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ORIGINAL ARTICLE

Thermodynamic enthalpy–entropy compensation effects observed in the complexation of basic drug substrates with β-cyclodextrin

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Abstract Measurement of the variation of inherent drug solubility (S_o) and 1:1 drug/cyclodextrin complex formation constants (K_{11}) with temperature were used to estimate the thermodynamic parameters (ΔH^o, ΔS^o and ΔG^o). A plot of $T\Delta S^o$ against ΔH^o indicates the extent of enthalpy–entropy compensation; that is, how much of the enthalpic gain is cancelled by entropy loss or vice versa (the slope indicates the fraction of conformational change contribution to enthalpy gain that is cancelled by an accompanying entropy loss). The remaining fraction of enthalpy gain contributes to complex formation. The intercept is the inherent contribution to complex stability, which is due to desovation. Extensive phase solubility studies combined with rigorous analysis were conducted in the temperature range 20–45°C for the following basic drugs complexing with β-cyclodextrin (**β-CD**): astemizole (**Astm**), cisapride (**Cisp**), dipyridamole (**Dipy**), ketotifen (**Keto**), pizotifen (**Pizo**), terfenadine (**Terf**), fexofenadine (**Fexo**), sildenafil (**Sild**), and celecoxib (**Celox**). The results indicate that inherent drug solubility is accompanied by unfavorable conformational changes to the extent of 86%, which are counterbalanced by opposite favorable entropy changes. Only 14% of the favorable enthalpy change contributes to drug solubility. The extent of solvation (hydration) accompanying solubility amounts to –30 kJ/mol, which retards solubility as an unfavorable entropy change. In contrast, 1:1 drug/**β-CD** complex formation is accompanied by favorable conformational changes to the extent of 94%, which are counterbalanced by unfavorable entropy changes. Only about 6% of enthalpy changes contribute to complex stability. However, the extent of favorable entropy change (desolvation) accompanying complex formation amounts to 26 kJ/mol.

Keywords Basic drug cyclodextrin complexation · Enthalpy–entropy compensation · Phase solubility diagrams · Thermodynamics

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Introduction

Cyclodextrins (CDs) have been widely used to improve the solubility of water insoluble compounds through inclusion complexation and were thus the subject of patents on CD complexation technologies. For example, CDs were used in different patents to improve the solubility of **Astm**, **Cisp**, **Fexo**, and **Terf** [1–4]. However, guest–host interactions of these drugs, in addition to **Keto** and **Pizo**, with CDs involving inclusion complex characterization have not yet been reported except for **Terf**.

The complexation of **Celox**, **Dipy**, **Sild** and **Terf** with CDs in solution and the solid state has been investigated by phase solubility techniques, differential

scanning calorimetry, powder X-ray diffractometry, proton nuclear magnetic resonance, infrared and molecular modeling [5–16]. However, in the above publications, thermodynamic investigation was conducted for **Celox**, **Sild** and **Terf** [5, 7, 9].

In the inclusion complexation of cyclodextrins, noncovalent interactions are involved. These include electrostatic, van der Waals, hydrophobic, hydrogen bonding, charge transfer, π–π stacking interactions, steric effects, or some combinations of these effects [17, 18].

There are many factors that contribute to the complexation thermodynamics, including penetration of the hydrophobic part of the guest molecule into the cyclodextrin cavity, dehydration of the organic guest, hydrogen bonding involved in complex stabilization, the release of water molecule from the cyclodextrin cavity to bulk water, and conformational changes or strain release from the cyclodextrin molecule upon complexation [17].

