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β-Cyclodextrin-Enhanced Solubilization of Phenylsulfonyl Carboxylates in Water

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Cyclodextrins (CDs) are glucose-based molecules and produced from the enzymatic degradation of starch by bacteria. There are three main cyclodextrins named as α,β,γ-cyclodextrin, which are comprised of 6,7,8 glucose units, respectively. β-cyclodextrin (β-CD) is produced at commercial scales and the least expensive one (Li et al. 1992; Frömming et al. 1994; Szejtli 1996). Cyclodextrins have hydrophilic outer surface and a somewhat lipophilic central cavity. Cyclodextirns are able to form water-soluble inclusion complexes with many lipophilic organic compounds in appropriate shape and size (Szejtli 1996). This property provides CDs with several capacities such as the solubility and bioavailability effect on the hydrophobic organic pollutants (Gao et al. 1998; Song et al. 1999; Wang and Brusseau 1993). The application of CDs as solubility-enhancing agents for remediation of contaminated soils and subsurface water has been investigated (Brusseau et al. 1994; Chatain et al. 2004; Ji and Brusseau 1998).

Aromatic sulfones are extensively used as intermediates in the manufacture of pesticides, herbicides and anthelmintics, and also as floatation agents and extractants in the petrochemical and metallurgical industries (Han et al. 1992). Lots of aromatic sulfones could be discharged into ecological environment and impact the environment in a number of ways. Consequently, there is a need to investigate the physicochemical properties and ecological effects of the compounds. Up to now, no reports have appeared concerning the cyclodextrin-complex effect on the environmental behaviors of aromatic sulfones.

To avoid the costly and time-consuming environmental testing, the quantitative structure–property relationships (QSPRs) have been effectively used to screen large classes of chemicals (Nirmalakhandan and Speece 1988). QSPRs between the descriptors of chemicals and their physicochemical properties have been extensively studied (Faucon et al. 1999). The development of QSPRs can aid to understand the mechanism and obtain a reliable model for predicting the properties

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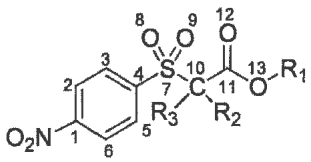
of new chemical substances. The electrotopological state (*E*-state) index combines the electronic state of the bonded atom within the molecule with its topological nature in the context of the whole molecular skeleton. The *E*-state indices have been used to develop models for many pysicochemical properties and put forward a significant method (Arupjyoti and Iragavarapu 1998; Hall et al. 1991; Huuskonen et al. 2000; Kier and Hall 1990).

In this paper, the ability of β-cyclodextrin enhancing the apparent aqueous solubility of 10 phenylsulfonyl carboxylates was determined and evaluated. With the octanol-water partition coefficients (K_{OW}) (Liu et al. 2001) and the electrotopological state (*E*-state) indices, the QSPRs models for the stability constants (K_S) of inclusion complexes were obtained. The quality of the two models and the mechanism of inclusion complexes are discussed.

MATERIALS AND METHODS

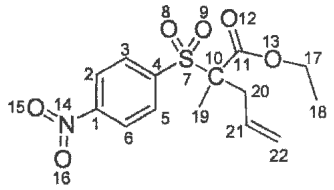
β-cyclodextrin (β-CD) was obtained from Sigma (St. Louis, MO, USA), and used without further purification. Ten phenylsulfonyl carboxylates (listed in Table 1) were supplied by the Laboratory of Organic Synthesis of Nanjing University. The purity was monitored by HPLC to ensure that no interference peaks occurred.

Table 1. List of phenylsulfonyl carboxylates.



No.	R_1	R_2	R_3
1	CH_3	H	CH_3
2	CH_3	CH_3	CH_3
3	CH_3	CH_3CH_2	CH_3CH_2
4	CH_3	$CH_3CH_2CH_2CH_2$	$CH_3CH_2CH_2CH_2$
5	CH_3CH_2	$CH_3CH_2CH_2CH_2$	$CH_3CH_2CH_2CH_2$
6	CH_3CH_2	CH_3	CH_2=$CHCH_2$
7	$(CH_3)_2CH$	$CH_3CH_2CH_2CH_2$	$CH_3CH_2CH_2CH_2$
8	CH_3	H	$CH_3CH_2CO_2CH_2$
9	$(CH_3)_2CH$	H	$(CH_3)_2CHCO_2CH_2$
10	$(CH_3)_2CH$	$CH_3CH_2CO_2CH_2$	$CH_3CH_2CO_2CH_2$

Table 2. List of the properties for the molecular skeleton of compound 6.



