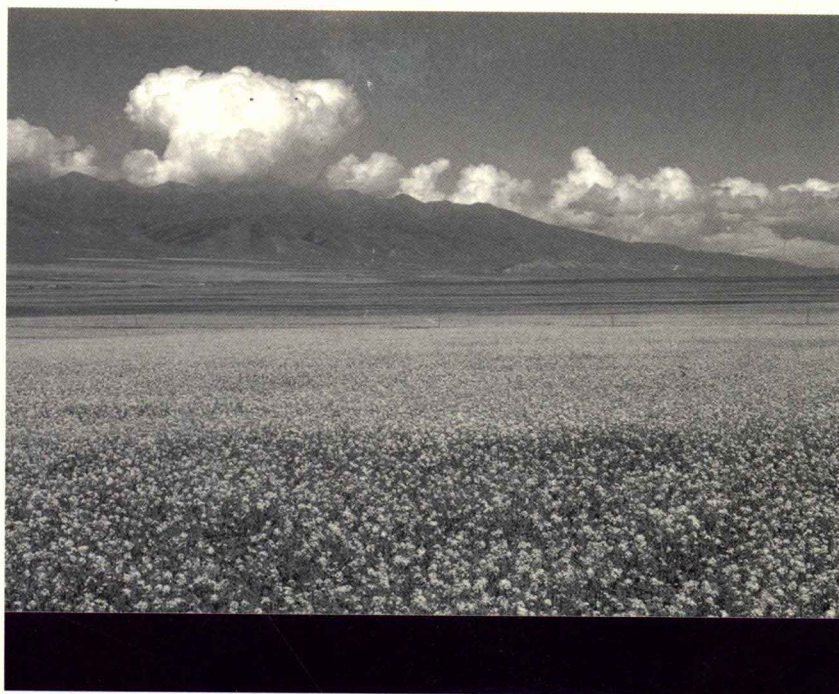


Wang Liansheng

王连生

Advances in Chemistry of Organic Pollutants

有机污染化学进展



Chemical Industry Press



化学工业出版社
环境·能源出版中心

图书在版编目 (CIP) 数据

Advances in Chemistry of Organic Pollutants/Wang Liansheng.

—北京：化学工业出版社，2005.10

ISBN 7-5025-7783-1

I. Advances… II. ①Wang… III. Organic-Chemistry-Advances
IV. X5-53

中国版本图书馆 CIP 数据核字 (2005) 第 125149 号

Advances in Chemistry of Organic Pollutants

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化学工业出版社 出版发行
环境·能源出版中心

(北京市朝阳区惠新里 3 号 邮政编码 100029)

购书咨询：(010) 64982530

(010) 64918013

购书传真：(010) 64982630

<http://www.cip.com.cn>

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新华书店北京发行所经销

化学工业出版社印刷厂印装

开本 787mm×1092mm 1/16 印张 22½ 字数 787 千字

2006 年 1 月第 1 版 2006 年 1 月北京第 1 次印刷

ISBN 7-5025-7783-1

定 价：98.00 元

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前 言

有机污染是当前人类面临的主要环境问题之一。有机污染物进入环境后，将会经历一系列复杂的过程，最终对生态环境产生影响，由于环境体系的复杂多变性以及环境有机污染物数量众多，有机污染问题也是目前最具挑战性的环境问题之一。有机污染化学是研究有机污染物环境变化过程的一门科学，是环境化学、生命科学、化学、数学等学科相互交叉、融合形成的一门新兴边缘学科，是环境科学前沿的研究领域之一。

本课题组从事有机污染化学的教学科研工作达 26 年之久，先后出版了多本相关的专著和教材，连续出版了《有机污染化学进展》第一卷（1991）和第二卷（1998），以及《Quantitative Structure-Activity Relationships》（1998），反映了相关领域的研究进展。

本书主要介绍了本课题组自 1998 年以来的部分研究工作，值得指出的是，书中的论文全部发表于 SCI 源刊物（中文版主要介绍国内刊物发表的内容，二者内容完全不同），因此相当程度上代表了国际相关领域的研究前沿。

有机污染物的微观分子结构是决定污染物外在性质的内因，研究有机污染物分子结构与其性质、生物活性的关系能对化学物质的环境行为和生物活性进行预测，从而为有毒化学品的风险评价和污染控制提供理论指导和便捷途径。本书共分三个部分，全面阐述了典型有机污染物的环境行为与生态毒性、分析技术和控制原理、结构-性质/活性关系和相关估算方法。

为了有效地解决环境有机污染问题，实现“污染预防”战略，必须对环境有机污染物的潜在危害性进行科学评价，这需要对有机污染物在环境中的迁移、转化行为和生态毒性效应等问题进行系统研究，对有机污染物的环境过程机制和毒性机理等具有科学、准确的认识。本书第一部分对典型有机污染物的环境行为和生态毒性效应进行了介绍。环境行为部分（第一章）内容包括有机污染物在复杂环境介质中的吸附、降解、分配、释放等行为，还涉及环境共存物质（例如环糊精）对有机污染物的环境行为的影响等。生态效应部分（第二章）包括典型有机污染物对生态系统不同层次终点的毒性效应及相关作用机理，例如对区域生态系统、对生物体内抗氧化系统酶系、对生物有效性等的影响以及有机污染物与共存重金属的联合效应等。

