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Electrochemical Studies of Cationic Drug Inclusion Complexes with α- and β-Cyclodextrins

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Abstract. Drug membrane selective electrodes have been constructed for the cationic drug propranolol hydrochloride, diphenhydramine hydrochloride, diphenylpyraline hydrochloride and also chlorcyclizine hydrochloride. The characteristics of these drug selective electrodes have been evaluated and the electrodes used to measure equilibrium constants of the inclusion compounds involving the drugs with both α- and β-cyclodextrins. The enthalpies and entropies associated with the formation of the inclusion complexes have also been estimated from the temperature dependence of the equilibrium constants.

Key words. Drug selective electrode, cyclodextrin, inclusion complexes.

1. Introduction

The cyclodextrins have proved to be useful model systems in the study of inclusion complexes involving host/guest interactions [1–3]. Such inclusion compounds have been widely studied for different purposes in the pharmaceutical, chemical and food industry [4, 5]. α- and β-Cyclodextrins which have been tested to be non-toxic if administered orally [6] may find use in the pharmaceutical industry, especially in reducing bitterness and side effects. They may also be used to increase the solubility of drugs and thus directly increase the bioavailability of these drugs. As a result, the emphasis on research work has been in the area of host/guest complexes.

Recently we have shown [7, 8] that electrodes selective to various drugs can be used to investigate the equilibrium properties of their inclusion complexes with α- and β-cyclodextrins. We describe here the continuation of this work and report measurements on the complexation of the drugs propranolol hydrochloride (PH), diphenhydramine hydrochloride (DPHH), diphenylpyraline hydrochloride (DPPH) and chlorcyclizine hydrochloride (CCH) with α- and β-cyclodextrins.

2. Experimental

2.1. CHEMICALS USED

The drugs used in this work were of the highest purity available. Table I lists the drugs used together with their structure and their suppliers. All the drugs exist as the amine hydrochloride and when dissolved in water dissociate to give the drug cation. The α- and β-cyclodextrins were purified commerical samples obtained from Aldrich.

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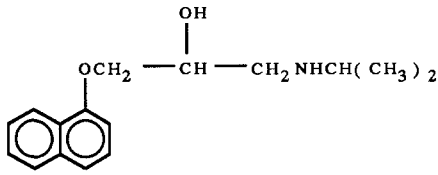
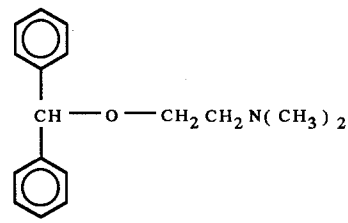
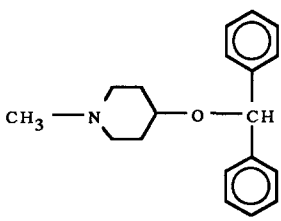
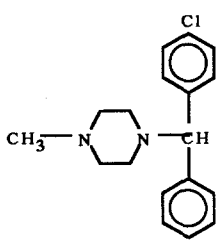
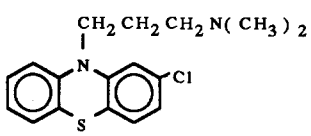
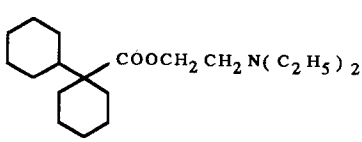
Table I. List of the cationic drugs used in this work

Drug	Structure	Supplier
Propranolol (PH)		ICI Ltd
Diphenhydramine (DPHH)		Smith Kline and French
Diphenylpyraline (DPPH)		Smith Kline and French
Chlorcyclizine (CCH)		Burroughs Wellcome Ltd. India
Chlorpromazine (CP)		Sigma
Dicyclomine (DC)		Vick Interational R and D Labs

2.2. CONSTRUCTION OF ELECTRODE

The drug selective membrane electrodes used in this work are based on modified versions of surfactant selective electrodes and thus were constructed by the method described previously [7]. In principle these electrodes monitor the drug monomer cation concentration in solution.