Atom ID	Atom type	*E-state* Symbol	*E-state* value	Atom ID	Atom type	*E-state* Symbol	*E-state* value
1	aasC	S_1	-0.268	12	dO	S_{12}	12.605
2	aaCH	S_2	1.074	13	ssO	S_{13}	4.379
3	aaCH	S_3	1.103	14	ddsN		-0.637
4	aasC	S_4	-0.017	15	dO		10.641
5	aaCH	S_5	1.103	16	dO		10.641
6	aaCH	S_6	1.074	17	$ssCH_2$		0.052
7	ddssS	S_7	-4.093	18	sCH_3		1.553
8	dO	S_8	12.735	19	sCH_3		1.220
9	dO	S_9	12.735	20	$ssCH_2$		-0.135
10	ssssC	S_{10}	-1.829	21	dsCH		1.319
11	dssC	S_{11}	-0.878	22	dCH_2		3.462

Table 3. The atom-type and grouped *E-state* properties of compound 6.

Atom-type *E*-state Symbol	Atom-type *E*-state Value	Atom-type *E*-state Symbol	Atom-type *E*-state Value	Functional Group	Grouped *E*-state Symbol	Grouped *E*-state Value
S_{sCH3}	2.773	S_{aaCH}	4.354	(>SO_2)	$S_{(>SO2)}$	21.377
S_{ssCH2}	-0.083	S_{aasC}	-0.285			
S_{ssssC}	-1.829	S_{ddssS}	-4.097	(–CO_2–)	$S_{(-CO2-)}$	16.115
S_{dCH2}	3.462	S_{dO}	59.357			
S_{dsCH}	1.139	S_{ssO}	4.379	(–NO_2)	$S_{(-NO2)}$	20.645
S_{dssC}	-0.878	S_{ddsN}	-0.637			

For the solubility measurements, 25 mL solution in varying concentrations of β-CD were poured in 50mL stoppered conical flask, and the compound was added in quantities in excess of the solubility limit. Triplicate flasks were prepared for each β-CD concentration. The blanks were prepared in an identical manner with no β-CD added. All samples were equilibrated on a reciprocating shaker for at least 2 days at 25±0.5℃ until the absorbency of solution did not change any longer. After equilibration, a 0.5 mL aliquot of the centrifuged supernatant was then withdrawn and diluted with 50:50 methanol/water solution in 10 mL volumetric flask. The role of methanol is to decompose the β-CD-solute complexes, thereby keeping the UV spectrum unchanged. Samples were then analyzed by UV-VIS

spectrophotometer (Perkin-Elmer). All tests were conducted in triplicate at each β-CD concentration.

The *E*-state indices of each atom in the compound molecular skeleton were calculated (Hall and Kier 1995); the atom-type and group-type *E*-state indices were acquired, respectively. In the molecular skeleton, all atoms of the same type are grouped and their *E*-state values are summed to make the atom-type *E*-state index. Likewise, the *E*-state values of the all functional group atoms are summed to make the grouped *E*-state index. The *E*-state indices were consisted of 13 atom *E*-state indices from S_1 to S_{13}, 12 atom-type and 3 grouped *E*-state ones. The properties for the molecular skeleton and *E*-state indices of Compound 6 are listed in Tables 2 and 3.

The QSPRs models between $\lg K_S$ and the structural descriptors were constructed by the stepwise regression analysis using the SPSS 11.5 software package (SPSS Inc., 1989-2002). The best fit of the predicted $\lg K_S$ values to the experimental data was performed by the linear least-squared method. The QSPRs model quality was measured by the squared correction coefficient (r^2_{adj}) (adjusted for degrees of freedom), the standard deviation (*SD*), the *F* test value (*F*), and the significance level of the *F* value (*P*).

RESULTS AND DISCUSSION

In the aqueous solution of β-cyclodextrin, the apparent solubility of phenylsulfonyl carboxylates is observed to increase linearly with the cyclodextrin concentration below $4.0 g \cdot L^{-1}$. The phenomenon is attributed to the formation of 1:1 inclusion complexes (Connors et al. 1987; Higuchi et al. 1965), as described by Equation 1.

$$S + CD \xleftrightarrow{K_S} CD - S \qquad (1)$$

Where K_s is the stability constant of complex, *S* is the uncomplexed dissolved compound, CD is the uncomplexed cyclodextrin and CD-S the complexed solutes.

In cyclodextrin solution where the free and complexed solutes exist, the total aqueous-phase solute concentration (S_t) includes both free and complexed species. For a solution in contact with a separate-phase organic compound, the free solute concentration can be regarded as the aqueous solubility (S_0) and the complexed solute concentration can be caculated from (S_t–S_0). The concentration of free cyclodextrin can be calculated by (C_0–S_t+S_0), in which C_0 is the initial concentration of cyclodextrin. For the low-solubility organic compounds, the relationship between S_t and S_0 is modeled by Equation 2.

