Structural Effects on the Binding of Amine Drugs with the Diphenylmethyl Functionality to Cyclodextrins. I. A Microcalorimetric Study

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Solution calorimetry has been employed to evaluate the stability constants and enthalpy changes associated with complex formation between α-, β, or γ-cyclodextrin (CD) and a group of amine compounds having the diphenylmethyl functionality. Data from thermal titrations of the compounds were analyzed using nonlinear least squares. The standard free energy decrease accompanying the formation of inclusion complexes is generally due to a negative standard enthalpy change ($\Delta H°$). The standard entropy change ($\Delta S°$) was negative, except in the case of complexes formed with γ-CD. Of the 13 compounds studied, only 2 formed complexes with 1:2 (compound:β-CD) stoichiometry, terfenadine · HCl and cinnarizine · 2HCl. All the others formed 1:1 complexes. The structural effect on the stability constants, thermodynamics, and inclusion geometry was explored by relating the calorimetric results to the chemical structures of the guest molecules and the cavity sizes of the CD molecules. The results suggest that one of the phenyl groups of the diphenylmethyl functionality resides in the CD cavity and is in van der Waals contact with the inside wall of the CD cavity. In the case of α- and β-CDs, van der Waals interaction dominates in the stabilization. On the other hand, the interaction between these compounds and γ-CD is largely entropically driven. Adiphenine · HCl forms a more stable complex with β-CD than proadifen · HCl, suggesting that hydrogen bonding to the carbonyl oxygen by the hydroxyl group on the rim of the CD ring can influence the strength of the binding interaction.

KEY WORDS: solution calorimetry; inclusion complex; diphenylmethyl derivatives; cyclodextrins (CDs).

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of six (α-CD), seven (β-CD), eight (γ-CD), or more D-glucose residues attached by α-(1,4) linkages. A CD molecule exhibits hydrophobic characteristics inside its cavity and hydrophilic characteristics outside, so one of the most important properties of cyclodextrins is the formation of inclusion complexes with a variety of organic molecules (1). This remarkable complexing ability and its effect on the solubility and stability of pharmaceuticals have prompted many investigations into their usefulness in formulation (2–5).

Several types of interaction are conceivable between guest molecules and cyclodextrin. Among these are van der Waals interaction, hydrogen bonding, dipole–dipole and/or electric charge interaction, and the hydrophobic effect (6,7). The nature of the main binding force for CD complexation and the complex geometry are still matters of controversy.

Many amine compounds used medicinally bear the diphenylmethyl functionality. Poor aqueous solubility and stability for some of these diphenylmethyl derivatives make them good candidates for cyclodextrin inclusion complexation. Previous studies of complexes of these amine compounds with CDs are very limited (2,8–10). No efforts were made to study systematically the structural effects on their binding.

In the present report, titration microcalorimetry was used to investigate the binding of some amine drugs with the diphenylmethyl functionality to α-, β-, and γ-cyclodextrins in aqueous solution at 25°C. These studies were performed in an attempt to explore the structural effects on the stability constants, thermodynamics, and inclusion complex geometry. Results of these efforts should enable us to obtain a better insight into the binding mechanisms involved in complexation.

MATERIALS AND METHODS

Materials

α-, β-, and γ-CDs, terfenadine, cinnarizine, diphenidol · HCl, diphenhydramine · HCl, orphenadrine · HCl, cyclizine · HCl, chlorcyclizine · HCl, meclizine · 2HCl, hydroxyzine · 2HCl, and adiphenine · HCl were obtained from Sigma Chemical Co. (St. Louis, MO) and were used without further purification. The amounts of hydrated water in the CDs were measured by thermogravimetry (Perkin-Elmer, TGA 7, Norwalk, CT) prior to preparation of the solutions used for titration, and the apparent molecular weights of the CDs were calculated accordingly. Bromodiphenhydramine · HCl was donated by Parke–Davis Co., and proadifen · HCl and diphenylpyraline · HCl by SmithKline Beecham. Diphenylpyraline · HCl was recrystallized from anhydrous ether. All solutions were prepared using double-distilled water. Figure 1 shows the structures of the amine compounds used in our studies.

Equipment and Methods

Thermometric titrations were performed using the Tronac Model 450 isoperibol solution calorimeter (Tronac Inc., Orem, Utah). The calorimeter reaction vessel was submerged in a water bath maintained at 25 ± 0.0004°C by a Tronac PTC-40 temperature controller.