本书第二部分对定量结构-性质/活性关系的理论方法及应用实践进行了重点介绍，内容包括 QSAR/QSPR 方法及其应用（第三章）、典型有机污染物的定量结构-毒性关系（第四章）、有机污染物理化性质的测定与估算方法（第五章）、分子全息与 3D-QSAR 方法的理论与应用（第六章）、混合有机物的定量结构-联合毒性关系（第七章）。定量结构-活性关系研究目前出现了几个发展趋势：传统的 QSAR 研究越来越依赖于对污染物量子结构的描述，因为基于量子力学计算得到的参数具有明确的物理意义，有利于对作用机理的解释；QSAR 建模方法越来越依赖于多变量统计和人工智能技术，因为后者具有强大的处理非线性复杂问题的能力；三维分子建模技术能够真实模拟污染物与生物体系受体分子之间在微观层次的复杂相互作用，可以更直观地解释化学-生物相互作用机理，基于三维分子结构模拟的 3D-QSAR 技术在环境科学中得到了越来越多的应用。对上述发展趋势，本书从理论和应用上都给予了详细介绍。目前结构-活性关系研究主要局限于单一污染物组分，然而现实中污染物却总是以多种污染物的复合体系存在，那么污染物复合体系具有什么样的环境行为规律和毒性作用特点？复合体系的性质/活性与单一体系之间具有什么样的关系？是否存在复合体系的定量结构-活性关系呢？这是世界范围内尚未得到很好解决的重大科学问题，本书对本课题组在混合有机物的联合毒性及结构-活性关

系方面的一些研究成果也进行了介绍。

有机污染物的分析技术是进行有机污染化学研究的基本手段，而控制原理是发展有机污染物治理技术和设备的基础前提。目前在世界范围内大家都非常关注持久性有机污染物（POPs）和环境内分泌干扰物质（EDCs）等，这些物质在环境中含量非常低，但是却具有很强的生物累积性，很难降解，并对高等生物和人类的生存和持续繁衍产生威胁，对这些物质的分析和控制是我们面临的巨大挑战。本书的第三部分介绍了典型有机污染物的分析技术与控制原理。第八章中介绍了大气、水体、土壤及沉积物中典型有机污染物的前处理和痕量分析技术，第九章介绍了部分有机污染物的控制原理以及影响因素，其中多处涉及持久性有机污染物的研究。

综上所述，本书为近几年来我们在有机污染化学领域部分科研工作结果的汇编，希望能够介绍给国内外同行，以便相互交流，共同促进该学科的发展，也为中国环境科学研究和教育事业尽一份力。本书的研究成果主要是在国家自然科学基金资助下完成的，在此表示感谢！

本书可以供环境科学、环境工程、生命科学、化学化工、药物化学、农业化学等专业的读者阅读，也可以供有关从事科研及管理的人员参考。

王连生
2005 年 8 月

Preface

Organic pollutant is of great concern and it is one of the most challenging environmental issues due to the complexity of environmental system and the vast number of the organic pollutants. The organic pollutants entering the environmental media will undergo various complicated processes and pose adverse effect on ecosystem and human health. Thus Chemistry of Organic Pollutants deal mainly with the changes of organic pollutants in the environment and it is formed by the interaction of Environmental Chemistry, Biology, Chemistry, Mathematics and so on. It covers many frontier research areas in Environmental Science.

The research activities of our group on organic pollutants have been lasting for more than 26 years and these researches resulted in many related monographs and textbooks. We also published "Advances in Chemistry of Organic Pollutants (Vol. 1, 1991 and Vol. 2, 1998)" and "Quantitative Structure-Activity Relationships (QSARs)(1998)", while as the English edition of Advances in Chemistry of Organic Pollutants, this edition cover part of the research work of our group after 1998.

The molecular structures determine the extrinsic properties/activities of organic pollutants, and the study on relationship between molecular structures and properties/activities will be helpful for the prediction of environmental behaviors and bio-activities of organic pollutants, thus provides theoretical guidance and handy tools for risk assessment and control of organic pollutants. The environmental behavior and ecotoxicology, analytical techniques and control principles, structure properties/activities relationships and relation estimation approaches are expounded in three parts in this book, individually.

To prevent the pollution of organic compounds, the risk of environmental organic pollutants must be scientifically evaluated and the transportation, transformation and ecotoxicology of organic pollutants and the related mechanisms must be explored. In Part I of this book, the environmental behavior and ecotoxicology of organic pollutants are introduced. In Chapter 1, the adsorption, degradation, partition, release of typical organic pollutants and the effect of coexisted substances such as cyclodextrin in complex environmental media, are addressed. In Chapter 2, the toxic effect and related mode of actions of selective organic pollutants to various tropical levels of organisms were addressed. This will includes the effect on regional ecosystem, enzymes in anti-oxidation system, bio-availability and the combined effect of organic pollutants and coexisted heavy metals.

In Part II, methodologies and application of QSAR/QSPRs were stressed, such as QSAR/QSPR related approaches and their application (Chapter 3), ecotoxicity and QSARs of selective organic pollutants (Chapter 4), determination and estimation approaches for physico-chemical properties of organic pollutants (Chapter 5), application of molecular hologram theory and 3D-QSAR methodologies (Chapter 6), the joint toxicity and QSARs of chemical mixtures (Chapter 7). Up to now, the development of QSAR/QSPR methodologies relies more and more on quantum chemistry, advanced statistical tools, molecular modeling and 3D structural description because these provide more powerful tools to get insight into the chem-bio interaction mechanisms and the complex nonlinear relationships between structure and bioactivity.

