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Simple Prediction of Stability Constants for Inclusion Complexes of β-Cyclodextrin with various Drug Molecules Using β-Cyclodextrin Bonded Phases(Cyclobond® I Column)

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SUMMARY

The stability constants(K_c) for inclusion complexes of cyclodextrin with sulfonamides, sulfonylureas and p-aminobenzoic acid esters were investigated by high performance liquid chromatography(HPLC) using the cyclodextrin bonded phase. The retention time(R_T) of these drugs on a Cyclobond® I column showed a good relationship to K_c values obtained by the solubility method and/or conventional HPLC method. The advantages of this method were that the K_c values could be rapidly predicted by a simple procedure using a minimum quantity of the drugs.

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INTRODUCTION

Several methods have been reported on the determination of K_c by means of solubility[1], potentiometry[2], polarography[3] and spectroscopic methods.[4] As a rule, a standard solubility method does not appear to be suitable for chemically unstable compounds because it takes a long time to reach the equilibrium state. It was previously reported that the determination of K_c using the HPLC method with an anion exchange support and addition of cyclodextrin into an aqueous mobile phase had many advantages in comparison with other methods.[5] However, it was necessary to select a proper ion exchange support for each drug group.

Cyclobond® columns are packed with a unique chromatographic stationary phase produced by chemically bonding cyclodextrins to a high purity silica gel. This unique column has been widely applied to the separation of some types of positional isomers[6], geometric isomers[7] and epimers.[8] This paper is concerned with the utility of cyclobond® columns as a simple method for estimating the K_c for inclusion complexes of cyclodextrin with sulfonamides, sulfonylureas and p-aminobenzoic acid esters.

EXPERIMENTAL

Materials p-Aminobenzoic acid esters were purchased from Tokyo Chemical Industry Co.,Ltd. Sulfonamides were purchased from Sigma Chemical Co.,Ltd. and Tokyo Chemical Industry Co.,Ltd. Sulfonylureas were the same as those described in a previous paper.[9] Those drugs

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were used without further purification. All other chemicals and solvents were of analytical reagent grade. Milli-Q water was also used.

Apparatus A high-performance liquid chromatograph with a SSC-Flow System 3100(Senshu Scientific Co.,Ltd. Tokyo), equipped with a stainless-steel column(250 x4.6 mm,i.d.) packed with β-cyclodextrin chemically bonded to a high purity silica gel(Cyclobond® I; Advanced Separation Technologies, USA) was used. Detection was effected spectrophotometrically at the absorption maximum of each drug, using a Shimadzu SPD-1 variable -wavelength UV detector(Kyoto,Japan). A Shimadzu Laboratory Recorder(model R-11) combined with an Shimadzu Chromatopac-E1A Integrator was used to monitor the chromatographic characteristics. The injector was a Rheodyne Model 7125(Berkeley Calif.USA) equipped with a 20 μl sample loop. A Yanaco pH-8D pH meter(Kyoto, Japan) was used to adjust the pH.

Chromatographic Condition The solvent flow rate was 1.0 $ml \cdot min^{-1}$, the chart speed was 0.25 $cm \cdot min^{-1}$ and the attenuation for full-scale deflection was 0.32 -0.64 A.U.

Procedure All experiments were done at room temperature. The sample solution of each drug was prepared at a concentration of about 300 $\mu g \cdot ml^{-1}$ in methanol. A 4 μl sample was injected into the HPLC. All the mobile phases were filtered through a 0.5 μm membrane filter, and degassed directly before use. The mobile phase composition of each drug group will be described later. The retention time was defined