Cyclodextrin solutions with concentrations of 0.0135 *M* for β-CD, 0.1000 *M* for α-CD, and 0.0730 *M* for γ-CD were titrated through Hamilton syringes (5 or 10 ml) at constant delivery rates into a 50-ml Dewar reaction vessel containing ligand solutions. The initial titrate volumes were 40 and 45 ml, depending on the sizes of syringes used. The total volume in the reaction vessel following titration was approximately 49 ml. Two initial ligand concentrations, 1 and 0.5 m*M*, were used for most of the cases. All the solutions were prepared immediately prior to use. A warm-up period of

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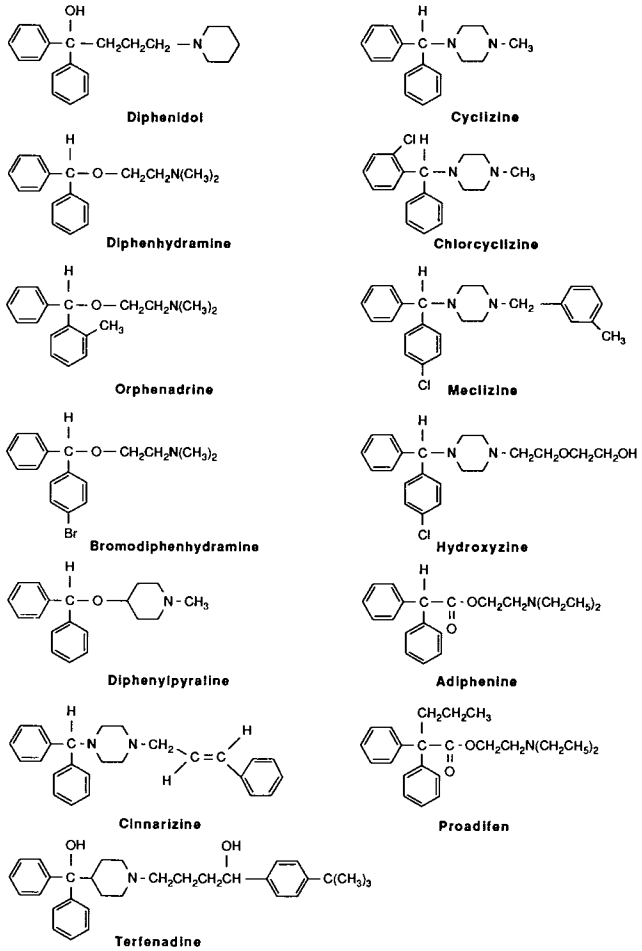

Fig. 1. Chemical structures of amine compounds with the diphenylmethyl functionality.

about 4 hr was employed to permit the water-bath temperature to stabilize. Prior to the run, the bridge was zeroed to the bath temperature. The temperature scale could then be read directly as the temperature difference between the reaction vessel and the constant-temperature bath.

A titration calorimetry run basically consists of three parts: the initial heat capacity run, the heat of reaction run, and the final heat capacity run. The voltage change, which is directly proportional to the temperature change within the Dewar reaction vessel, was monitored at constant time intervals by means of an Apple II+ computer interfaced with the Tronac calorimeter through an analog–digital connector and voltage amplifier. The data acquisition program CALT was used for data collection. Data analysis consisted of four parts. The program WIN was used to calculate the initial and final heat capacities and, also, to correct the titration runs for extraneous heat effects. The program HK SEQFILE was then used for subtraction of the heat of dilution curve, which was measured separately, and to put the corrected data in a format for use with the modified NLLSQ program. Finally, the modified NLLSQ program was used to solve the thermograms for ΔH° and K associated with each step in the proposed series complexation model. All the programs applied were developed in this laboratory (11).

The solid complexes of adiphenine · HCl and proadifen · HCl with β-CD were prepared by a freeze-drying method (12) using the freeze-dryer Dura-Stop MP Model TDS-2B-MP and Dura-Dry MP Model FB-8-85B-MP (FTS Systems Inc., Stone Ridge, NY). The calculated and accurately weighed (1:1 molar ratio) amounts of adiphenine · HCl or proadifen · HCl and β-CD were dissolved in the appropriate volume of water, then sealed in a flask, and the solution was stirred for 2 days and lyophilized. The physical mixtures were prepared by mixing exactly weighed (1:1 molar ratio) amounts of adiphenine · HCl or proadifen · HCl and β-CD in an agate mortar in the Wig-L-Bug mixer.

Infrared spectra were obtained using the Nicolet Model 5DXB spectrometer, equipped with a DTGS detector and diffuse reflectance cell (Collector Cell, Spectra Tech, Inc.). Infrared spectra were the result of 300 coadded scans at a resolution of 4 cm^{-1} and a detector gain of 4. Spectra were ratioed to the background spectrum of potassium chloride powder (particle size, <44 μm). Mixtures of each sample (2%) were prepared in KCl using the Wig-L-Bug mixer, filled into the macro sample cup (4 × 2 mm) of the Collector Cell, and leveled with a spatula. The Collector Cell was previously aligned on a removable baseplate to ensure optimal throughput. A 5-min purge was allowed prior to the collection of all spectra to equilibrate water and CO_2 vapors.