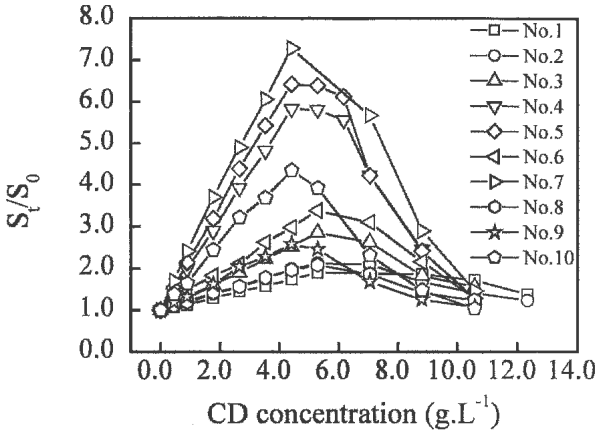


Figure 1. Plot of S_t/S_0 versus the initial concentration of β-CD.

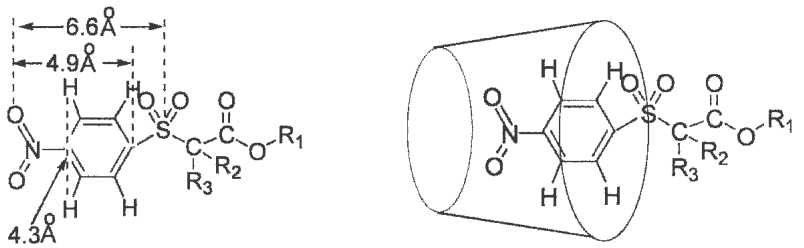


Figure 2. Molecular dimensions of compounds and configuration of complexes.

$$S_t = S_0(1 + K_S C_0) \qquad (2)$$

The relative aqueous-phase concentration (S_t/S_0) of the compounds is plotted against the β-CD concentration in Figure 1. The results show that the solubility of phenylsulfonyl carboxylates is not linearly increased with β-CD concentration. When the compound concentration is low (less than 4.0g·L^{-1}), the apparent solubility of phenylsulfonyl carboxylates is linearly increased with increasing β-CD concentration. The plot may be ascribed to the formation of 1:1 inclusion complexes in solution.

For the cyclodextrin molecule, the hydrophilic surface with hydroxy groups generates good aqueous solubility and the hydrophobic cavity provides a favorable environment in which a typically hydrophobic molecule pronounced as "guest

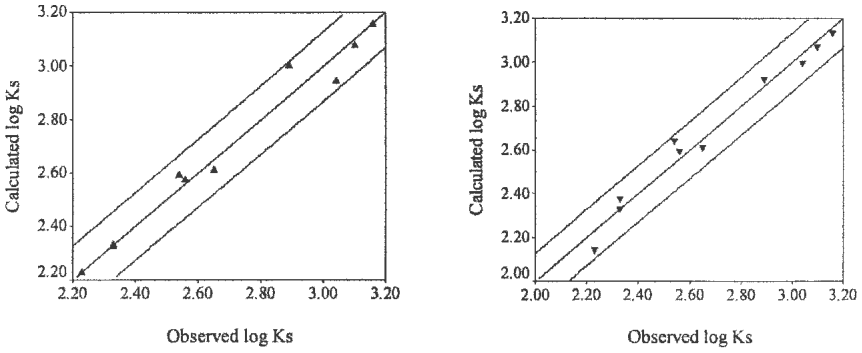


Figure 3. Plot of observed versus predicted lgK_S values from Equations 3 and 4.

molecule" is suitable. Many studies have demonstrated that there exists a quantitative relationship between CD association constants and the hydrophobic property of guest molecules.

Figure 2 illustrates the schematic illustration of inclusion complexation of phenylsulfonyl carboxylates. For phenylsulfonyl carboxylates, the low-polarity phenyl groups are important functional groups and suitable for the hydrophobic β–CD cavity. For the inclusion complexes, the phenyl groups are proposed to be located inside the β–CD cavity and the high-polarity groups such as >SO_2 and –CO_2– stay outside of β–CD cavity.

It has been generally accepted that the binding forces involved in the formation of inclusion complex are (i) van der waals interactions (or hydrophobic interactions) between the hydrophobic moiety of guest molecules and the cyclodextrin cavity, (ii) hydrogen bonding between the polar functional groups of guest molecules and the hydroxyl groups of cyclodextrin, (iii) release of "enthalpy rich" water molecules from the cavity in the complex formation process.

