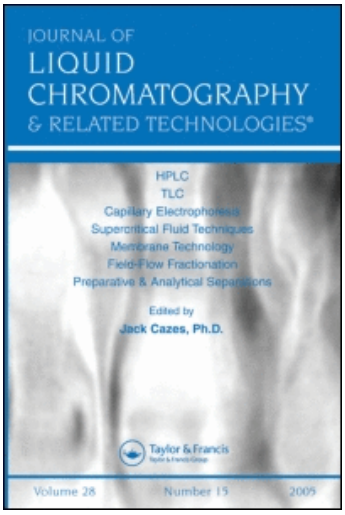

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COMPUTATIONAL CHEMICAL ANALYSIS OF THE CHIRAL RECOGNITION OF BINUCLEAR COPPER (II) OF N-SALICYLIDENE (R)-2-AMINO-1,2-BIS(2-BUTOXY-5-*tert*.BUTYLPHENYL)-3-PHENYL-1-PROPANOL IN LIQUID CHROMATOGRAPHY

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SUMMARY

The chiral recognition of a binuclear copper (II) complex of N-salicylidene-(R)-2-amino-1,2-bis(2-butoxy-5-tert.-butylphenetyl)-3-phenyl-1-propanol was analyzed by computational chemical calculation. The difference in the final energy calculated by molecular mechanics indicated the elution order of enantiomers on this chiral selective molecule.

INTRODUCTION

Chiral recognition is an important means of controlling normal metabolism. The required chiral form is usually the L-form for amino acids and D-form for saccharides, and that of drugs depends on the situation. The prediction of chiral selectivity is therefore very important for drug development. However, such a system is under development. Enantiomers can be separated chromatographically by the selection of an appropriate column and eluent. Such selection is however tedious, and the development of a basic rule is required. On the other hand, differences in molecular interactions have been identified as an energy value difference by computational chemical analysis. The method was applied to study the enantiomer selection of the chiral phase of chromatography.

Chiral recognition mechanism indicated by means of a comparison of the chromatographic behavior of modified chiral phases [1]. The analysis of chiral complexes by NMR and IR indicated that hydrogen bonding is important [2]. Furthermore, hydrogen bonding formation was analyzed by X-ray crystallography [3]. First the conformation of chiral phases derived from N-(3,5-dinitrobenzoyl)amino acids was theoretically studied [4], followed by the chiral recognition of (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol [5]. Further analysis of chiral phases with different analytes indicated that hydrogen bonding was important role for chiral recognition [6]. Complexes of (S)-methyl N-(2-naphtyl)alaninate with N-(3,5-dinitrobenzoyl) leucine n-propylamide were studied from the perspective of the interaction energy difference calculated by AM1, and through-space field effects was important for chiral recognition [7]. The chiral selectivity of (S)- and (R)-(1-naphthylethyl)-carbamoylated β-cyclodextrin bonded phases was studied using experimentally obtained free energy. The feasibility of predicting enantiomer separation was proposed [8].

The chiral recognition of N-butylylvaline-tert.-butylamide for (R)- and (S)-4-nitrobenzoyl amino acids was investigated using molecular mechanics calculation of CAChe™ [9]. Chiral recognition has been studied based upon the ligand exchange mechanism of binuclear copper (II) complex of N-salicylidene-(R)-2-amino-1,1-bis(2-butoxy-5-tert.-butyl-phenyl)-3-phenyl-1-propanol [10].

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).

RESULTS AND DISCUSSION

A chiral recognition molecule, binuclear copper (II) complex of N-salicylidene-(R)-2-amino-1,2-bis(2-butoxy-5-tert.-butylphenetyl)-3-phenyl-1-propanol and its analytes were constructed using the molecular editor program and their structure was optimized by molecular mechanics (MM2). The optimization was performed as the energy change was less than 10^{-6} Kcal/mol. The molecular weight of the chiral phase was 1449, and the final and van der Waals energies were 77.04 and -8.77 Kcal/mol, respectively. Three dimensional analysis suggested that the binding site is at the front of the structure shown in Fig. 1, due to the wide open space compared with the other side, where the site of the copper atom was very narrow. The nitrogen atom of the amino group or oxygen ion of carboxy group of analytes was bound with one copper atom which was more visible than the other. The water molecule, however was not bound to the copper atom which forms a hexadentate complex, because it did not geometrically interrupt the complex formation and the location should be opposite that of the analyte.