Theoretical Aspects of Solution Calorimetry

The conceptual basis of isoperibol solution calorimetry is that the reaction heat effect Q_R represents a quantitative measure of the amount of product formed, A_p, that is

$$Q_R = A_p \cdot \Delta H^\circ \tag{1}$$

where ΔH° is the standard enthalpy change associated with the reaction (13,11).

For a one-step reaction [Eq. (2)], given Eq. (3) for the equilibrium system depicted in (2), Eq. (4) can be derived and SL_1 solved for using the quadratic formula. The reaction heat can then be expressed as a function of moles of SL_1 produced [Eq. (5)].

$$S + L \underset{\Delta H_1^\circ}{\overset{K_{11}}{\rightleftharpoons}} SL_1 \tag{2}$$

$$K_{11} = \frac{[SL_1]}{[S][L]} \tag{3}$$

$$SL_1^2 - SL_1\left(S_T + L_T + \frac{\text{Vol}}{K_{11}}\right) + S_T L_T = 0 \tag{4}$$

$$Q_R = SL_1 \cdot \Delta H_1^\circ \tag{5}$$

where K_{11} and ΔH_1° are the binding constant and enthalpy change for the defined reaction, L_T is the amount of total ligand, L is the amount of free ligand, S_T is the amount of total substrate, S is the amount of free substrate, and Vol is the volume of solution in the reaction vessel.

The strategy for multiple-step series reactions as defined in Eq. (6) is the same. From mass balance, total ligand − total bound ligand − free ligand = 0, where total bound ligand is defined in Eq. (7). Once the free ligand concentration is determined for the current K estimates, the moles of complex SL_n are calculated as defined by Eq. (9). The reac-

tion heat is then calculated for the current ΔH° estimates according to Eq. (10).

$$S + L \underset{\Delta H_1^\circ}{\overset{K_{11}}{\rightleftharpoons}} SL_1 + L \underset{\Delta H_2^\circ}{\overset{K_{12}}{\rightleftharpoons}} \cdots\cdots \underset{\Delta H_n^\circ}{\overset{K_{1n}}{\rightleftharpoons}} SL_n \quad (6)$$

$$\text{total bound ligand} = S_T \cdot \frac{\sum_{i=1}^{n}\left(i[L]^i \prod_{j=1}^{i} K_{1j}\right)}{1 + \sum_{i=1}^{n}\left([L]^i \prod_{j=1}^{i} K_{1j}\right)} \quad (7)$$

$$S = \frac{S_T}{1 + \prod_{i=1}^{n}\left([L]^i \prod_{j=1}^{i} K_{1j}\right)} \quad (8)$$

$$SL_n = S[L]^n \prod_{i=1}^{n} K_{1i} \quad (9)$$

$$Q_R = \Delta H_1^\circ(SL_1 + SL_2 \cdots\cdots + SL_n) + \Delta H_2^\circ(SL_2 + \cdots\cdots + SL_n) + \cdots\cdots + \Delta H_n^\circ(SL_n) \quad (10)$$

ΔH° and K for the binding reaction can be simultaneously obtained by solving Eq. (5) or Eq. (10) using a nonlinear least-squares curve-fitting program. Once these values are known, other thermodynamic parameters can then be calculated from Eq. (11).

$$\Delta G^\circ = -RT \ln K = \Delta H^\circ - T\Delta S^\circ \quad (11)$$

RESULTS AND DISCUSSION

The thermodynamic parameters and binding constants for the complexation of α-, β-, and γ-cyclodextrins with amine drugs bearing the diphenylmethyl functionality are given in Tables I, II, III, and IV.

Figures 2 and 3 show some typical titration curves and fitted results for the complexation reactions. Curve fitting was performed using a total of 238 points. The small residual is randomly distributed around the zero-point line and shows no systematic error.

Five titration runs were performed for the complexation of compounds with β-CD; three runs and two runs with α- and γ-CDs, respectively. The results of five runs of the diphenhydramine · HCl-β-cyclodextrins interaction are listed in Table V. Good reproducibility between runs was observed.

Two different concentrations of titrate were used in the titration for the compounds whenever solubility limitations and the sensitivity of the calorimeter permitted. The results showed no significant dependence of the parameters on the substrate concentrations, suggesting that other effects such as dimerization of substrate and ionic strength changes during the titration were negligible in the determination of binding parameters.