The emf measurements (± 0.2 mV) were made using a digital pH/millivolt meter (Corning Ion Analyser 250). In all the experiments the temperature was controlled to within ± 0.1°C by circulating thermostatted water through a double walled glass cell and the sample solution was continuously stirred using a magnetic air driven stirrer. During the emf measurements the concentration of the sample solution was changed successively by adding a small amount of a highly concentrated solution of the drug to the initial sample volume (30 mL) using an Alga micrometer syringe system. The response of the drug electrode was tested in the concentration range of 10^{-5}–10^{-2} mol dm^{-3} at 25°C. The reference electrode used in the present work was either a calomel (Corning) electrode, or in the case of diphenhydramine, the solution was doped with a sufficiently low concentration of sodium chloride (10^{-4} mol dm^{-3}) to cause minimum disruption to the inclusion process and a sodium electrode (Kent 1048) used as a reference. The results were found to be consistent in all cases and for both types of reference electrode. The binding measurements were carried out for both α- and β-cyclodextrins. The principle used in these measurements is as follows:

It is assumed that in solution the drug forms an inclusion compound with cyclodextrin which can be represented by the following equation:

$$\text{Drug} + \text{Cyclodextrin} \rightleftharpoons \text{Inclusion Compound} \quad (1)$$

When such an equilibrium exists then the drug selective electrode monitors the free monomer concentration of drug.

First the emf of the drug electrode relative to the calomel (or sodium reference electrode) was measured as a function of increasing drug concentration in the range 10^{-5}–10^{-2} mol dm^{-3}. In this concentration range the drug exists in solution in its monomer cationic form and the emf data produced good Nernstian responses for all electrodes as typically shown in Figures 1 and 2. The characteristics of the

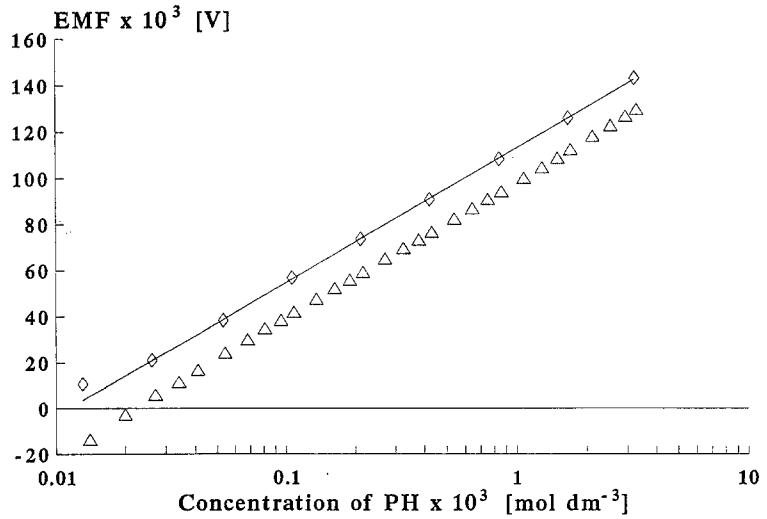


Fig. 1. Nernst plot of electrode potential at 298 K versus total drug concentration for the drug Propranolol; (◇) – drug only; (△) – in the presence of β-CD [5×10^{-3} mol dm^{-3}].