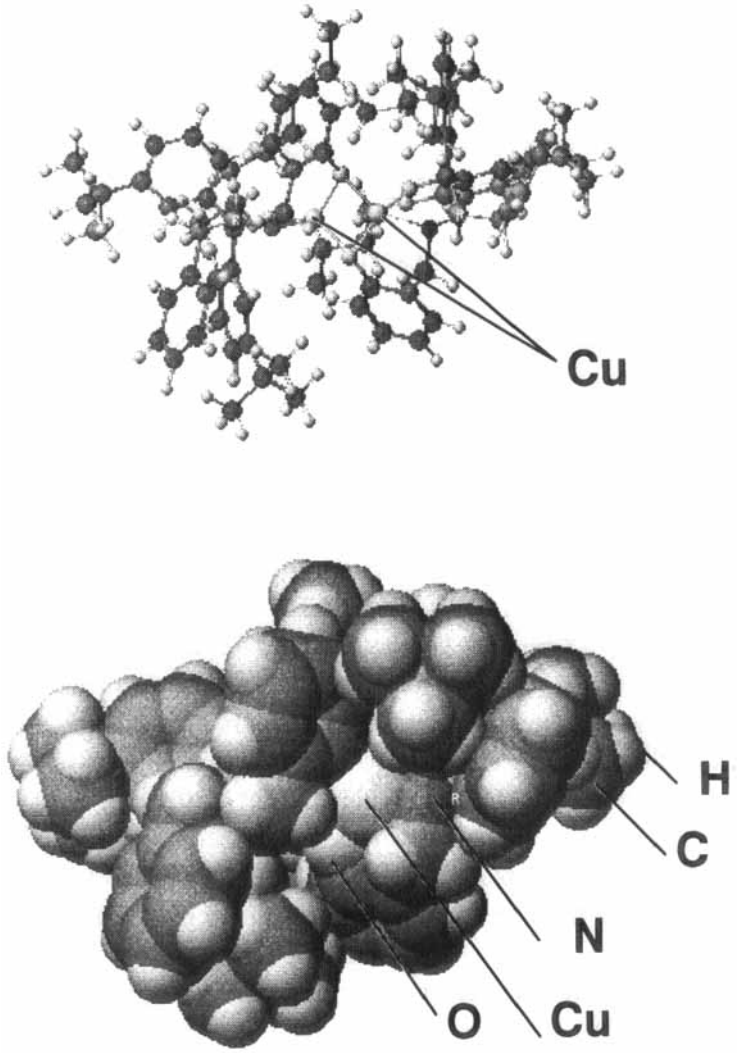

Fig. 1 Molecular structure of N-salicylidene-(R)-2-amino-1,2-bis(2-butoxy-5-tert.-butylphenetyl)-3-phenyl-1-propanol drawn at different atomic sizes (100 and 20%)

The calculated final and van der Waals energies are summarized in Table 1 with the values of the separation factor (α) taken from the literature [11]. The difference in the final energy value calculated from the molecular mechanics indicated chiral selectivity. The higher energy value of the complexes means that the elution is faster. The more stable the complex form is, the lower are the energy values. The energy difference roughly indicated the a values, however the correlation was not good enough for predictive accuracy. This may be due to the geometrical difference. The calculation was achieved in unlimited space, and the separation was performed in a very limited space if the packing material was well coated. The separation factor was also affected by the selectivity of the eluent.

The values of the van der Waals energy did not indicate the elution order, however, they were usually low for stable complexes. An example of complexes with (R)- and (S)-tyrosines is shown in Fig. 2a-d. Figure 2a and b shows front views of complexes with (R)- and (S)-tyrosines, and Fig.2c and d show upper views of complexes with (R)- and (S)-tyrosines.

The final energy values of the (R)- and (S)-tyrosine complexes are 77.5 and 68.3 Kcal/mol, respectively. These values are greater than the sum of the chiral phase (77.0 Kcal/mol) and tyrosine (-13.3 Kcal/mol). When the complex was formed at the opposite side of chiral phase, the final energy of the (S)-tyrosine complex was 153.1 Kcal/mol and that of the (R)-tyrosine complex was 141.0 kcal/mol. The energy difference indicted enantiomer separation, however the energy values were too big, and such complex formation is doubtful. The final energy of other complexes on the opposite side such as those of octamine, phenylglycinol, phenylglysine, 2-amino-1-phenylethanol and 1,2-diphenylethylamine, was also about 150 Kcal/mol. Complex formation on this side is undesirable.

Furthermore, chiral selectivity was studied by means of the molecular interaction model used in the analysis of enanti-