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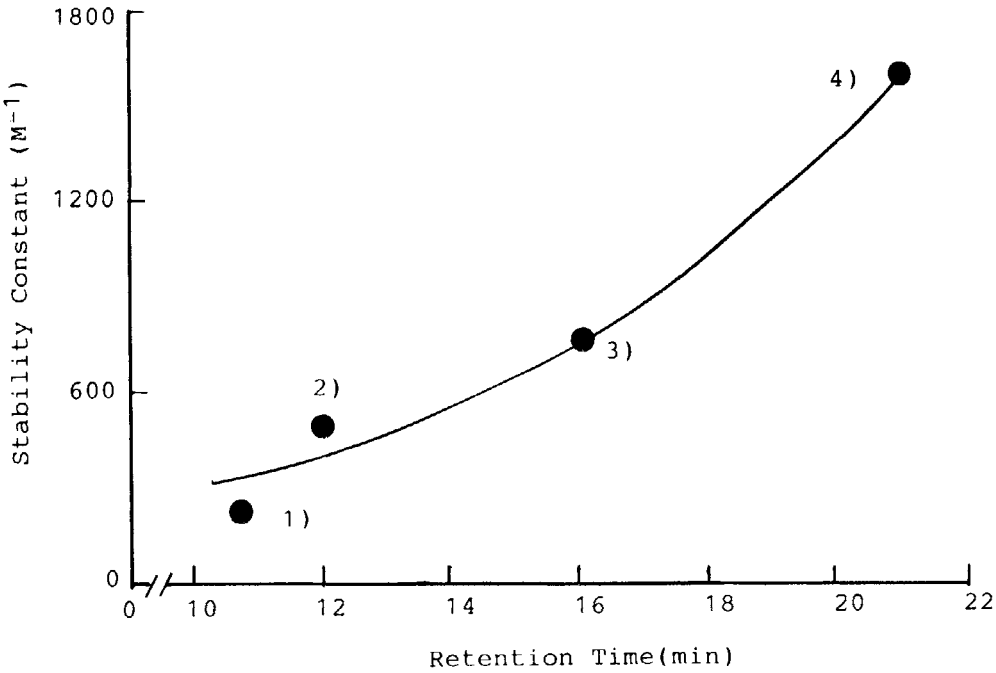

Figure 1

Relationship between Retention Times[a] of p-Aminobenzoic Acid Esters on a Cyclobond® I Column and Stability Constants[b] of p-Aminobenzoic Acid Esters/β-Cyclodextrin Systems

1: Methyl p-aminobenzoate, 2: Ethyl p-aminobenzoate, 3: Propyl p-aminobenzoate, 4: Butyl p-aminobenzoate.

a) Mobile phase: methanol:buffer=70:30.
b) All literature values determined by solubility method.[12]

as the elapsed time between injection and maximum peak on the chromatogram.

RESULTS AND DISCUSSION

The mobile phase used was a mixture of methanol and 0.05 M sodium phosphate buffer(pH 7.0)(85/15 and/or 70/30, V/V), since phosphate anions do not interfere

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with inclusion complexation.[5,10] As a simple phosphate buffer gave extremely long retention times with marked tailing because of the highly hydrophobic nature of each molecular drug, a suitable methanol concentration and pH adjustment of the mobile phase were required for obtaining a distinct peak with a reasonable retention time.

Figures 1 and 2 show the plots of R_T of p-amino-benzoic acid esters and sulfonylureas versus their K_c values respectively. In both cases, there was a fair relationship between R_T and K_c . In Figure 2, chlor-pentazaide could not be correlated in sulfonylureas. The reason is not obvious, but one factor that should be considered is the very low partition coefficent[11] of the drug itself in comparison with other sulfonyl-ureas. Further investigations with a number of sulfonylurea derivatives should be made to determine the reason.

The R_T values obtained from the sulfonamides are shown in Table I. The R_T values increased more or less with an increase in the K_c values, so the R_T values on a Cyclobond® I column may be considered as a reliable indication of the complexation of β-cyclo-dextrin and drug molecules. The R_T of sulfisoxazole is shorter than predicted by a linear relationship, while in sulfapyridine it is longer than predicted. This may be explained by considering the pK_a's of both sulfonamides as about 4.79 and 8.57 and thus, the hydrophobic and hydrophilic balance of a molecule is very sensitive to the complexation of β-cyclodextrin under the present experimental conditions(pH 7.0).

