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学　位　論　文　概　要
Dissertation Summary

学位請求論文（Dissertation）
題名（Title）耐溶剤型キラル固定相の開発、およびキラル・アキラル分離への応用と分子認識機構の研究
（英訳）（Title in English）*Development of immobilized chiral stationary phases, and studies on their applications to chiral and achiral separations and on their molecular recognition mechanisms*

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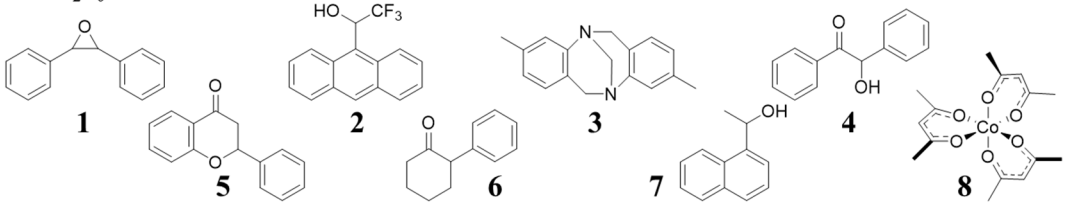
学位論文概要（Dissertation Summary）

For the purpose of this dissertation, the following terminologies are defined accordingly. “Chiral selector” is defined as an asymmetric chemical structure or a molecule, which enables to separate a pair of other enantiomers to each enantiomer through the non-equivalent interaction between its asymmetric structure and one of the enantiomers. “Chiral stationary phase (CSP)” is defined as a stationary phase for chromatography, in which a chiral selector is coated or immobilized on a support such as silica gel. “Chiral separation” is defined as a chromatographic separation of a pair of enantiomers. “Achiral separation” is defined as a chromatographic separation of molecules other than a pair of enantiomers, which is commonly recognized as an ordinary chromatographic separation. This dissertation deals with chiral and achiral separations by CSPs with a chiral selector, such as a

Table 1. Chromatographic separation factor α for CSPs with cellulose tris(3,5-dimthylphenylcarbamate) as chiral selector.

CSP Type		Conventional CSP	Immobilized CSP, Prototype	Immobilized CSP, Improved
Immobilization Technique		No immobilization (Coating)	Cross-linking, pending optimization	Cross-linking, after optimization
Separation Factor α	Enantiomers 1	2.6	1.0	1.9
	Enantiomers 2	3.1	1.9	2.4
	Enantiomers 3	1.7	1.1	1.2
	Enantiomers 4	1.6	1.2	1.4
	Enantiomers 5	1.4	1.1	1.3
	Enantiomers 6	1.3	1.1	1.1
	Enantiomers 7	1.3	1.8	1.5
	Enantiomers 8	1.2	1.1	1.0

$\alpha = \frac{t_1-t_0}{t_2-t_0}$. t_0: retention time of non-retained component. t_1 and t_2: retention times of enantiomers.



cellulose derivative, an amylose derivative, and a crown ether. To summarize, in this dissertation, CSPs with immobilized chiral selectors were developed by cross-linking technique. The improved cross-linking technique resulted in improved resistance of CSPs to a wide range of solvents while sacrificing the chromatographic separation factor (α) to a limited degree compared to the conventional CSPs prepared by the coating technique; 94% of enantiomers investigated were successfully resolved by the immobilized CSPs. Computational chemistry such as quantum chemical calculations gained insights to the molecular recognition mechanisms by chiral selectors.

(a) Development of CSPs with immobilized chiral selectors

High performance liquid chromatography (HPLC) technique coupled with a chiral stationary phase has been widely utilized for chiral separations since the development and commercialization of such stationary phases in 1980s. In those initial commercial products of CSP, chiral selectors were merely coated on silica gel, leaving a room for improvement in resistance to certain solvents such as ones swelling or dissolving the chiral selectors. In this dissertation, as continuous efforts by Daicel Corporation in improving the solvent resistance, immobilization of chiral selectors on CSPs were studied.