Table 4. The QSPR models of the stability constants (K_S) of inclusion complexes.

No.	QSPRs models (n = 10)	r^2_{adj}	SD	F	p
3	$\lg K_S = 1.896 + 0.310 \lg K_{OW}$	0.972	0.057	315.96	<0.001
4	$\lg K_S = -4.673 + 0.341 S_{(>SO_2)}$	0.971	0.059	302.47	<0.001

For the compounds, the van der Walls forces between the low-polar phenyl and the hydrophobic cavity of CD are important factor. The OH group of cyclodextrin plays a major role in the aqueous solubility of cyclodextrin and the stability of inclusion complexes. The stability of inclusion complexes are enhanced by hydrogen-bonding interaction between the oxygen atom of $>SO_2$ and hydrogen atom of OH at CD port. Compared with the water molecules as the solvent, the H_2O inside cyclodextrin cavity cannot possess its tetrahedral hydrogen bonding capacity and has high energy. The release of "high energy" water molecules from the cyclodextrin cavity can make the CD inclusion system more stable.

Table 5. The lgK_{OW}, sulfonyl group *E-state* values, the observed, calculated and residual values of lgK_S.

No.	lg K_S			Residuals (lgK_S)		lgK_{OW}	$S_{(>SO2)}$
	Observed	Calculated					
		Eq.3	Eq.4	Eq.3	Eq.4		
1	2.23	2.23	2.14	0.00	0.07	1.06	20.00
2	2.33	2.32	2.33	0.01	0.00	1.38	20.55
3	2.54	2.59	2.64	-0.05	-0.10	2.24	21.47
4	3.04	2.94	3.00	0.10	0.04	3.38	22.50
5	3.10	3.08	3.07	0.02	0.03	3.81	22.73
6	2.65	2.61	2.61	0.04	0.04	2.30	21.38
7	3.16	3.16	3.14	0.00	0.02	4.06	22.91
8	2.33	2.33	2.38	0.00	-0.05	1.40	20.69
9	2.56	2.57	2.60	-0.01	-0.04	2.18	21.33
10	2.89	3.00	2.92	-0.11	-0.03	3.56	22.29

For further study on the mechanism of inclusion complexes, the octanol-water partition coefficient K_{OW} and *E-state* index of chemicals are introduced to simulate the stability constant (K_S) of complexes, and the regression equations 3 and 4 were presented in table 4. The calculated and residual results are listed in table 5. Figure 3 illustrates the prediction of K_S versus observed values. The high squared correlation coefficients of 0.972 and 0.971 as well as the low standard deviations show that the models are reliable. Figure 3 illustrates that the models are remarkably predictive, and the residues between -0.11 and 0.10 log units (Table 5) show that the models are reliable. It is believed that QSPRs models 3 and 4 could be used to evaluate the stability constants of CD inclusion complexes of the kind of compounds.

In Model 3, the positive correlation relationship between the stability constant (K_S) and the octanol/water partition coefficients (K_{OW}) indicates that the hydrophobic

interaction plays the dominant role in the formation of the β-CD inclusion complexes. In Equation 4, the positive correlation relationship between $\lg K_S$ and the *E*-state value $S_{(>SO2)}$ shows the hydrogen-bonding interaction has a significant influence on the stability of the β–CD inclusion complexes as well. The *E*-state index of sulfonyl group $S_{(>SO2)}$ stands for the characteristic structure information of the chemicals. In the sulfonyl group $>SO_2$, the high *E*-state value of oxygen atom and the low *E*-state value of sulfur atom indicate that the $>SO_2$ is high-polarity group. The structure analysis of compounds indicates that the hydrophobicity of R_2 and R_3 groups has a positive effect on the *E*-state value $S_{(>SO2)}$ and the stability of inclusion complexes. For the compounds of No.1-4 and No.7,9,10, the structure analysis indicates that the *E*-state value $S_{(>SO2)}$ of sulfonyl group and the stability of inclusion complexes increase with the more hydrophobility of alkyl-group R_1.

On the basis of 1:1 β-cyclodextrin inclusion complexes, β-CD can enhance greatly the aqueous solubility of the investigated phenylsulfonyl carboxylates. The stability constants $\lg K_S$ of β-CD inclusion complexes have good linear correlation with the hydrophobic capacity (K_{OW}) and the *E*-state value $S_{(>SO2)}$ of sulfonyl group $>SO_2$. For the aromatic sulfones, the compound hydrophobicity, the van der Waals force and hydrogen-bonding interaction between "guest molecule" and "main body" play an important role in the stability of inclusion complexes, and these properties can enhance the solubilization of phenylsulfonyl carboxylates in water.

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