The issues of mixtures are among the far from resolved scientific problems in environmental science. The study on QSAR focuses on single pollutant up to now, while all pollutants existed in the environmental media in mixtures. We know nothing about the difference of single pollutant and the pollutants mixtures on their environmental behaviors regularity and ecotoxic mode of action, we neither know if the frameworks of QSAR can be expanded in to the area of chemical mixtures. In this part, some research results of our group on the combined toxicity and structure-activity relationships of chemical mixtures are introduced.

Analytical techniques are basic tools for scientific study in Chemistry of Organic Pollutants and control concepts are preconditions for development of treatment technologies and equipments for organic pollutants. Scientists, public and the governments all over the world are staring at the so-called persistent organic pollutants (POPs) and environmental disrupting chemicals (EDCs). These pollutants existed in extreme low concentration in the environmental media while they are highly bio-accumulative, non-degradable, and toxic, thus pose risk on the survival and sustainable reproduction of advanced animals and human beings. In Part III the analytical techniques and control concepts of some organic pollutants are involved. In Chapter 8 the pretreatment and trace analytical techniques of some organic pollutants in atmosphere, water body, soils and sediments are introduced and in Chapter 9 the concepts and the influencing factors for the control of organic pollutants (especially POPs) are involved.

In one word, this edition is a collection of research results of our group on organic pollutants. We sincerely wish the publication of this edition will promote the communication and interaction of the researchers in this area, speed the development of chemistry of organic pollutants and contribute to the scientific research and education of environmental science of China. We acknowledge National Natural Science Foundation of China for their financial support for the research work.

This edition will be useful for the researchers, teachers and governors in environmental science, environmental engineering, life sciences, chemistry and chemical engineering, medicinal chemistry, agrochemistry.

Wang Liansheng
2005. 8

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Part I Environmental Behavior and Ecological Effect of Organic Pollutants

(第一部分 有机污染物的环境行为与生态效应)

Chapter 1 Environmental Behavior of Organic Pollutants (第一章 有机污染物的环境行为)

1 Solubilization of polycyclic aromatic hydrocarbons by β -cyclodextrin and carboxymethyl- β -cyclodextrin

Gao Shixiang, Wang Liansheng, Huang Qingguo, Han Shuokui

(Adapted from Chemosphere, 1998, 37 (7): 1299-1305)

Abstract: The solubilization of six polycyclic aromatic hydrocarbons (PAHs) by β -cyclodextrin and carboxymethyl- β -cyclodextrin (CMCD) has been investigated. The presence of β -CD and CMCD greatly enhance the solubility of PAHs in water. The solubilization effect of cyclodextrins is caused by formation of inclusion complexes of PAHs with cyclodextrin. The degree of solubilization power is related to the "fit" of PAH structure within the cavity of β -CD or CMCD. The better the fit of the molecule, the greater the solubilization power. β -CD shows higher solubilization power than CMCD at low concentration.

Keywords: solubilization, β -cyclodextrin, carboxymethyl- β -cyclodextrin, PAHs

Polycyclic aromatic hydrocarbon (PAHs) are poorly soluble, hydrophobic organic compounds that have been released to the environment on a large scale. They are distributed in air, water, and soil. Because many PAHs are carcinogens, their presence in the environment is undesirable. Especially PAHs in soil, which can be accumulated and transported into agricultural plants, may cause raised PAH contents in grains.

The cleanup of soil contaminated by low polarity organic compounds usually use the method of solubilization of cosolvents of surfactants, which can improve the transport speed of contaminants from soil into the water phase^[1,2]. However, each of these methods has its drawbacks. The solubilization of cosolvents is usually not significant until their volume-fraction concentrations are above 10%; and surfactants may form high viscosity emulsions that are difficult to remove. It has been reported that cyclodextrins may be considered as alternative solubilization reagents for soil cleanup. Hydroxypropyl- β -cyclodextrin can enhance the water solubility of several low-polarity organic compounds significantly^[3]. Because the extremely low

solubility of PAHs in water, cyclodextrins and their derivatives may be attractive reagents for enhancing water solubilities of PAHs.

Cyclodextrins, first isolated in 1891^[4], are cyclic oligomers of glucose produced by the action of certain bacterial enzymes on starch^[5]. Cyclodextrins have a doughnut-shaped structure with a relatively hydrophilic exterior and a relatively hydrophobic interior "hole"^[6]. Low-polarity organic substances with a size and shape complementary to the hole form inclusion complexes with cyclodextrins^[7]. Because of the hydrophilic exterior, the solubility of organic compound-cyclodextrin complexes are usually much higher than the pure compounds, hence increasing the apparent solubility of organic compounds in water. Cyclodextrins have found several other applications in the environmental area. β -Cyclodextrin was used to form inclusion complexes with pesticides and related compounds to suppress toxicity in activated sludge system, leading to enhanced biological detoxification of industrial wastewater^[8]. PAHs could be removed from wastewater by contacting with cyclodextrins anchored on water insoluble media^[9]. Hydroxypropyl- β

cyclodextrin could enhance the transport of low-polarity organic compounds through soil^[10].