It was found in some early work that, when cellulose tris(3,5-dimethylphenylcarbamate) as a chiral selector was immobilized on silica gel by a cross-linking technique. HPLC experiments with the immobilized CSP revealed that this prototype of immobilized CSP ended up with poorer chromatographic separation factors (α) than corresponding conventional coating type CSP (Table 1). Through the investigation for the poor performance, the slightly reduced degree of substitution with 3,5-dimethylphenylcarbamoyl groups and the higher order structure formed in the immobilizing process are the key factors. Taking the findings into consideration, reaction conditions such choice of cross-linker, amount of cross-linker, and the likes were optimized, leading to improved chromatographic separations (Table 1).

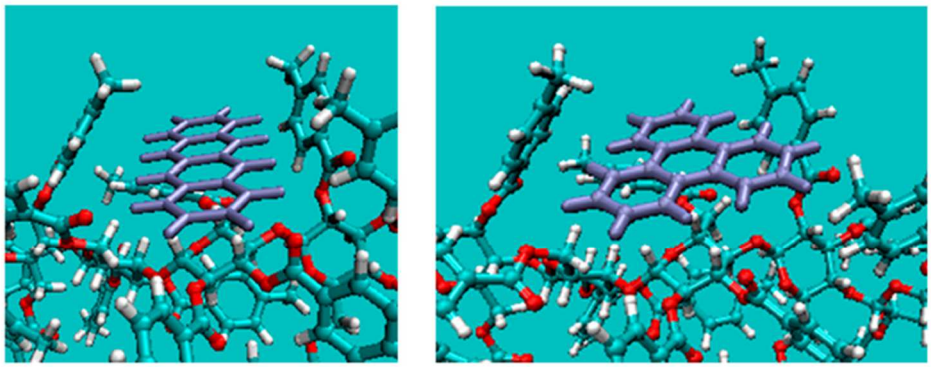


Figure 2. Models predicted *in silico* for the association of cellulose tris(4-methylbenzoate with naphthacene (left) and triphenylene (right), respectively.

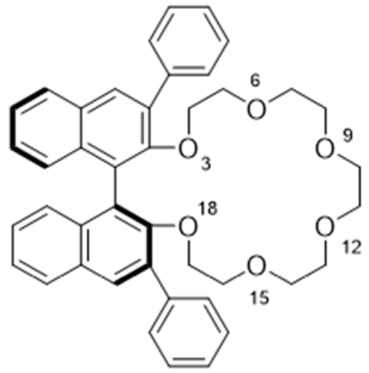
(b) Study on the applications of the immobilized CSPs to chiral separation

It is important to note that, as expected, the immobilization lead to a significant increase in choice of solvents as a mobile phase, which improved the success rate of chiral separation. With a view to further improving the success rate, six immobilized CSPs in total were developed. The chiral selectors were (i) amylose tris(3,5-dimethylphenylcarbamate), (ii) cellulose tris(3,5-dimethylphenylcarbamate), (iii) cellulose tris(3,5-dichlorophenylcarbamate), (iv) amylose tris- (3-chlorophenylcarbamate), (v) amylose tris(3,5-dichlorophenylcarbamate) ,and (vi) amylose tris(3-chloro-4-methylphenylcarabamate). Among 123 pairs of enantiomers tested, 115 pairs (94% of the enantiomers tested) were successfully separated by means of one or more of the 6 CSPs developed.

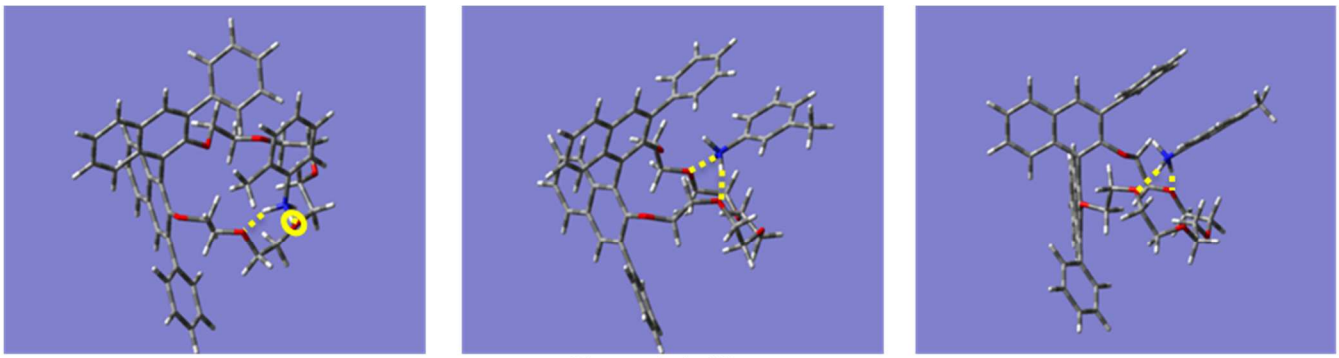
(c) Studies on the applications of CSPs to achiral separation, and the molecular recognition mechanisms