The objective of this work was to measure the phase solubility diagrams for different drugs with ***β*-CD** at different temperatures, and to obtain estimates of inherent drug solubilities (S_o) and 1:1 complex formation constants (K_{11}) under controlled conditions of same buffer species, buffer concentration and pH. Subsequently the thermodynamic parameters (ΔH^o, ΔS^o and ΔG^o) were calculated and a quantitative estimate of the contribution of conformational changes and desolvation to complex stability and to inherent drug solubility were evaluated (Scheme 1)

Materials and methods

Materials

All drugs and ***β*-CD** were provided by The Jordanian Pharmaceutical Manufacturing Company (JPM). Four of the drugs used (**Fexo**, **Keto, Pizo**, and **Sild**) were available as the hydrochloride, fumarate, malate and citrate salts, respectively. The neutral forms of these drugs were prepared by neutralization with dilute NaOH solution. The salts of **Fexo**, **Keto**, **Pizo** and **Sild** (10 mmoles each) were shaken in sufficient amounts of 0.1 M NaOH, and the neutral drugs precipitates were collected and dried at 40 °C for 2 days. All other chemicals were of analytical or HPLC grades obtained from Merck/Germany and Surechem/England. Doubly distilled deionised water was used for all aqueous solutions involved in phase solubility and thermodynamic measurements.

Methods

Instrumentation

The instruments used were UV/Visible spectrophotometer (Du-650i, Beckman, USA), Thermostatic bath shaker (1086, GFL, Germany), pH-meter (3030, Jenway, England), and High performance liquid chromatography (Gold System, Beckman, USA).

pH solubility profiles

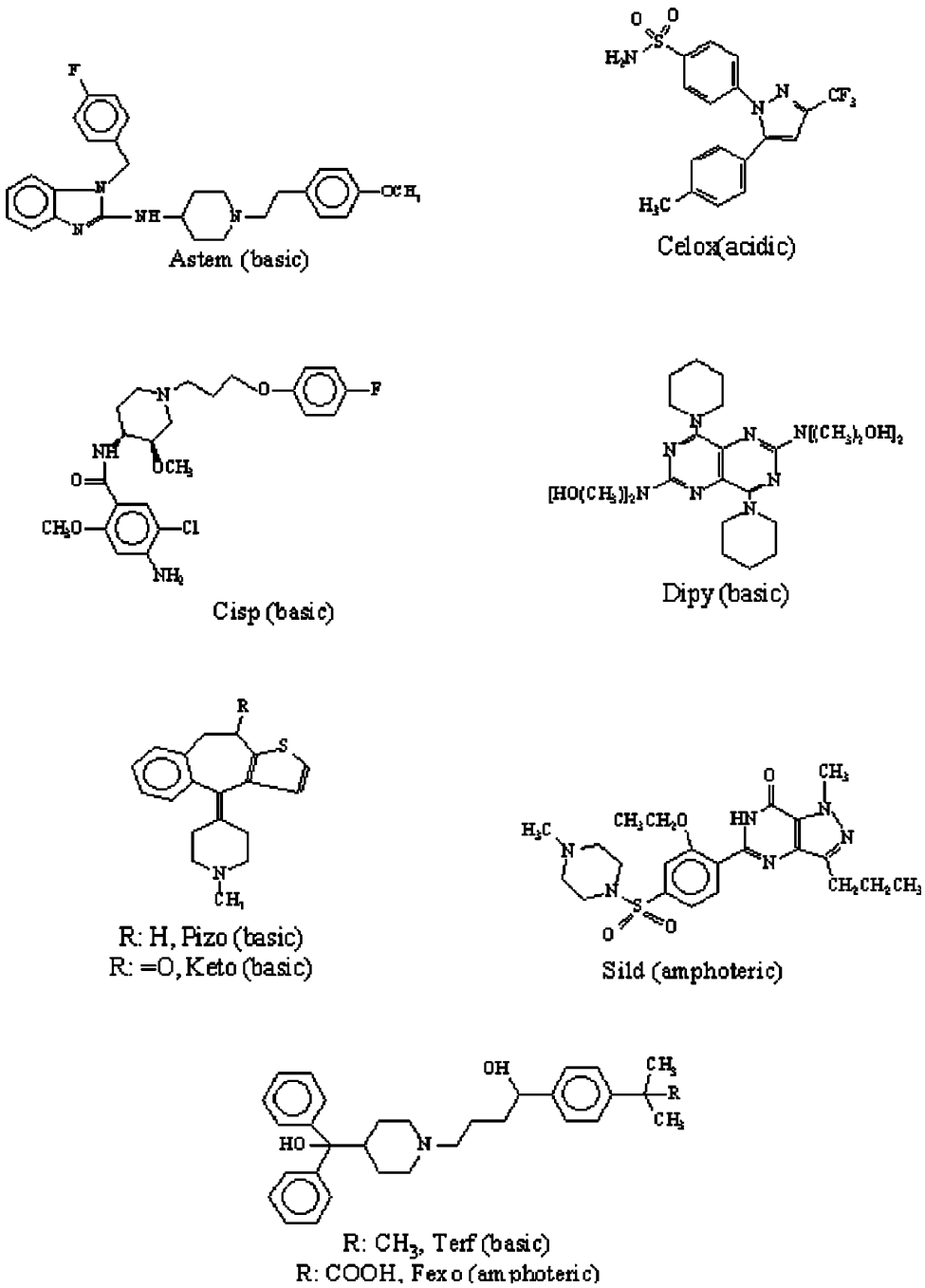
Excess amounts of the drugs were added to 50 ml of 0.05 M citrate buffer at different pHs ranging from 1 to 12. The pH of buffer solutions was adjusted by diluted sodium hydroxide solution. The samples were mechanically shaken in a thermostatic bath shaker at 30 °C to attain equilibrium, an aliquot was filtered using a 0.45 μm filter (cellulose acetate, Advantec MFS Inc., Duplin, USA). The pH of the filtrate was measured by calibrated pH-meter. The concentration of drug in each solution was determined by the HPLC method (Table 1).