The purpose of this study is to investigate the solubilization power of β -cyclodextrin and one of its derivative carboxymethyl- β -cyclodextrin (CMCD) to several PAHs.

Materials and Methods

Materials PAHs used in this study are phenanthrene, 2-methylphenanthrene, fluorene, 1-methylfluorene, 1,2-benzofluorene, and β -bromonaphthalene, in which phenanthrene was purchased from Aldrich; fluorene was provided by Ultra Scientific; β -naphthalene was produced by Shanghai First Reagent Plant; 2-methylphenanthrene, 1-methylfluorene and 1,2-benzofluorene were prepared in this laboratory. β -Cyclodextrin was purchased from the Food and Fermentation Institute of Jiangsu Province. CMCD was synthesized by reacting β -CD with chloroacetic acid followed by purification. Its average degree of carboxymethyl substitution is 1.3, and its average molecular weight is 1210.

Method The solubilization experiments were conducted by use of the generator column method. The column used was a 40cm long, 2.5cm diameter glass column with a sintered glass bed at the outlet end. The PAH samples (0.05-0.1g) were dissolved in 20ml ethanol, and the solutions were mixed with analytical pure silica sand with a size of 0.05-0.1mm, followed by evaporating of the ethanol. The sand coated with samples were packed into the column with glass wool placed above the glass bed to prevent the loss of silica sand. The column was flushed with 200ml distilled water before use.

The solutions with β -CD or CMCD were passed through the column and a fraction of the effluent was taken in each 0.5 hours, and analyzed immediately to determine the concentration of the solute. The remaining effluent was repeatedly passed through the column until a constant solute concentration was obtained. The samples for concentration measurement were about 0.5-5.0ml, prediluted with same volume methanol and diluted to 10ml with 1:1 methanol-water solution. The role of methanol is to decompose the complexes of cyclodextrin-PAH, thereby keeping the aqueous-based UV spectrum of the compounds unchanged. The concentrations were measured by 751G UV-Vis Spectrophotometer (manufactured by Shanghai Analytical Instrument Plant). The maximum ab-

sorption wavelength used for detection of each PAH were 260nm for phenanthrene and fluorene, 254nm for 2-methylphenanthrene, 265nm for 1-methylfluorene, 263nm for 1,2-benzofluorene, and 230nm for β -bromonaphthalene. CMCD solution has a weak response in the UV range. This effect was eliminated by subtracting the UV response of blank CMCD solution from the total UV response of the sample solution.

Results And Discussion

Solubilization effect of β -CD and CMCD to PAHs The solubilization effect of β -CD and CMCD on selected PAHs was shown in Fig. 1-5. Linear regression of the relative aqueous concentration of PAH versus cyclodextrin concentration gives very good correlation factors for five PAHs studied except for β -bromonaphthalene with β -CD as solubilization reagent. These linear relationship could be expressed by the following equation;

$$S_t/S_o = K_{cw} C_o + 1$$

in which S_t is the equilibrium aqueous concentration of PAH with cyclodextrins presented; S_o is the water solubility of PAH without cyclodextrins; K_{cw} is the equilibrium constant of the PAH partitioning in water and cyclodextrin cavity; C_o is the concentration of β -CD or CMCD. In Fig. 1-5 K_{cw} is the slope of the regression line which reflects the solubilization power of cyclodextrin to PAH.

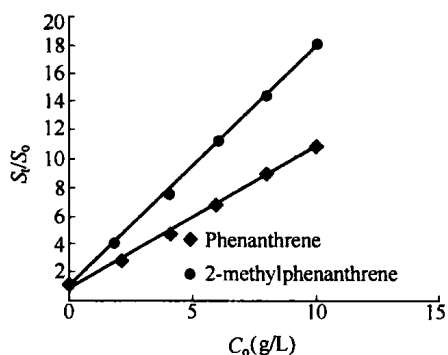


Fig. 1 Solubilization of β -CD to phenanthrene and 2-methylphenanthrene

S_t is the equilibrium aqueous concentration of PAH with cyclodextrins presented; S_o is the water solubility of PAH without cyclodextrins; C_o is the concentration of β -CD

The linear relationship between the relative aqueous-phase concentrations (S_t/S_o) of the PAHs and concentrations of β -CD and CMCD indicates that the solubilization of PAHs by β -CD and CMCD are in ac-

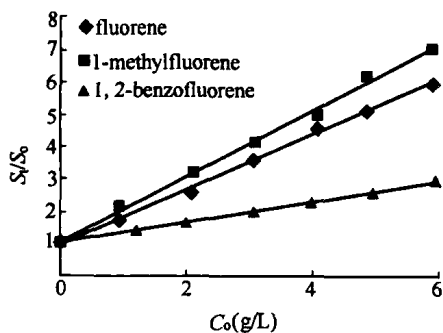


Fig. 2 Solubilization of β -CD to fluorene, 1-methylfluorene and 1,2-benzofluorene

S_i is the equilibrium aqueous concentration of PAH with cyclodextrins presented; S_0 is the water solubility of PAH without cyclodextrins; C_0 is the concentration of β -CD