It has been recognized that CSPs are often useful for achiral separations. In this dissertation, achiral separations by chiral CSPs with cellulose derivatives as a chiral selector, and a CSP with immobilized crown ether ligand were studied. A series of condensed aromatic hydrocarbons were employed as achiral analytes for the cellulosic CSPs. Aniline and substituted anilines were employed as achiral analytes for the crown ether CSP.

Computational chemistry such as quantum chemical calculations gained insights to the molecular recognition mechanisms by chiral selectors; in the case of cellulosic chiral selectors such as cellulose tris(4-methylbenzoate), a space surrounded by main chain glucose units and side chains could play an important role for the molecular recognition (Figure 2). In the case of chiral selector with crown ether ligand (Scheme 1), the quantum chemical calculations suggested that, contrary to the well known three-point binding mechanism presented by Cram, a two-point binding or an anomalous three-point biding was expected to take place between anilines and the ligand (Figure 3).



Scheme 1. Ligand structure of CROWNPAK® CR-I (+), (*S*)-(+)-(3,3-diphenyl-1,1-binaphtyl)20-crown-6



(a) 2-methylaniline (most stable structure) (b) 3-methylaniline (c) 4-methylaniline

Figure 3. Models predicted *in silico* for the association of crown ether ligand and anilines.

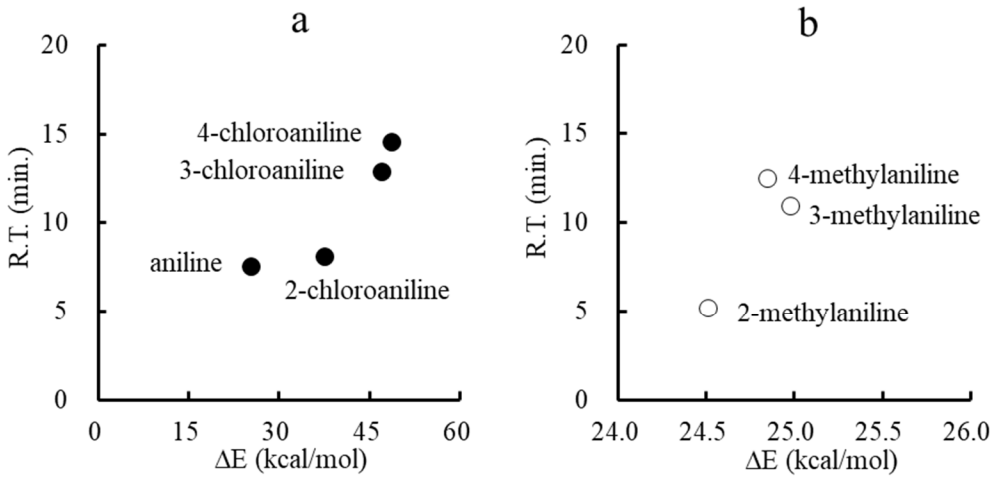


Figure 4. Retention time (R.T.) of anilines in achiral separation by CSP with crown ether ligand, (S)-(+)-(3,3-diphenyl-1,1-binaphtyl)20-crown-6 as a function of stabilization energy (ΔE) derived from quantum chemical calculation.
a: chloroanilines. b: methylanilines.

The

stabilization energies derived from the quantum chemical calculations were in good accordance with the elution behaviors of a series of chloroanilies (Figure 4a). The correlation between the stabilization energies and the elution behavior of methylanilines was not as clear as that of chloroanilines; however, it is important to note that, even in the case of methylanilines, the quantum chemical calculation approach reproduced the tendency that the ortho substituted one is to be retained in the weakest manner (Figure 4b). These results gain insights to the potential and limitations of the quantum chemical calculation approach in the fields of chiral and achiral separations.

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