The standard free energy decrease accompanying the formation of inclusion complexes is generally due to a negative standard enthalpy change (ΔH°). The standard entropy change (ΔS°) was negative, except in the case of complexes formed with γ-cyclodextrin.

Generally, the largest stability constants and enthalpy decreases were found in the case of complexes formed with β-CD. When a methyl or a halogen substituent is on the aromatic ring, stability constants are higher, suggesting greater van der Waals interaction energy. This is also an indication of the participation of van der Waals forces in the inclusion process. In the case of the α- and γ-cyclodextrin complexes, the K values for binding with substituted diphenylmethyl derivatives are typically near 1000 M^{-1} except for the binding of γ-CD with bromodiphenhydramine · HCl, which has a K value of about 2500 M^{-1}. The K values for the binding with other compounds having no substituent on the aromatic ring were only about 100 M^{-1} for α-CD and 500 M^{-1} for γ-CD.

The cavity sizes of α-, β-, and γ-CDs are 5.5–6, 7.0–8, and 9–10 Å, respectively (1,14). The size of the diphenylmethyl group, taking into consideration the van der Waals

Table I. Summary of the Thermodynamic Parameters and Binding Constants for the Association of Diphenylmethyl Derivatives with β-CD in Aqueous Solution at 25°C (1:1 Stoichiometry)

Compound	ΔH° (kJ/mol)[a]	K (M^{-1})[a]	ΔG° (kJ/mol)	ΔS° (J/mol · K)
Diphenidol · HCl	−33.65 ± 1.06	936.9 ± 86.1	−16.96	−56.0
Diphenhydramine · HCl	−29.40 ± 0.98	1148.5 ± 39.3	−17.47	−40.0
Orphenadrine · HCl	−31.27 ± 0.83	1282.0 ± 85.1	−17.74	−45.4
Bromodiphenhydramine · HCl	−25.44 ± 1.01	2156.1 ± 271.5	−19.03	−21.5
Diphenylpyraline · HCl	−27.82 ± 0.64	2281.5 ± 132.9	−19.14	−29.1
Cyclizine · HCl	−28.83 ± 1.46	1215.2 ± 95.4	−17.61	−37.6
Chlorcyclizine · HCl	−24.08 ± 1.25	2461.9 ± 338.0	−19.36	−15.8
Chlorcyclizine · 2 HCl	−22.77 ± 0.97	2404.5 ± 96.5	−19.36	−11.4
Meclizine · 2 HCl	−22.55 ± 0.92	2238.1 ± 254.0	−19.12	−11.5
Hydroxyzine · HCl	−24.19 ± 0.41	2316.7 ± 101.4	−19.21	−16.7
Proadifen · HCl	−29.52 ± 1.22	914.4 ± 51.7	−16.90	−42.3
Adiphenine · HCl	−31.94 ± 0.78	2750.4 ± 172.3	−19.63	−41.3

[a] Average ± SD (n = 5).

Table II. Summary of the Thermodynamic Parameters and Binding Constants for the Association of Diphenylmethyl Derivatives with α-CD in Aqueous Solution at 25°C (1:1 Stoichiometry)

Compound	$\Delta H°$ (kJ/mol)[a]	K (M^{-1})[a]	$\Delta G°$ (kJ/mol)	$\Delta S°$ (J/mol · K)
Terfenadine · HCl	−49.37 ± 0.75	51.9 ± 0.5	−9.79	−132.8
Cinnarizine · 2 HCl	−38.40 ± 0.94	28.5 ± 0.8	−8.30	−101.0
Diphenidol · HCl	−20.42 ± 0.29	43.8 ± 0.8	−9.37	−37.1
Diphenhydramine · HCl	−16.18 ± 0.16	44.3 ± 0.6	−9.40	−40.7
Orphenadrine · HCl	−20.97 ± 0.30	35.4 ± 0.6	−8.84	−40.7
Bromodiphenhydramine · HCl	−27.34 ± 0.46	1355.7 ± 89.15	−17.88	−31.7
Diphenylpyraline · HCl	−19.83 ± 0.30	31.5 ± 0.8	−8.55	−37.8
Cyclizine · HCl	−20.04 ± 1.00	48.4 ± 3.65	−9.62	−35.0
Chlorcyclizine · HCl	−24.43 ± 0.80	1114.1 ± 66.3	−17.39	−23.5
Chlorcyclizine · 2 HCl	−23.44 ± 0.92	1116.6 ± 9.5	−17.40	−20.3
Meclizine · 2 HCl	−22.71 ± 0.09	865.0 ± 13.9	−16.76	−19.9
Hydroxyzine · HCl	−22.00 ± 1.08	1158.7 ± 60.10	−17.49	−15.1
Hydroxyzine · 2 HCl	−21.05 ± 0.55	1153.97 ± 37.01	−17.52	−12.3
Proadifen · HCl	−20.83 ± 0.53	184.2 ± 8.0	−12.93	−26.5
Adiphenine · HCl	−25.52 ± 1.61	11.5 ± 0.8	−6.05	−65.3