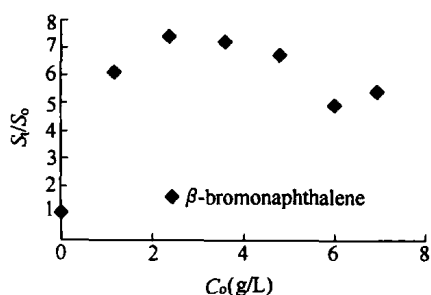


Fig. 3 Solubilization of β -CD to β -bromo-naphthalene

S_i is the equilibrium aqueous concentration of PAH with cyclodextrins presented; S_0 is the water solubility of PAH without cyclodextrins; C_0 is the concentration of β -CD

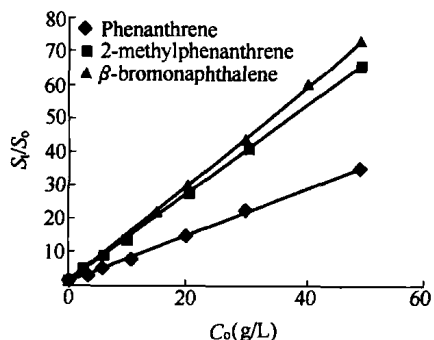


Fig. 4 Solubilization of CMCD to Phenanthrene, 2-methylphenanthrene, and β -bromonaphthalene

S_i is the equilibrium aqueous concentration of PAH with cyclodextrins presented; S_0 is the water solubility of PAH without cyclodextrins; C_0 is the concentration of CMCD

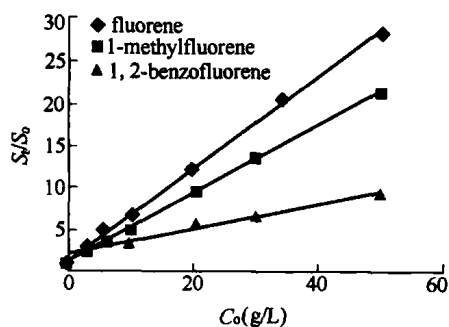


Fig. 5 Solubilization of CMCD to fluorene, 1-methylfluorene, and 1,2-benzofluorene

S_i is the equilibrium aqueous concentration of PAH with cyclodextrin presented; S_0 is the water solubility of PAH without cyclodextrins; C_0 is the concentration of CMCD

cordance with the linear partition model proposed by Chiuo and colleagues for the solubilization of NOCs by dissolved organic mater and surfactants^[11]. Because the solubilization of cyclodextrins to low polarity organic compounds are caused by complexation of organic compounds with cyclodextrin cavities, the complexation process can also be considered as partitioning of PAH from water into cyclodextrin cavity, and the stability constants K_s of cyclodextrin-PAH complexes can be considered as partition coefficient K_{cw} when the concentration of cyclodextrins is much greater than the water solubility of PAH^[3]. The partition coefficients of water-cyclodextrins (K_{cw}) for six PAHs, obtained from linear regression of S_i/S_0 versus cyclodextrin concentrations C_0 , are listed in Table 1.

Influence of PAH structure on the solubilization Inspection of the K_{cw} for six PAHs reveals that the solubilization of PAHs by β -CD and CMCD are strongly structure dependent. Greatest solubilization effect is obtained from β -bromonaphthalene-CMCD system ($K_{cw} = 1.48$). Although the data from the solubilization experiments of β -CD to β -bromonaphthalene did not give a linear relationship, the cause of this phenomenon was attributed to the formation of insoluble aggregates of β -CD- β -bromonaphthalene complexes at high β -CD concentration. From the low β -CD concentration data strong solubilization effect could still be seen. The least effectiveness of solubilization were achieved from β -CD and CMCD to 1,2-benzofluorene which has a greatest molecular size. These results indicate that the mechanism for solubilization of PAH by cyclodextrins are different from solubilization of NOCs by cosolvents and surfactants. Because the cyclodextrin

Table 1 Solubilization Data of β -CD And CMCD To PAHs

PAH	K_{cw} (β -CD)	K_{cw} (CMCD)	S_w mg/L	$\log K_{ow}$	Molecule width	Size(nm) length
fluorene	0.865	0.544	1.68	4.18	0.48	0.89
β -bromonaphthalene		1.480	5.34	4.3	0.49	0.74
phenanthrene	1.005	0.698	1.60	4.53	0.58	0.78
1-methylfluorene	0.872	0.425	1.09	4.97	0.58	0.89
2-methylphenanthrene	1.698	1.312	0.27	5.10	0.58	0.98
1,2-benzofluorene	0.324	0.152	0.045	5.68	0.73	0.94

cavity has a fixed size, only the compounds with a similar molecular size and appropriate structure could be included into the cavity. Other compounds with a bigger or smaller size or inappropriate structure could only achieve partial inclusion, causing decreased solubilization effect. Possible structures of β -cyclodextrin-phenanthrene inclusion complexes and β -cyclodextrin-fluorene inclusion complexes are shown in Fig. 6 and Fig. 7. From Fig. 6, we can see phenanthrene can be included in two ways. In structure (a) phenanthrene can fit into the β -CD cavity completely, which will give a equilibrium constant of the complexation. In structure (b) phenanthrene can only achieve a partial inclusion. The structure of fluorene is different from phenanthrene. Because the length of fluorene molecule is greater than the diameter of the β -CD cavity, it could only be included in one way as in Fig. 7. Hence, it could only achieve a partial inclusion. That is why the solubilization power of β -CD and CMCD for phenanthrene and 2-methylphenanthrene are much greater than that for fluorene and 1-methylfluorene.

