	-18.56	14.63
	Valine	1.02	R	B	-66.19	-16.75	12.18	-66.11	-16.77	11.48

Symbols: See Table 1. The details of A and B: see in text.

The complex form shown in Fig. 4 seemed to be an ideal form occurring in liquid chromatography, even though the van der Waals energy values were higher than complexes of form 3A and 3B as listed in Table 3C. The final energy difference between complexes with the (R)- and (S)-N-3,5-dinitrobenzoylamino acid methyl esters was not significant compared to the results of N-acetylamino acid methyl esters, and supported the poor separation.

The optimized complex forms of Phase II with (R)- and (S)-N-acetylalanine methyl esters are shown in Fig. 5, where the complex of (R)- and (S)-amino acids is drawn using atomic symbols. The shadow molecule is Phase II and the clear molecules having cylinder bonds are (R)- and (S)-N-acetylalanine methyl esters. The complexes of Fig. 5A formed two hydrogen bonds. The positions of (R)- and (S)-form analytes can be rotated and the calculated energy values were nearly equivalent as shown in Table 4A. The final energy value of the complex with the (R)-N-acetylalanine methyl ester shown in Fig. 5A was -66.99 Kcal/mol and that with the (S)-N-acetylalanine

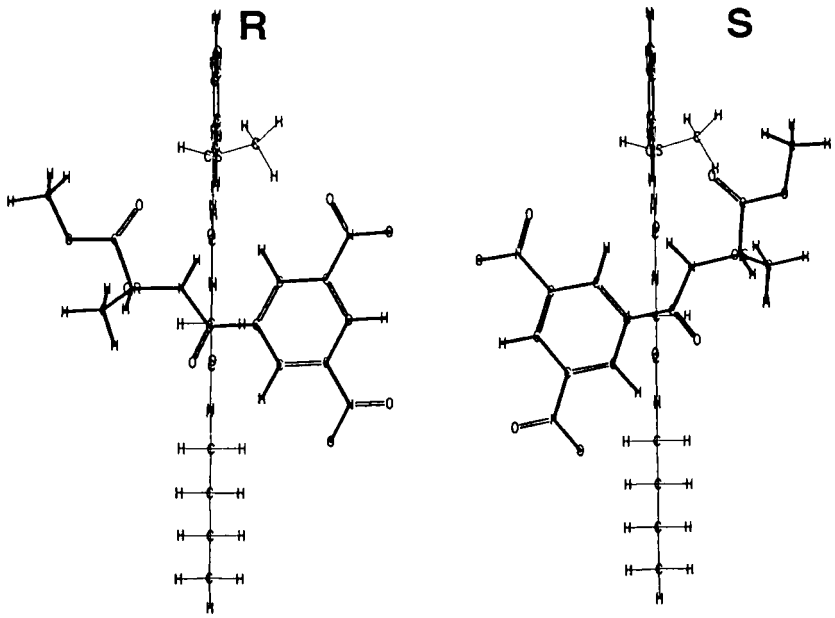

Figure 6. Chiral complex conformations (R)- and (S)-N-3,5-dinitrobenzoylalanine methyl esters with Phase II. Molecules having cylinder bonds are analytes.

methyl ester was -67.51 Kcal/mol. The complexes formed with Phase II like those shown as Fig. 5B seemed more stable than their van der Waals energy values. The final energy difference of other amino acid enantiomer complexes with Phase II was also not large. These calculated values summarized in Table 4B support the experimental results that the enantiomer separation was difficult in Phase II.

Analysis of chromatographic behavior of N-3,5-dinitrobenzoylamino acid methyl esters was not simple. The complex forms of Phase II with (R)- and (S)-form analyses are shown in Figs. 6 and 7, and the energy values of the complexes are given in Table 5. The complexes shown in Fig. 6 formed two hydrogen bonds. There was no significant difference in the final energy values of enantiomer complexes with Phase II, and the values are shown in Table 5A. However, the energy values of complexes with (R)-form methionine and phenylalanine were lower than those with (S)-forms due to the steric effect of the methyl group of the chiral center of Phase II.