[a] Average ± SD (n = 3).

radii of the aromatic hydrogens, is estimated from molecular modeling to be 9.2–10 Å. Therefore, only one of the aromatic rings can possibly penetrate into the α- or β-CD cavity at one time. The enhancement of the binding by substituents suggests that the substituted benzene ring is most probably residing in the CD cavity.

"Combined hydrophobic" interaction (6,15) seems to provide a suitable explanation for our experimental results. This combined interaction is presumed to be comprised of the following elemental interactions: (i) van der Waals interaction between the ligand molecule and the CD cavity; (ii) entropy gain due to the destruction of the water assembly around the ligand molecule; (iii) entropy loss due to "freezing" of the freedom for motion of the ligand molecule in the CD cavity; and (iv) enthalpy gain due to the releasing of the "high-energy" water from the CD cavity.

Considering the size of the CD cavities, α-CD can hold the phenyl ring in certain tightly bound configurations, resulting in a substantial loss in the translational and rotational degrees of freedom for the ligand molecule. γ-CD, on the other hand, appears to bind the phenyl ring more loosely, leading to low van der Waals interaction energy and a larger entropy of complexation. The best fit between β-CD and an aromatic ring of the diphenylmethyl functional group resulted in a relatively large binding energy and moderate entropy loss. According to Griffiths and Bender (15), the "empty" CD contains water molecules that are unable to form their full complement of hydrogen bonds to adjacent water molecules and, thus, may be considered to be "enthalpy rich." The inclusion of a guest molecule would then displace this high-energy water from the CD cavity, leading to a net increase in solvent–solvent hydrogen bonds and a favorable enthalpy of association. If this is the case, the standard enthalpy ($\Delta H°$) decreases for γ-CD complexation should be relatively large. More water molecules should be released from the γ-CD cavity, even though as the size of the CD cavity increases, the energy released per water molecule displaced from the cavity would be expected to decrease as

Table III. Summary of the Thermodynamic Parameters and Binding Constants for the Association of Diphenylmethyl Derivatives with γ-CD in Aqueous Solution at 25°C (1:1 Stoichiometry)

Compound	$\Delta H°$ (kJ/mol)[a]	K (M^{-1})[a]	$\Delta G°$ (kJ/mol)	$\Delta S°$ (J/mol · K)
Cinnarizine · 2 HCl	−20.34 ± 0.34	78.43 ± 1.8	−10.81	−32.0
Diphenidol · HCl	−2.39 ± 0.03	373.5 ± 10.4	−14.68	41.2
Orphenadrine · HCl	−2.91 ± 0.07	964.3 ± 114.2	−17.03	47.4
Bromodiphenhydramine · HCl	−10.01 ± 0.08	2430.3 ± 50.3	−19.32	31.2
Diphenylpyraline · HCl	−2.84 ± 0.02	777.7 ± 19.6	−16.50	45.8
Cyclizine · HCl	−4.11 ± 0.03	731.9 ± 18.1	−16.35	41.1
Chlorcyclizine · HCl	−8.16 ± 0.07	1298.9 ± 51.2	−17.77	32.2
Chlorcyclizine · 2 HCl	−7.21 ± 0.05	1108.5 ± 35.9	−17.38	34.1
Meclizine · 2 HCl	−9.40 ± 0.16	843.0 ± 11.6	−16.70	24.5
Hydroxyzine · HCl	−8.71 ± 1.15	1194.8 ± 59.7	−17.59	29.6
Hydroxyzine · 2 HCl	−6.68 ± 0.28	1307.1 ± 90.9	−17.79	37.3
Proadifen · HCl	−14.46 ± 0.43	1125.2 ± 50.1	−17.42	9.9
Adiphenine · HCl	−5.10 ± 0.04	404.9 ± 7.5	−14.88	32.8

[a] Average ± SD (n = 2).