Rigorous nonlinear regression of experimental data corresponding to plot of S_o (inherent solubility of drug) against pH was conducted using the Marquardt-Levenberg finite difference algorithm utilized by the SPSS statistical package (SPSS 10.0 for Windows Statistical Package, SPSS Inc., 233 S. Wacker Drive, Chicago, Illinois), and data plots were linked to Microsoft Excel for reproduction.

Phase solubility studies

Solubility studies were performed as described by Higuchi and Connors [19]. Excess amounts of the drug were added to 50 ml flasks containing 25 ml buffered aqueous β-CD solutions of various concentrations (0–18 mM). The solutions were let to shake for a period of time sufficient at constant temperature to establish equilibrium for each of the drugs (2–14 days), then let to settle for 24 h and filtered. This procedure was repeated for other temperatures within the range 20–45°C. The drug assay was conducted using first derivative spectrophotometry at about 285 nm for **Astm**, 270 nm for **Celox**, **Fexo** and **Terf**, 278 nm for **Dipy**, 320 nm for **Cisp** and **Keto**, 267 nm for **Pizo** and 311 nm for **Sild**. HPLC methods (Table 1) were used to measure the inherent drug solubility (S_o) whenever it proved immeasurable by first derivative spectrophotometric methods. The complex formation constants were estimated from the measured phase solubility diagrams

Scheme 1 Chemical structures of drugs used in this work



obtained at constant pH and temperature using rigorous procedures described earlier [20].

Estimation of thermodynamic parameters

By using Gibbs and Van't Hoff equations, the thermodynamic functions of complexation ΔH^{o}, ΔS^{o} and ΔG^{o} are estimated according to

$$\Delta G^{o} = \Delta H^{o} - T\Delta S^{o} \quad (1)$$

$$\ln K = \Delta S^{o}/R \; - \Delta H^{o}/RT \quad (2)$$

where K represents K_{11}^{x} or S_{o}^{x}, while the superscript (^{x}) denotes the mole fraction standard state (Both S_o and K_{11}, that were initially estimated from the phase solubility diagrams in molar concentration units, were converted to mole fraction units) [7].

A plot of ln K versus $1/T$ yields a slope = $-\Delta H^{o}/R$ and intercept = $\Delta S^{o}/R$.