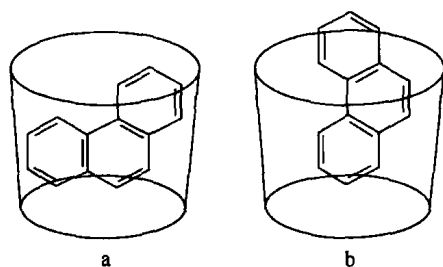


Fig. 6 Structure of Cyclodextrin-Phenanthrene Complexes

Wang^[3] has reported that the solubilization power of hydroxypropyl- β -cyclodextrin (HPCD) to low polarity organic compounds was parallel to their octanol-water partition coefficients $\log K_{ow}$. The present result of our experiments does not verify this tendency. Structure deference seems to be a more important factor to the solubilization of PAHs by β -CD and CMCD.

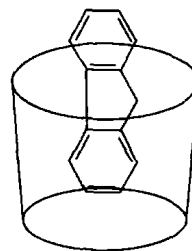


Fig. 7 Structure of Cyclodextrin-Fluorene Complex

Difference in solubilization power of β -CD and CMCD on PAHs Comparing the K_{cw} of PHAs solubilized by β -CD and that of CMCD reveals that the K_{cw} with β -CD is much greater than that with CMCD for the same PAH, which indicates that the solubilization power of β -CD is greater than its derivatives CMCD at the same concentration. This phenomenon may be explained by the special structure of CMCD. Substitution of carboxymethyl group at the outside of the cavity may impede the diffusion of PAH molecule into the cavity, making the formation of inclusion complex difficult, decreasing the solubilization power of CMCD. Although the solubilization power of β -CD is greater than that of CMCD, unfortunately β -CD has only a limited water solubility of about 18.7g/L at 23°C, and its complexes are thereby only slightly water soluble. In this study the greatest solubilization of β -CD was achieved with 2-methylphenanthrene. When β -CD concentration was 10g/L, the water solubility of 2-methylphenanthrene was only increased about 18 fold. Comparing with β -CD, CMCD has unlimited water solubility, its concentration used for solubilization of PAHs could be very high. For example, When CMCD concentration reaches 50g/L, the apparent water solubility of β -bromonaphthalene could be increased more than seventy times. Because CMCD could be easily synthesized from β -CD, it might be a better choice for the cleanup of PAHs in the environment.

Conclusion

The results from this study indicate that β -CD and CMCD could significantly increase the apparent water solubilities of PAHs. Linear relationship was observed between the relative aqueous-phase concentration of PAH and the concentration of β -CD and CMCD for all PAHs studied. The solubilization power of β -CD and CMCD to PAHs are dependent on the structure of PAH. The solubilization power of β -CD is greater than CMCD to the same PAH. Because of the solubility difference between β -CD and CMCD, CMCD is an attractive solubilization reagent for PAHs. Further studies should be focused on removal of PAHs from soil by CMCD and the influence of CMCD on the biodegradation and photodegradation of PAHs.

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2 Solubilization of substituted indole compounds by β -cyclodextrin in water

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(Adapted from *Chemosphere*, 2000, 40: 1411-1416)

Abstract: The solubilization of four pairs of substituted indole compounds (SICs) by β -cyclodextrin (β -CD) in water was investigated. The results show that 1,2,3,4-tetrahydrocarbazole and *N*-methyl-1,2,3,4-tetrahydrocarbazole form 1 : 1 inclusion complexes with β -CD, while the other six SICs form 1 : 2 inclusion complexes, respectively. To each pair of SICs with similar structures, the differences between their solubilization in β -CD/water solutions has been explained by the difference of their contact area within the β -CD cavity, the difference of their molecule polarity, or the presence of hydrogen bond between SIC molecule and β -CD molecule.

Keywords: Substituted indole compounds, β -cyclodextrin, Inclusion complex, Stability

1 Introduction

The cyclodextrins are cyclic oligomers of D-glucose produced by the action of certain microbial enzymes on starch (Bender and Komiyama, 1978). They have a doughnut-shaped cavity with a relatively hydrophilic exterior and a relatively hydrophobic interior. The commercially available members of the cyclodextrin family are α -cyclodextrin (α -CD), β -cyclodextrin (β -CD) and γ -cyclodextrin (γ -CD), having 6, 7, 8 glucose units, respectively. Through forming host-guest inclusion complex, cyclodextrins can enhance the solubility of non-polar or low-polar organic compounds, which has made cyclodextrin available in many fields (Bender and Komiyama, 1978; Gao and

Wang, 1998; Lin et al., 1998; Mamoru and Nakamura, 1995). Among the cyclodextrins, β -CD is widely used as cheap production, but it has poor solubility in water (25°C, 1.85%) because of the complete hydrogen bond net in its molecule (Wenbin et al., 1994).