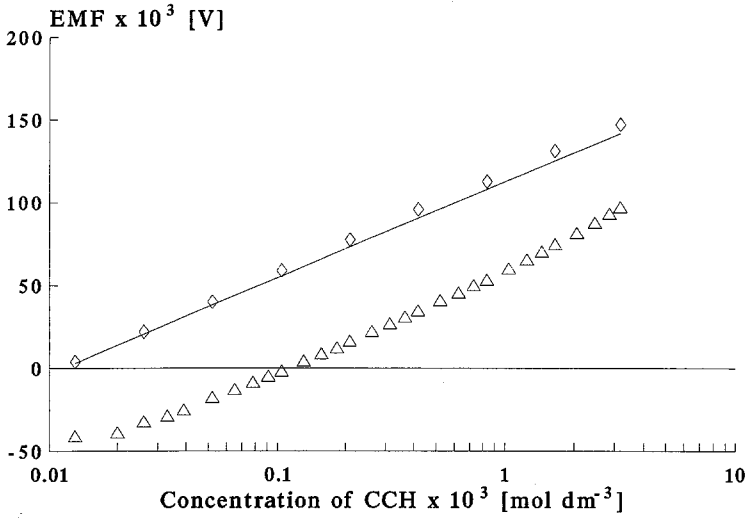


Fig. 2. Nernst plot of electrode potential versus total drug concentration for the drug Chlorcyclizine; (◇) – drug only; (△) – in the presence of α-CD [8.0×10^{-3} mol dm^{-3}].

electrodes are listed in Table II. Recent work [7] has shown that the operation of the drug electrode is unaffected over the pH range of ~2–8 and hence buffering was not required. The experiment was then repeated by measuring the emf of the drug electrode in the presence of a constant concentration of the cyclodextrin. The concentration of the cyclodextrin used during the experiment (between 2–5×10^{-3} mol dm^{-3}) was determined in a trial and error test and was chosen on the basis of a measurable shift in the emf as a result of the binding. Check measure-

Table II. The emf characteristics of the drug selective electrodes.

Drug Electrode	Temperature [K]	Nernst Slope [mV $decade^{-1}$]	Intercept [mV]	Reference electrode
Chlorcyclizine (CCH)	293	58.2	291.1	Calomel
	298	60.1	299.9	
	303	59.9	302.4	
	308	60.8	305.3	
Propranolol (PH)	293	56.7	281.4	Calomel
	298	58.2	286.7	
	303	59.4	291.3	
	308	61.1	289.1	
Diphenylpyraline (DPPH)	293	57.5	286.6	Calomel
	298	59.4	295.4	
	303	59.8	295.4	
	308	60.1	296.5	
Diphenhydramine (DPHH)	298	58.1	364.0	Na^+ ion

ments were also carried out by diluting a concentrated drug/cyclodextrin solution to confirm the reversibility of the inclusion process.

Once the emf measurements relating to the cyclodextrin/drug solutions were completed, the emf of the electrode was then rechecked against the monomer drug to ensure consistency. From these data it is possible to evaluate the drug monomer concentration m_1 for each total concentration of drug in a constant concentration of cyclodextrin solution. In the present work, as in previous studies [7], we did not find any evidence to use activities instead of concentration terms.

The measurements were also carried out in the temperature range 20–35°C in an attempt to estimate the thermodynamic parameters associated with the binding process.

3. Analysis of Data

Equation 1 is a general equation describing the inclusion phenomenon. In many cases it is possible that more than one inclusion complex is formed with different stoichiometry e.g. 1:1, 1:2, 2:1, etc. In the present work the data that we have available are the monomer drug concentration, total drug concentration and the total concentration of cyclodextrin that was used in the experiment. The next question to address is to determine the stoichiometry of the inclusion compound. In the process it is first assumed that a 1:1 complex is formed in which case, the data as they stand, can be treated using the classical Benesi–Hildebrand equation in the form:

$$\frac{1}{v} = \left(\frac{1}{Km_1}\right) + 1 \tag{2}$$

where

$$v = \frac{\text{concentration of drug complexed to cyclodextrin}}{\text{total concentration of cyclodextrin}}$$

and K is the complexation constant.

With the exception of the data for DPPH binding with α-cyclodextrin all the inclusion complexes studied in the present work were of 1:1 stoichiometry with typical plots shown in Figures 3 and 4. We did not find any evidence of significant binding involving propranolol with α-cyclodextrin. The data associated with DPPH and α-cyclodextrin indicated complex binding but unfortunately we have been unable to analyse data in a satisfactory manner which will give information covering the number and stoichiometry of the complexes. The only comment that we are able to make is that more than one inclusion complex exists. The K values are listed in Table III together with similar data on other drug inclusion compounds which have been reported previously [7, 8].