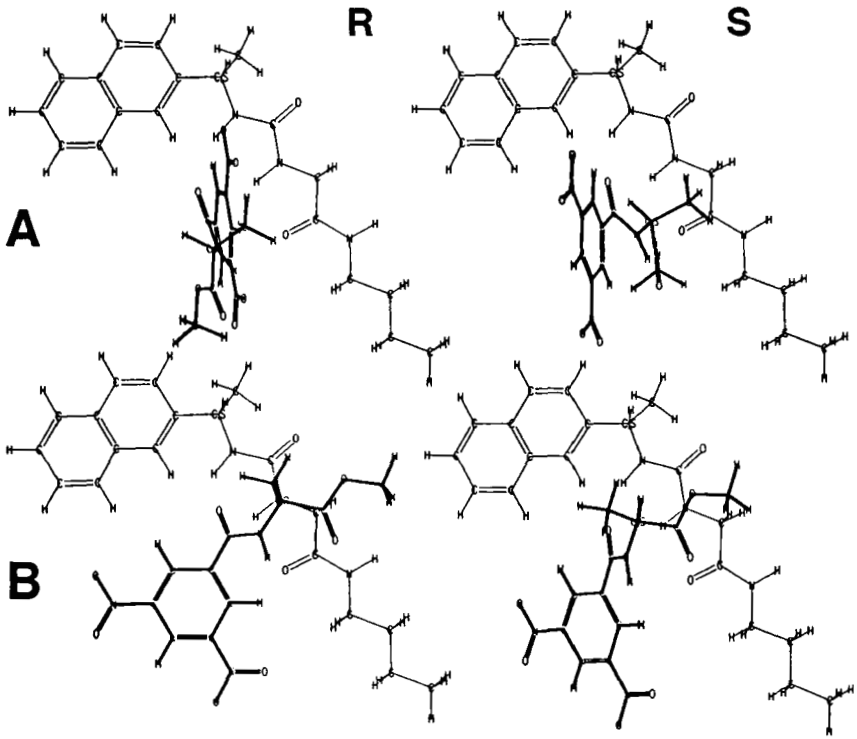

Figure 7. Chiral complex conformations (R)- and (S)-N-3,5-dinitrobenzoylalanine methyl esters with Phase II. Molecules having cylinder bonds are analytes.

The energy values were low for complexes of N-3,5dinitrobenzoylamino acid methylester when these complexes formed with Nos. 30 and 31 hydrogens in Phase II shown in Fig. 7A. The energy values were identical for the (R)- and (S)-complexes. Such large molecules could not form tight complexes with the relative small-sized Phase II, and this complex form is unlikely if the space between the chiral recognition center and the silica gel surface is estimated from Fig. 7A. The large naphthyl group of Phase II should cover the surface of the stationary phase, and the outside of the chiral phase may be opened for chiral recognition. The calculated values are summarized in Table 5B. These enantiomers were not separated in Phase II by the calculation, however they were chromatographically separable. Different complexes of N-3,5-dinitrobenzoylamino acid methyl ester with Phase II were further studied. The energy values of complex form of (R)- and (S)-N-3,5-dinitrobenzoylamino acid

Table 5

Physical Properties and Separation Factor (α) of N-3,5-Dinitro-Benoylamino Acid Methyl Esters Complexes with Chiral Phase II

Complex Form			R-form					S-form			
	Compounds	α	1*[1]	e*[2]	FE*[3]	HE*[4]	VE*[5]	FE*[3]	HE*[4]	VE*[5]
A	Alanine	1.69	R	B	-73.90	-20.20	19.48	-74.06	-20.62	18.95
	Leucine	1.45	R	B	-76.77	-21.08	18.21	-76.02	-20.72	18.27
	Methionine	1.68	R	B	-81.96	-21.32	17.08	-80.89	-21.32	17.60
	Phenylalanine	1.25	R	B	-92.91	-25.21	16.84	-91.31	-23.40	16.90
	Phenylglycine	1.11	S	B	-85.89	-18.82	19.91	-85.81	-18.33	20.07
	Valine	1.79	R	B	-77.25	-22.21	17.19	-76.57	-21.43	17.41
B	Alanine	1.69	R	B	-74.26	-25.31	23.26	-74.24	-24.84	22.95
	Leucine	1.45	R	B	-75.17	-22.62	19.37	-75.29	-25.30	21.52
	Methionine	1.68	R	B	-80.68	-25.71	21.67	-80.65	-25.42	21.61
	Phenylalanine	1.25	R	B	-95.50	-25.97	14.65	-94.73	-24.74	14.89
	Phenylglycine	1.11	S	B	-92.76	-26.69	18.48	-93.59	-27.31	16.89
	Valine	1.79	R	B	-75.51	-21.84	19.35	-74.98	-24.26	21.86
C	Alanine	1.69	R	B	-74.94	-20.75	17.60	-74.43	-21.46	18.22
	Leucine	1.45	R	B	-77.44	-21.63	16.41	-76.86	-22.28	16.43
	Methionine	1.68	R	B	-81.62	-21.53	15.31	-81.92	-22.16	14.96
	Phenylalanine	1.25	R	B	-92.00	-24.40	16.01	-92.75	-24.52	15.28
	Phenylglycine	1.11	S	B	-90.53	-23.54	17.28	-89.72	-23.63	18.23
	Valine	1.79	R	B	-76.77	-21.52	16.48	-77.35	-22.22	16.21

Symbols: See Table 1. The details of A~C: see in the text.

methyl esters with Phase II as shown in Fig. 7B indicate stability. This seemed to be the most stable complex form due to the lowest van der Waals energy values. However, the final energy values given in Table 5C also did not support the enantiomer separation.

CONCLUSION

Phase I demonstrated the excellent chiral recognition for small molecule N-acetylamino acid methyl esters, and the final energy value difference of

complexes indicated the possibility of enantiomer separation. The hydrogen bond energy values also indicate chiral selectivity. The van der Waals energy values do not clearly indicate the chiral selectivity, but the values were useful for analyzing the fit of their chiral complexes. On the other hand, Phase II did not show chiral selectivity by the calculation, but were chromatographically separable. This contradiction may have been due to geometry. The question regarding Phase II has to be solved when it is bound using an alkyl chain longer than the propyl group. The difference is the chiral recognition space, which is unlimited for computational chemical calculation and limited for chromatographic separation, is the major concern in the computational chemical analysis of molecular recognition. In this study, a one-to-one complex was used; however, this may not be suitable, especially for analyses with larger molecular size than the chiral recognition molecule. It would be better to make a large chiral phase like an amino phase where the selectivity of saccharides in liquid chromatography has been analyzed successfully.[4] However, this requires a powerful computer.

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