Indole and its derivatives are used in many fields (Beregi et al., 1968; Bass et al., 1975; Glamkowski and Fortunato, 1982). Some researches have been done on the cyclodextrin/indole inclusion complex, it is reported by Örstan and Alexander Ross (1987) that the stoichiometry of the inclusion complex of indole with β -CD is 1 : 1 and the *N*-1 hydrogen of indole is hydrogenbonded to one of the hydroxyl groups sur-

rounding the edges of the β -CD cavity and Ricci (1984) reported that the stoichiometry of the complex of indole with α -cyclodextrin (α -CD) is 1 : 2.

The purpose of this paper is to investigate the solubilization of β -CD to the selected SICs in water. The differences of solubilization between these compounds with similar structures, such as: 2-(4'-methyl-phenyl)-indole and 2-(2',4'-dimethyl-phenyl)-indole, 2-(*p*-diphenyl)-indole and 2-(2'-naphthyl)-indole, 2-(4'-fluoro-phenyl)-indole and 2-(4'-chloro-phenyl)-indole, 1,2,3,4-tetrahydrocarbazole and *N*-methyl-1,2,3,4-tetrahydrocarbazole, were also tried to be explained from the viewpoint of the stability of the inclusion complex.

2 Experiment

2.1 Instruments and Chemicals

UV-VIS Recording Spectrophotometer (UV2201, Japan). Eight SICs were offered by the Organic Synthesis Laboratory of Nanjing University, their serial numbers and molecular structures were listed in Fig. 1. β -CD was purchased from Food and Fermentation Institute of Jiangsu Province (purity > 99%) and was utilized directly.

by batch method. Twenty ml of the solution, containing varying concentration of β -CD, were added to centrifuge tubes. The selected SIC was added to each tube in quantities in excess of the solubility limit. Double tubes were prepared for each β -CD concentration. Blanks were prepared in an identical manner with the exception that no β -CD was added. All samples were equilibrated on a temperature-controlled shaker for over 48h at 25°C until the absorbency of the solutions in UV-VIS Recording Spectrophotometer did not change any longer. After equilibration, the samples were centrifuged for 10min, the aliquot of the supernatant was then withdrawn and diluted with methanol/water (50/50, *v/v*). The concentrations of SICs were determined with UV-VIS spectrophotometer. The maximum absorption wavelengths used for detection of the eight SICs I-VIII (the SIC no. is in accordance with that in Fig. 1) were 280, 290, 300, 285, 322, 300, 309 and 301 nm, respectively.

The molecule sizes of SICs were calculated with molecular modeling package AICHEMY II¹⁴.

3 Results and discussion

3.1 Equilibrium equation for β -CD/SICs inclusion complex

According to previous studies, two equilibrium equations can be used to describe the interaction between dissolved SICs (*S*) and β -CD:

$$S + \beta\text{-CD} = S(\beta\text{-CD}) \quad (1)$$

$$S + 2\beta\text{-CD} = S(\beta\text{-CD})_2 \quad (2)$$

Eqs. (1) and (2) demonstrate that SICs form 1 : 1 and 1 : 2 inclusion complex with β -CD, respectively. The associated relationship between relative aqueous-phase concentration (S_t/S_0 ; S_t is the apparent solubility of SICs in equilibrium solutions, S_0 is the aqueous solubility of SICs in water) and the concentration of β -CD can be given:

$$S_t/S_0 = 1 + K_1[\beta\text{-CD}]_0 \quad (3)$$

$$S_t/S_0 = 1 + K_2[\beta\text{-CD}]_0^2 \quad (4)$$

where K_1 , K_2 are the equilibrium constants of Eqs. (1) and (2), respectively. They also demonstrate the stability of the 1 : 1 and 1 : 2 β -CD/SICs complexes. Eq. (3) suggests the linear relationship between S_t/S_0 and $[\beta\text{-CD}]_0$ and Eq. (4) suggests the linear relationship between S_t/S_0 and $[\beta\text{-CD}]_0^2$.

3.2 Solubilization of investigated SICs in β -CD /water solutions

The relative aqueous-phase concentration (S_t/S_0) was plotted versus the β -CD concentration ($[\beta\text{-CD}]_0$)

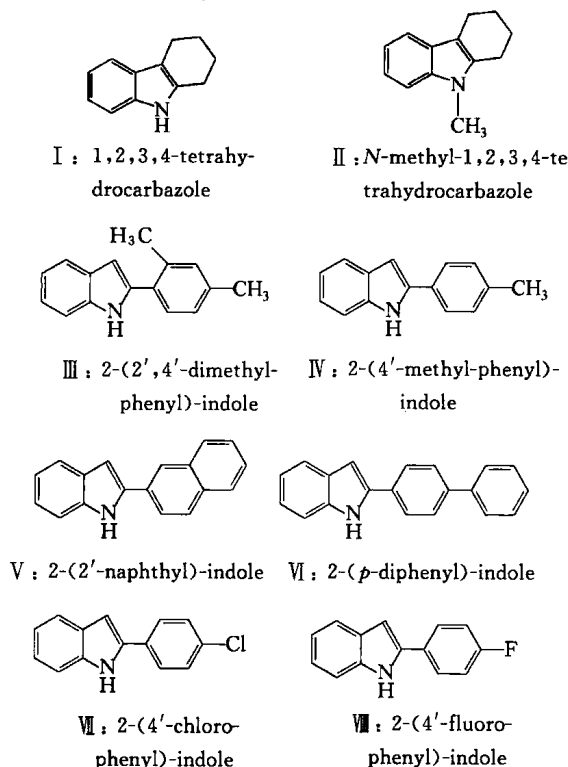


Fig. 1 The structures and the numbers of the studied SICs

2.2 Solubilization experiment

Solubilization experiments of SICs were conducted

in Fig. 2.