Table 1 HPLC method parameters[a]

Drug	Mobile phase	Stationary phase	λ (nm)	Flow rate (ml/min.)
Astm	ACN:MeOH:0.13 M NH_4AC:DEA (550:470:300:1)[a]	C8 (Hypersil BDS, 250 × 4.6 mm, 5 μm, Hypersil, UK)	220	2.0
Celox	ACN:MeOH:Phosphate buffer (5:1:4 v/v)	C18 (Hypersil BDS, 250 × 4.6 mm, 5 μm, Hypersil, UK)	250	2.0
Cisp	ACN:0.2M NH_4AC (1:1 v/v)	C18 (Hypersil BDS, 250 × 4.6 mm, 5 μm, Hypersil, UK)	270	1.5
Keto	ACN:H_2O:TEA (550:450:3)	C18 (Hypersil ODS, 100 × 4.6 mm, 5 μm, Hypersil, UK)	300	1.0
Pizo	ACN:H_2O:TEA (550:450:3)	C18 (Hypersil ODS, 100 × 4.6 mm, 5 μm, Hypersil, UK)	270	2.0
Terf	ACN:DEA Phosphate buffer (6:4 v/v)	C8 (Hypersil BDS, 250 × 4.6 mm, 5 μm, Hypersil, UK)	217	2.0

[a] ACN, acetonitrile; MeOH, Methanol; TEA, triethylamine; DEA, diethylamine; DEA·PO_4, Diethylammonium, NH_4AC, ammonium acetate

Entropy–enthalpy compensation effect

The relationship between enthalpy and entropy is indicated by [17, 18]:

$$T \cdot \Delta\Delta S^{o} = \alpha \cdot \Delta\Delta H^{o} \quad (3)$$

which upon integration yields

$$T \cdot \Delta S^{o} = \alpha \cdot \Delta H^{o} + T\Delta S^{o}_{o} \quad (4)$$

Substitution into the Gibbs-Helmholtz equation yields

$$\Delta\Delta G^{o} = \Delta\Delta H^{o} - T\Delta\Delta S^{o} \quad (5)$$

$$\Delta G^{o} = (1 - \alpha) \cdot \Delta\Delta H^{o} \quad (6)$$

The slope (α) of a $T\Delta S^{o}$ against ΔH^{o} plot indicates the extent to which an enthalpic gain ($\Delta\Delta H^{o}$) induced by changes in host, guest, and/or solvent is cancelled by an accompanying entropic loss ($\Delta\Delta S^{o}$). Only a fraction $(1 - \alpha)$ of the enthalpic gain may contribute to complex stability. The intercept $T\Delta S^{o}_{o}$ denotes the value of the inherent complex stability (ΔG^{o}) in the absence of any enthalpic contribution ($\Delta H^{o} = 0$); i.e., the complex would be stabilized even in the absence of enthalpic stabilization where $T\Delta S^{o}_{o} > 0$. Obviously, α is a measure of the extent of conformational changes accompanying complex formation, while $T\Delta S^{o}_{o}$ is a measure of desolvation (dehydration) that accompany complex formation [17, 18].

Results and discussion

Figure 1 depicts the phase solubility diagrams obtained for the nine drugs against β-CD concentration in 0.05 M citrate buffers at 25°C. The corresponding drug inherent solubility (S_o) and 1:1 complex formation constant (K_{11}) are listed in Table 2. The standard thermodynamic functions (ΔG^{o}, ΔH^{o} and ΔS^{o}) ob-