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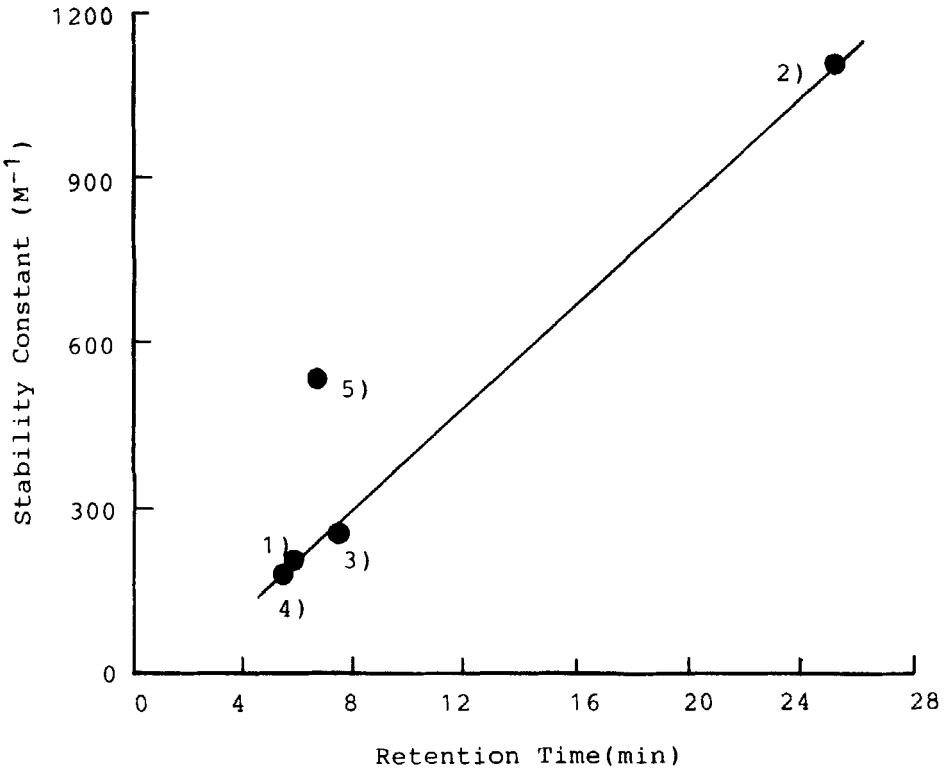

Figure 2

Relationship between Retention Times[a] of Sulfonylureas on Cyclobond® I Column and Stability Constants[b] of Sulfonylureas/β-Cyclodextrin Systems

1: Chlorpropamide, 2: Acetohexamide, 3: Tolbutamide, 4: Carbutamide, 5: Chlorpentazaide.

a) Mobile phase: methanol:buffer=85:15.
b) All literature values determined by conventional HPLC method.[5]

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Table I Retention Times of Silfonamides on a Cyclobond® I Column

Compound	R_T(min)[a]	K_C(M^{-1})[b]	pKa[c]
1) Sulfamerazine	4.76	220	6.85
2) Sulfisoxazole	6.47	730	4.79
3) Sulfaphenazole	5.74	420	5.87
4) Sulfathiazole	24.8	1860	7.23
5) Sulfamethomidine	5.92	300	7.06
6) Sulfadimethoxine	5.52	340	5.98
7) Sulfadiazine	5.02	340	6.37
8) Sulfisomidine	5.92	140	7.47
9) Sulfapyridine	13.0	450	8.57

a) Mobile phase: methanol:buffer=85:15.
b) All literature values determined by conventional HPLC method.[5]
c) Dissociation of amide proton.

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In sulfonylureas and sulfonamides; however, it has been demonstrated that no linear correlations between K_c values and pK_a as well as partition coefficients are generally found, which may be ascribed to the heterogeneous character of the drug substituents.[5] Therefore, it seems resonable to say that such an effect may appear on the basis of a combination of various factors.

Consequently, we cannot discuss the direct estimation method of K_c values using a Cyclobond® I column. From present results, it may be suggested that Cyclobond® columns are available as a simple method for predicting the K_c values for inclusion complexes of cyclodextrins with a number of new systematically synthesized derivatives.

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