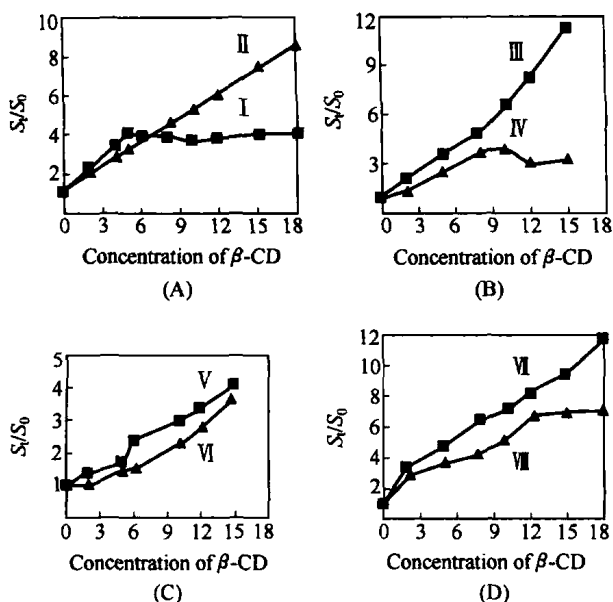


Fig. 2 Solubilization curves of investigated SICs in β -CD/water solutions

As can be seen from Fig. 2 that only for compound II (1,2,3,4-tetrahydrocarbazole), the regression between S_t/S_0 and $[\beta\text{-CD}]_0$ exhibits an excellent correlation ($R^2=0.985$), supporting the 1 : 1 stoichiometry between 1,2,3,4-tetrahydrocarbazole and β -CD in their complex. The increase in S_t/S_0 for compounds III, V, VI and VII is a nonlinear function of the β -CD concentration, but the regression between S_t/S_0 and $[\beta\text{-CD}]_0^2$ of them give excellent correlation (R^2 is 0.972, 0.975, 0.979 and 0.996, respectively). The results indicate that compounds III, V, VI and VII form 1 : 2 complex with β -CD, respectively.

The effect of β -CD on the solubility of compounds I, IV and VIII in water are complicated. The S_t/S_0 ratios of compounds I, IV and VIII initially increase with the increasing β -CD concentration, reach a maximum value, and then decrease or do not change at higher β -CD concentration. It is important to note that the initial increase of S_t/S_0 with the increasing β -CD concentration for compound I (*N*-methyl-1,2,3,4-tetrahydrocarbazole) is linear as described by Eq. (3) (R^2 is 0.990), informing the existence of 1 : 1 β -CD/*N*-methyl-1,2,3,4-tetrahydrocarbazole complex, and the initial increase of S_t/S_0 with the increasing $[\beta\text{-CD}]_0^2$ for compounds IV and VIII is linear (R^2 is 0.945 and 0.956, respectively), informing that the compounds IV and VIII form 1 : 2 complexes with β -CD, respectively. The decrease of S_t/S_0 at higher β -CD

concentration is most likely due to the formation of insoluble aggregates.

The solubilization constants (K_1 or K_2) of the eight SICs were listed in Table 1.

3.3 Predicted structure of the β -CD/SICs complexes

In order to evaluate the effect of SIC structure on the nature of their complexes with β -CD, it is necessary to examine the configurations of their complexes. As can be deduced from the experimental results that 1,2,3,4-tetrahydrocarbazole and *N*-methyl-1,2,3,4-tetrahydrocarbazole form 1 : 1 inclusion complexes with β -CD, and the other six SICs form 1 : 2 inclusion complexes with β -CD. The orientation of these SICs in their complexes can be predicted based on the principle of size matching and maximum contact between SICs and the β -CD cavity (Xiaojiang and Brusseau, 1994), also it should be favorable for the hydrogen bond to form between SIC molecule and β -CD molecule because *N*-hydrogen can form H-bond with the hydroxyl groups of β -CD molecule and H-bond can greatly improve the complex stability. The predicted structures of the β -CD/SICs complexes were illustrated in Figs. 3-5.

Table 1 The solubilization constants of eight SICs

SICs	K	SICs	K
I	0.62	V	0.023
II	0.41	VI	0.020
III	0.030	VII	0.042
IV	0.028	VIII	0.031

The number I-VIII is in accordance with that in Fig. 1.

3.4 Influence of the contact within the β -CD cavity on the solubilization

The sizes of four groups of compounds III-VI were calculated with molecular modeling package AICHEMY II^[14] and listed in Table 2.

Table 2 The sizes of four groups

Group	Length(Å)	Width(Å)
2',4'-Dimethyl-phenyl	6.37	5.55
4'-Methyl-phenyl	6.37	4.95
2'-Naphthyl	7.60	5.53
<i>p</i> -Diphenyl	9.65	4.95

Data in Table 2 show that the length of 2',4'-dimethyl-phenyl group and 4'-methyl-phenyl group are less than the depth of the β -CD cavity (7.90Å) and the width of them are less than the diameter of the β -CD cavity (7.0Å); so, according to the principle of maximum contact, 2',4'-dimethyl-phenyl group and