Once the value of the inclusion equilibrium constant K is known the next step is to derive the normal equilibrium thermodynamic parameters ΔG^0, ΔH^0 and ΔS^0, respectively, the Gibbs free energy, enthalpy and entropy changes associated with inclusion. Before proceeding with this exercise it is first necessary to convert the K values (in units of $\text{mol}^{-1}\ \text{dm}^3$) to the dimensionless quantity K_D defined as the mole fraction of inclusion complex. In the present work $K_D = 55.53$ K, i.e. taking into

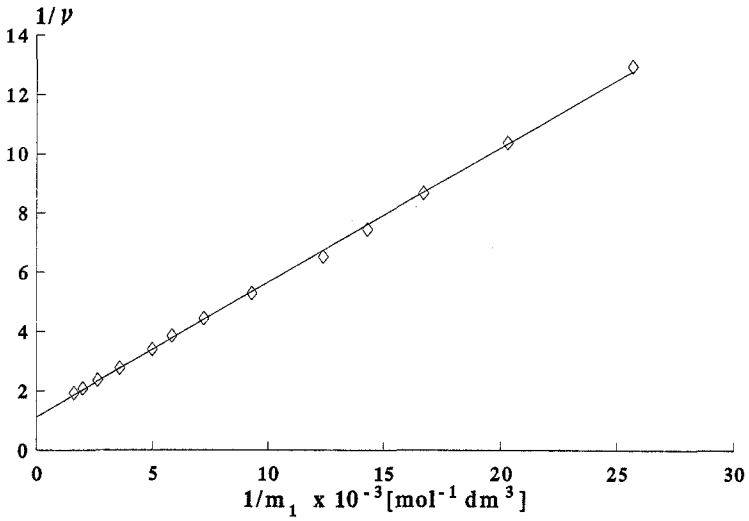


Fig. 3. Benesi–Hildebrand plot for the drug diphenhydramine in the presence of β-CD [2.0×10^{-3} mol dm^{-3}].

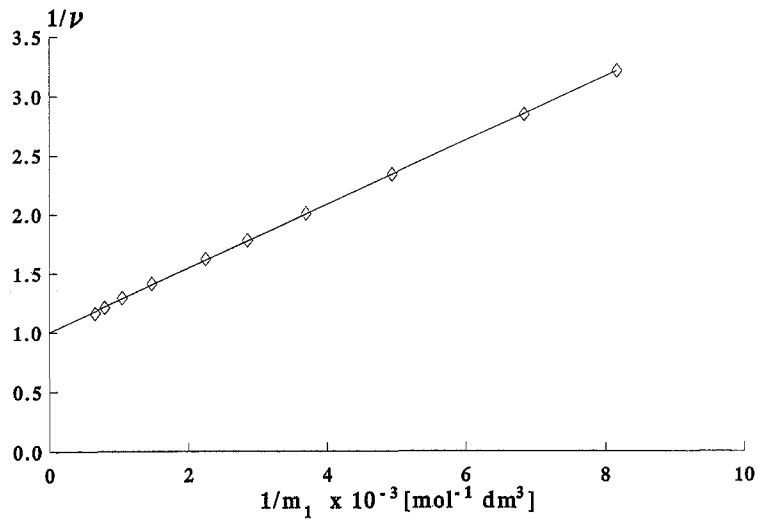


Fig. 4. Benesi–Hildebrand plot for the drug diphenylpyraline in the presence of β-CD [2.0×10^{-3} mol dm^{-3}].

account the number of moles of water in 1 dm^3 of solution. ΔG^0 the Gibbs free energy change follows from:

$$\Delta G^0 = -RT \ln(K_D)$$

and ΔH^0 and ΔS^0 are found, respectively from the slopes and intercepts of the plot of $\ln(K_D)$ against $1/T$ in the usual manner (Figure 5). The values of the thermodynamic parameters found in this work are also in Table III.