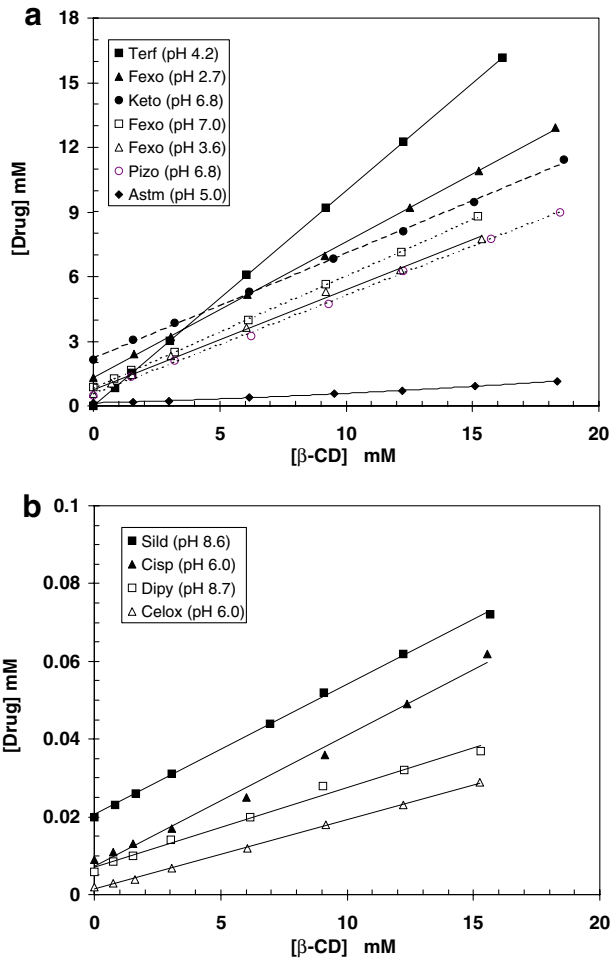


Fig. 1 Phase solubility diagrams of the nine drugs with **β-CD** in 0.05 M citrate buffer at 25 °C

tained from van't Hoff plots for S_o and for K_{11} are also listed in Table 2. Aside from **Pizo** and **Keto**, 1:1 drug/β-CD complex formation is apparently driven by favorable enthalpic and entropic changes. It is also noted that for the zwitter ionic form of **Fexo**, the entropic change is slightly unfavorable due to the possible affinity of **β-CD** towards the neutral tautomer of **Fexo**, which coexists with the zwitterion but is less solvated in water than the zwitterion.

Drug solubility (S_o) is generally retarded both by unfavorable enthalpic changes (except for **Pizo** and **Keto)**, and by unfavorable entropic changes (except for protonated **Astm** and **Fexo**, and for neutral **Celox**). Overall, there appears to be entropy–enthalpy compensation, where stronger binding forces (lower ΔH) are accompanied by loss in entropy (lower ΔS).

To check the extent of entropy–enthalpy compensation, Figure 2a and b depict plots of $T\Delta S^o$ against ΔH^o for S_o and 1:1 complex formation, respectively. Figure 2a indicates that drug solubility is accompanied by unfavorable conformational changes (in drug and/or water) to the extent of 86% (slope), which are counterbalanced by opposite favorable entropy changes. Only 14% of any favorable enthalpy change contributes to drug solubility. The extent of solvation (hydration) accompanying solubility amounts to –30 kJ/mol, which retards solubility as an unfavorable entropy change.

As to 1:1 drug/**β-CD** complex formation, Figure 2b indicates that the process is accompanied by favorable conformational changes (in drug, drug/**β-CD** and/or water) to the extent of 94%, which are counterbalanced by unfavorable entropy changes. Only about 6% of enthalpy changes contribute to complex stability. However, the extent of favorable entropy change (desolvation) accompanying complex formation amounts to about 26 kJ/mol. Earlier studies showed similar trends for a wide range of guest molecules [17], where only 80% of favorable enthalpic changes are counterbalanced by entropy loss, while only 20% of enthalpic changes contribute to complex stability. Therefore, the larger and more flexible basic drug molecules used in this work appear to undergo more conformational changes (94% of ΔH^o) on complex formation.

Conclusion

Basic drug/**β-CD** complex formation is generally driven both by favorable enthalpy and entropy changes. Where enthalpy changes are unfavorable, entropy

Table 2 Thermodynamic parameters for the drug solubility (S_o) and drug/**β-CD** complexation in 0.05 M citrate buffer as obtained from the van't Hoff plots

Drug solubility (S_o)

Drug	pH/Species	pK_a	S_o (mM)	ΔG^o (kJ/mol)	ΔH^o (kJ/mol)	ΔS^o (J/K.mol)
Astm	5.0/Protonated	7.5 (basic)	0.147	31.8	49.5	59
Celox	6.0/Neutral	9.7 (acidic)	0.001	44.2	49.3	17
Cisp	6.0/Protonated	8.2 (basic)	0.0091	38.7	11.9	–90
Dipy	8.6/Neutral	6.4 (basic)	0.0056	39.9	31.1	–30
Fexo	2.7/protonated	10.2 (basic), 4.2 (acidic)	1.297	26.4	29.8	12
	3.6/protonated		0.556	28.5	28.9	1.2
	7.0/Zwitter ion		0.834	27.5	7.8	–66
Keto	6.8/Protonated	8.5 (basic)	2.16	25.2	–11.3	–122
Pizo	6.8/Protonated	8.9 (basic)	0.51	28.7	–18.3	–158
Sild	8.6/Neutral	10.3 (acidic), 7.1 (basic)	0.0197	36.8	14.3	–76
Terf	4.2/Protonated	9.5 (basic)	0.112	32.5	19.5	–43