Table IV. Summary of the Thermodynamic Parameters and Binding Constants for the Association of Diphenylmethyl Derivatives with β-CD in Aqueous Solution at 25°C (1:2 Stoichiometry)

Compound	$\Delta H°$ (kJ/mol)[a]	K (M^{-1})[a]	$\Delta G°$ (kJ/mol)	$\Delta S°$ (J/mol · K)
Terfenadine · HCl (1:1)[b]	−19.24 ± 0.50	20269 ± 2976	−24.58	17.91
Terfenadine · HCl (1:2)[b]	−35.97 ± 1.64	644.9 ± 81.2	−16.04	−66.85
Terfenadine · HCl (1:1)[c]	−20.00 ± 0.33	18680 ± 1860	−24.38	14.69
Terfenadine · HCl (1:2)[c]	−32.73 ± 0.24	556.6 ± 17.6	−15.67	−57.22
Cinnarizine · 2HCl (1:1)	−17.34 ± 0.37	2910.6 ± 202.7	−19.77	8.15
Cinnarizine · 2HCl (1:2)	−26.62 ± 2.19	207.7 ± 17.2	−13.23	−44.91

[a] Average ± SD (n = 5).
[b] Initial terfenadine · HCl concentration, 0.8994 mM.
[c] Initial terfenadine · HCl concentration, 0.4497 mM.

the energy content of the included water slowly approaches that of the bulk water. Our results show that the standard enthalpy ($\Delta H°$) decreases for γ-CD complexation with diphenylmethyl derivatives that were relatively small. Therefore, van der Waals interaction energy should be mainly responsible for the relatively small favorable enthalpy changes.

All the compounds were studied in their HCl salt form. For bifunctional amine compounds such as chlorcyclizine and hydroxyzine, both HCl and 2 · HCl salts were studied. The results show independence of the thermodynamic parameters on the degree of protonation, indicating that amine functional groups do not penetrate into the CD cavity. Also, the close similarity of the thermodynamic parameters for the binding of β-CD with two amine compounds bearing markedly different amine functional groups, diphenhydramine · HCl and cyclizine · HCl, suggests that the diphenylmethyl groups of these compounds are the structural features which interact with the cyclodextrin cavity.

It is worthwhile comparing the results obtained with proadifen · HCl and adiphenine · HCl. The only difference between these two compounds is that proadifen · HCl has a propyl group attached to the diphenylmethyl group, while adiphenine · HCl has a hydrogen atom at this position. Figure 4 summarizes the binding constants for the interactions between these two compounds and three CDs. Adiphenine · HCl forms a more stable complex with β-CD but a less stable complex with γ-CD, while both of them form unstable complexes with α-CD. Hydrogen bonding of the carbonyl oxygen in adiphenine · HCl with the hydroxyl group on the rim of the CD ring might possibly enhance the binding of adiphenine HCl to β-CD. On the other hand, the propyl group in proadifen · HCl might inhibit deep penetration of the aromatic ring into the cavity, therefore preventing the formation of such a hydrogen bond. In the case of γ-CD, the propyl group in proadifen · HCl might give rise to stronger van der Waals attraction between proadifen · HCl and cyclodextrin. Neither of the compounds penetrates into the α-CD cavity very deeply, so a substituent on the diphenylmethyl group does not seem to affect the binding.

To support this explanation, the adiphenine · HCl and proadifen · HCl-β-CD complexes were prepared using a freeze-drying method. The FTIR spectrum of the adiphenine · HCl-β-CD complex showed a shift in the carbonyl stretching region to a higher frequency. This shift was not found in the spectrum of the adiphenine · HCl-β-CD physical mixture, the proadifen · HCl-β-CD complex, or the physical mixture. This suggests that hydrogen bonding occurs in the adiphenine HCl complex or that the carbonyl

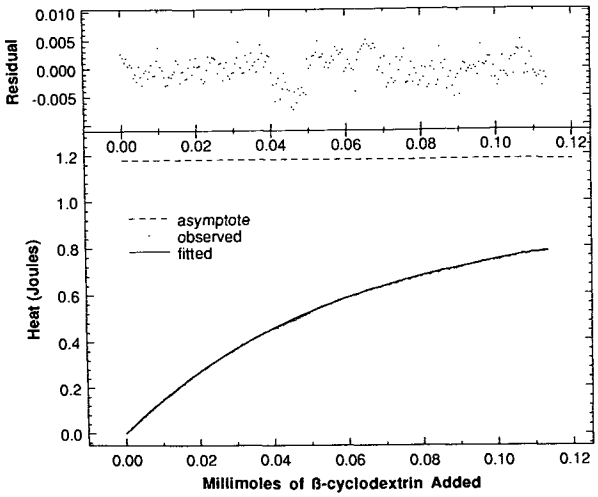

Fig. 2. Calorimetric titration curve and residual plot for the interaction between diphenhydramine · HCl and β-CD in aqueous solution at 25°C.