Table 1 Physical properties and separation factor (α) of enantiomers

Compounds	α	1*1	e*2	R-form FE*3	R-form VE*4	S-form FE*3	S-form VE*4
Amino alcohols							
2-Amino-1-phenylethanol	1.19		A	72.63	-5.41	70.24	-5.30
Atenolol	1.07		A	92.13	-1.98	94.99	-6.54
p-Hydroxynorephedrine (1R2S & 1S2R)	1.13		A	77.73	-3.40	79.01	-0.02
Norphedrine(1R2S & 1S2R)	1.11		A	80.26	-3.12	81.67	1.48
Normetanephrine	1.15		A	71.10	-5.28	71.66	-6.46
Norphenylephrine	1.23		A	69.96	-5.45	70.60	-6.14
Phenylalaninol	2.04		A	86.58	0.35	81.61	-2.30
Phenylglycinol	1.35		A	83.20	-6.50	74.55	-5.94
Propranolol	1.06		B	186.49	43.34	166.13	29.14
Amines							
α-Amino-e-caprolactam	1.91		A	94.38	-4.47	85.26	-6.17
Homocysteine thiolactone	1.19		A	110.58	-10.26	104.36	-8.55
Octopamine	1.30		A	69.19	-7.28	67.89	-5.47
Ketamine	1.26		B	173.54	32.55	188.35	34.80
1,2-Diphenylethylamine	1.64		B	68.41	-2.69	65.97	-6.38
1-Phenyl-2-(p-tolyl)ethylamine	1.62		C	68.38	-1.59	62.01	-7.60
Amino acids							
Aspartic acid	1.11	S	A	73.85	-4.21	77.23	-3.62
Histidine	1.18	R	A	96.72	-8.62	89.58	-10.66
Isoleucine	1.15	S	A	97.24	-0.91	99.47	-4.12
Leucine	1.09	S	A	90.96	-6.82	96.14	-6.93
t.-Leucine	1.34	S	A	97.36	0.43	109.10	3.51
Methionine	1.30	R	A	69.19	-7.28	67.89	-5.47
Phenylglycine	1.24	R	A	79.49	-1.66	71.86	-5.01
Proline	1.22	S	A	84.79	-8.34	91.32	-7.95
Serine	1.19	R	A	89.40	-5.87	86.51	-4.27
Tyrosine	2.06	R	A	77.50	-5.28	68.31	-6.97
Valine	1.29	S	A	89.24	-4.93	95.32	-2.83
3-Aminobutyric acid	1.20		A	88.01	-3.05	83.14	-3.37
3-Amino-2-methylpropionic acid	1.08		A	81.79	-6.92	80.23	-3.76
Phenylalanine	1.74	R	B	79.67	-5.48	72.36	-6.92
Tryprophan	2.05	R	B	83.61	-4.32	76.55	-8.52
Hydroxy acids							
Glyceric acid	1.13		B	84.55	-7.63	87.22	-8.25
2-Hydroxybutylic acid	2.19		B	94.71	-4.76	88.95	-9.12
3-Hydroxybutylic acid	1.16		B	76.81	-9.72	76.51	-8.97
Lactic acid	1.56		B	80.10	-7.56	86.29	-8.01

1: first eluted compound, 2: eluent A: 1mM copper(II) sulphate in water, B: 2mM copper (II) sulphate in 15% aq. acetonitrile, C: 2mM copper (II) sulphate in 20% aq. acetonitrile , 3: final energy (Kcal/mol), 4: van der Waals energy (Kcal/mol).

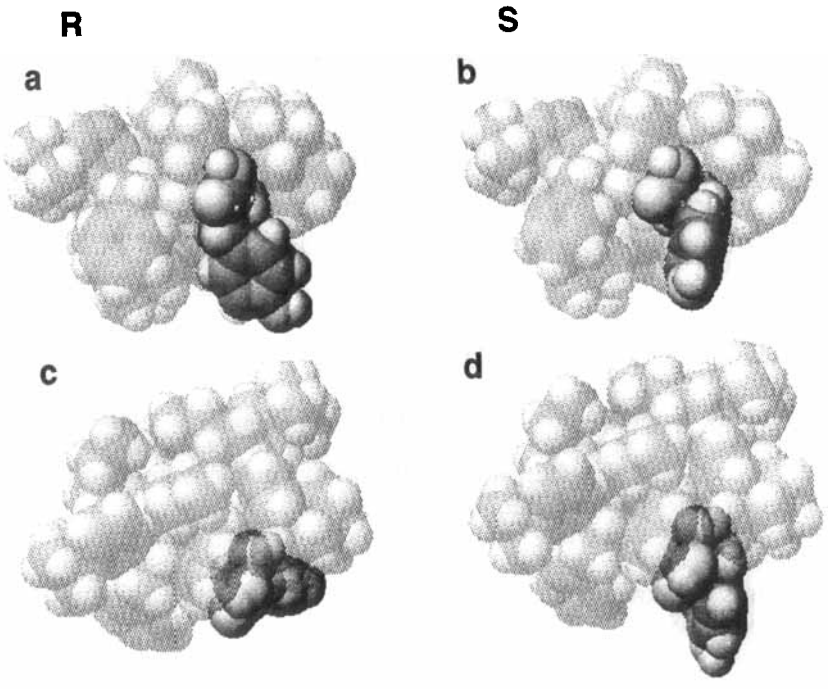

Fig. 2 (R)- and (S)-tyrosine complexes with N-salicylidene-(R)-2-amino-1,2-bis(2-butoxy-5-tert.-butylphenetyl)-3-phenyl-1-propanol. a and b : front view, c and d : upper view, respectively

omer selectivity in normal phase liquid chromatography [9]. The molecular mechanics calculation was performed after the amino group of an analyte was placed near the copper atom, but not bound to it. The calculated energy was low compared that of bound compounds, and the values of (R)- and (S)-form complexes were nearly equal, which did not indicate chiral recognition. The final energy values of the molecular interaction for (R)- and (S)-phenylglycine with this chiral phase were 58.4 and 60.9 Kcal/mol. Those for (R)- and (S)-1,2-diphenylethylamine, (R)- and (S)-octamine were 57.3, 58.2, 59.8 and 59.8 Kcal/mol, respectively. Further study of other

chiral recognition models will result in a method of column selection, and help to design new chiral phases.

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