*Drug/**β-CD** complex formation* (K_{11})

Drug	pH/species	K_{11} (M^{-1})	ΔG^o (kJ/mol)	ΔH^o (kJ/mol)	ΔS^o (J/K.mol)
Astm	5.0/Protonated	169	–22.7	–11.0	31
Celox	6.0/Neutral	1756	–28.5	–21.8	23
Cisp	6.0/Protonated	256	–23.7	–8.9	50
Dipy	8.6/Neutral	327	–24.3	–14.8	32
Fexo	2.7/protonated	1492	–28.1	–11.9	54
	3.6/protonated	1695	–28.4	–20.9	25
	7.0/Zwitterion	1414	–27.7	–23.2	15.2
Keto	6.8/Protonated	442	–25.0	7.5	109
Pizo	6.8/Protonated	1690	–28.4	2.9	105
Sild	8.6/Neutral	182	–22.9	–19.8	10
Terf	4.2/Protonated	8830	–32.5	–13.4	64

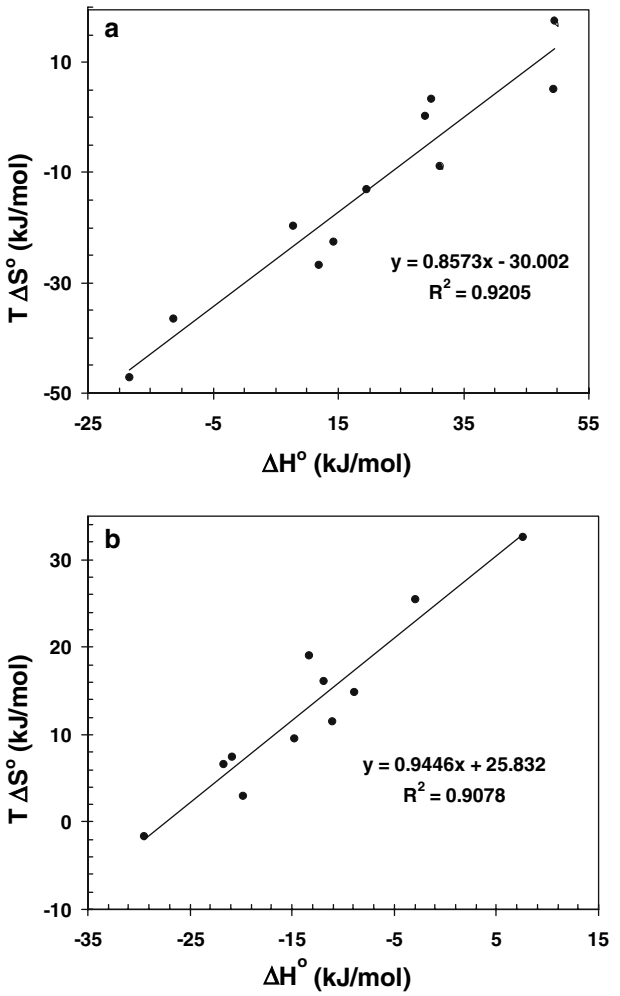


Fig. 2 Entropy–enthalpy plots for (**a**) drug inherent solubility (S_o) and (**b**) for 1:1 complex formation of the nine drugs with ***β*-CD** in 0.05 M citrate buffer

changes become more favorable (entropy–enthalpy compensation).

Entropy–enthalpy compensation indicates that almost 94% of favorable enthalpy changes accompanying complex formation are due to conformational changes, which are completely counterbalanced by entropy loss. Only 6% of favorable enthalpy changes contribute to complex stability. Inherent complex stability due to desolvation (water molecules lost to the bulk) amounts to about 26 kJ/mol for these rather large drug molecules.

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