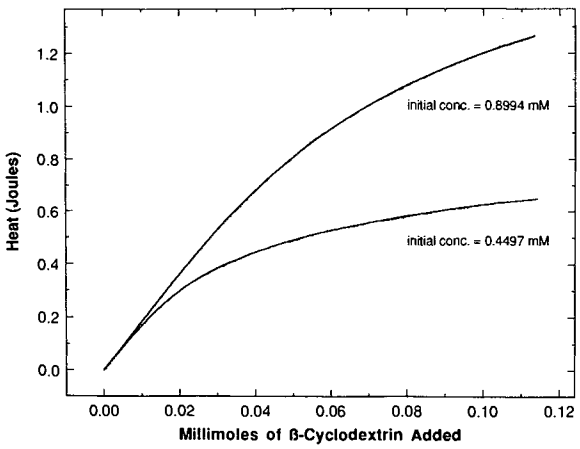

Fig. 3. Calorimetric titration curves for the interaction between terfenadine · HCl and β-CD in aqueous solution at 25°C (the initial concentrations of terfenadine · HCl solution are labeled).

Table V. Five Calorimetric Titration Runs for Diphenhydramine · HCl-β-CD Interaction in Aqueous Solution at 25°C

Run	$\Delta H°$ (kJ/mol)	K (M^{-1})
1	−29.26 ± 0.07	1176.4 ± 7.6
2	−29.42 ± 0.09	1173.9 ± 9.6
3	−29.35 ± 0.06	1098.9 ± 6.4
4	−30.56 ± 0.08	1113.0 ± 7.6
5	−28.38 ± 0.07	1180.5 ± 7.7
Average ± SD	−29.40 ± 0.78	1148.5 ± 39.3

group might be partially included in the β-CD cavity. The IR spectra are shown in Figures 5 and 6.

Of the 13 compounds studied, only β-CD complexes with terfenadine · HCl and cinnarizine · 2HCl have 1:2 (compound:CD) stoichiometry. For each substrate, $\Delta H°$ is more favorable and $\Delta S°$ is less favorable for the 1:2 complex than for the 1:1 complex. The addition of the second CD molecule to the 1:1 complex significantly restricted the motional freedom of the guest molecule in the CD cavity and resulted in an unfavorable entropy change. The phase solubility method (8) and kinetic studies (9) have shown evidence of 1:2 (cinnarizine:β-CD) stoichiometry for the complexation between cinnarizine and β-CD in pH 2.0 HCl–KCl buffer solution. The binding constants reported, however, are substantially smaller than our results. In part this could be due to the different reaction conditions used. The calorimetric studies of this complex by other workers (10) could confirm only the 1:1 complex. The $\Delta H°$ value reported is in good agreement with that obtained in our work. From the structural point of view, both terfenadine · HCl and cinnarizine · 2HCl should be able to form 1:2 complexes with α- and γ-CDs. It is possible that the heat released in the second step of the stepwise complexation process is too small to be evaluated in our calorimeter.

In conclusion, the above results suggest the following.

1. Generally, among the three CD's, β-CD forms the strongest interactions with amine drugs bearing the diphenylmethyl functionality. The stability of the complexes is in the order β-CD > γ-CD > α-CD.
2. Basically only one phenyl group in the diphenylmethyl functionality can fit into the α- or β-CD cavity at one time, whereas there exists the possibility that both benzene groups might fit into the γ-CD cavity.
3. Amine functional groups in these molecules do not seem to penetrate into the CD cavities.
4. A methyl or halogen substituent on the aromatic ring enhances the binding.
5. van der Waals interaction plays a very important role in diphenylmethyl derivative–CD interactions. In the case of α- and β-CDs, van der Waals interaction dominates in the stabilization. In contrast, the interaction between these compounds and γ-CD is largely entropically driven.
6. The existence of a close spatial fit between the diphenylmethyl derivatives and the CD cavity is a neces-

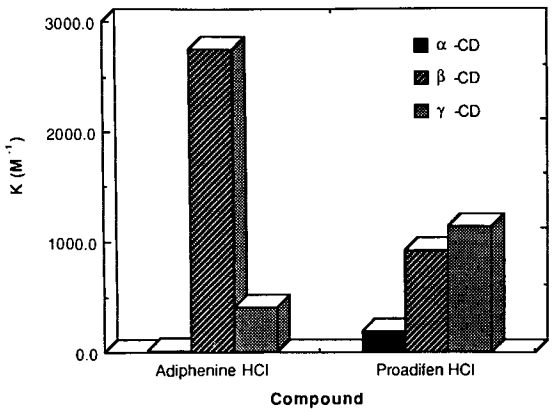

Fig. 4. Comparison of the binding constants for the interaction of adiphenine · HCl and proadifen · HCl with α-, β-, and γ-CDs.

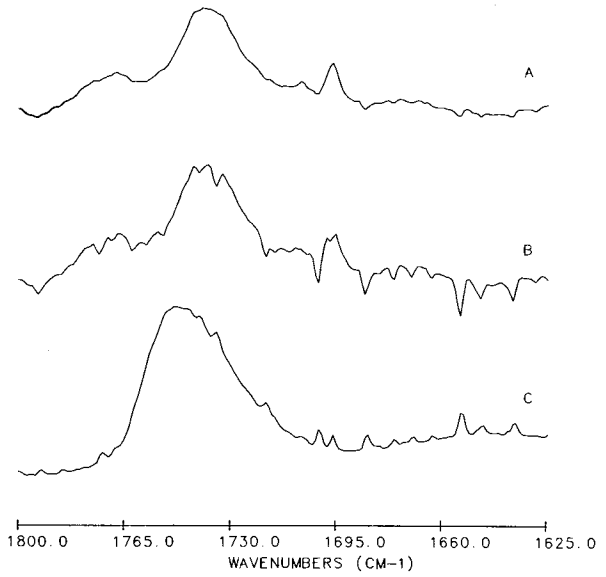

Fig. 5. IR spectra for the adiphenine · HCl-β-CD system. (A) Adiphenine · HCl alone; (B) adiphenine · HCl-β-CD physical mixture; (C) adiphenine · HCl-β-CD complex.

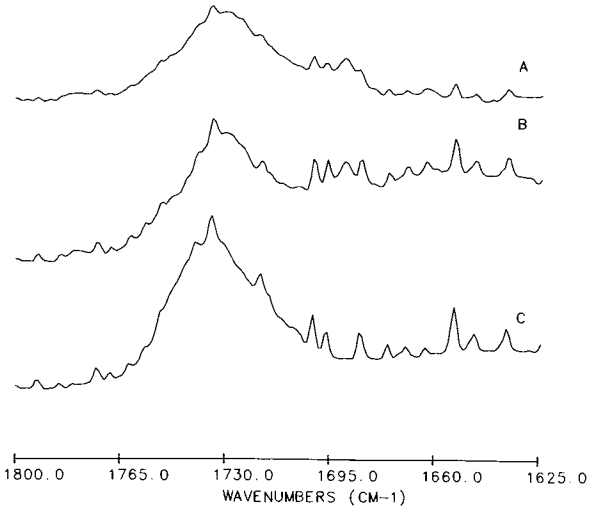

Fig. 6. IR spectra for the proadifen · HCl-β-CD system. (A) Proadifen · HCl alone; (B) proadifen · HCl-β-CD physical mixture; (C) proadifen · HCl-β-CD complex.

sary requirement for the formation of a stable inclusion complex.

7. In 1:1 complexes, a remote substituent away from the diphenylmethyl functionality does not seem to distort the complex.

In order to illustrate better the structural effects on the binding constants and complex geometries, the molecular modeling program, SYBYL (16), was recently used to perform molecular mechanical calculations on the compounds and complexes. The gas-phase binding energies, ΔE's, defined as $E_{components} - E_{complex}$, were found to correlate well with the binding constants (ln K). A plot of ΔE vs ln K for β-CD complexes is shown in Fig. 7. This suggests that the van der Waals interaction between the compounds studied and β-CD is a very important contributor to the stability of the inclusion complexes and that molecular mechanical calculations can be useful in predicting the ability of a potential guest molecule to penetrate the CD cavity. A detailed discussion of this approach will be given in the second part of our series of reports on the structural effects on the binding of amine drugs with the diphenylmethyl functionality to cyclodextrins.

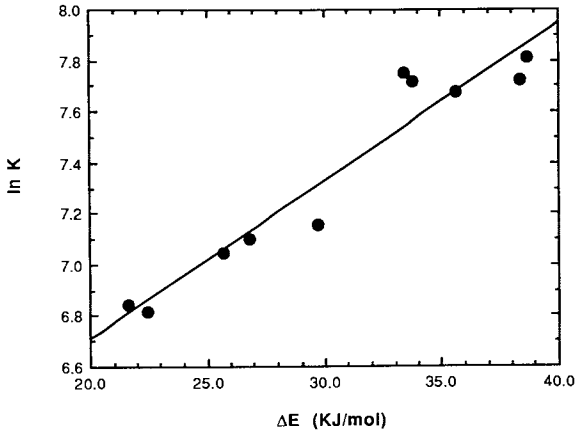

Fig. 7. Correlation between calculated interaction energies (ΔE's) and binding constants from calorimetric titrations (ln K). $R^2 = 0.924$ for linear regression.

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