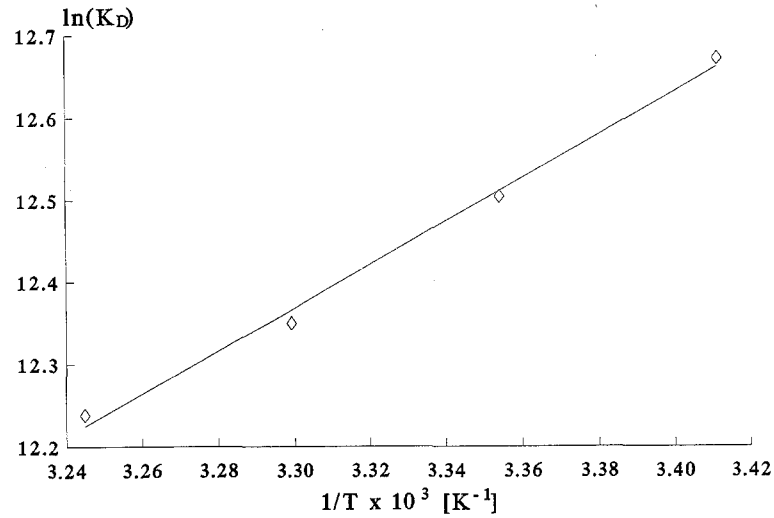


Fig. 5. Determination of ΔH^0 and ΔS^0 for the drug chlorcyclizine in the presence of β-CD [2.0×10^{-3} mol dm^{-3}].

4. Discussion

The most noteworthy achievement in the present work has been to demonstrate that drug selective electrodes can be used successfully to evaluate equilibrium data associated with the inclusion compounds of cationic drugs with cyclodextrins. With the exception of PH/α-CD, where no binding was observed, and also the system DPPH/α-CD which showed complicated binding behaviour all other drug/CD systems formed 1 : 1 complexes.

The structure of the drug cations listed in Table I can be generally described qualitatively as having two entities:

i. a positively charged end group at the end of a 'hydrophobic' tail;
ii. a heterocyclic base.

As a result, aqueous solutions of these drugs exhibit surface active properties and in many cases they form aggregates, sometimes micellar in nature, at high concentrations. If one compares the behaviour of a simple surfactant (S) in the presence of cyclodextrins (CD), compared to the surface active drugs used in this work, it is found that in the case of surfactants [9, 10] the binding data indicate that more CD is bound to the surfactant than predicted by a 1 : 1 complex, giving rise to two complexes S(CD) and $S(CD)_2$ whereas the drug only form 1 : 1 complexes. It is surprising that only 1 : 1 complexes are formed since simple molecules which model the 'hydrophobic' and 'heterocyclic' moieties of the drugs are known to form inclusion compounds with CD [1–3, 10, 11].

The next question to address is which part of the drug is included in the CD complex? Despite the fact that a comprehensive set of thermodynamic parameters is listed in Table III it is unfortunately difficult to draw any firm conclusions concerning the structure of the inclusion compound. The main reasons for this are the absence of direct structural data, and the fact that there are no systematic

Table III. Thermodynamic parameters of the drug/CD inclusion process.

Drug	CD	Temp [K]	K [mol^{-1} dm^3]	$-\Delta G^0$ [kJ mol^{-1}]	ΔH^0 [kJ mol^{-1}]	ΔS^0 (298 K) [J mol^{-1} K^{-1}]
Propranolol (PH)	α	298	No Binding			
	β	293	210 ± 7	23 ± 3	-25 ± 15	4 ± 2.5
		298	168 ± 5	23 ± 3		
		303	138 ± 5	23 ± 3		
		308	128 ± 4	23 ± 3		
Diphenhydramine (DPHH)	α	293	122 ± 1	22 ± 2		
	β	293	2100 ± 130	28 ± 2		
Diphenylpyraline (DPPH)	α	Complex binding				
	β	293	4140 ± 360	30 ± 4	-15 ± 9	11 ± 7
		298	3730 ± 320	30 ± 4		
		303	3390 ± 355	31 ± 4		
		308	3060 ± 310	31 ± 4		
Chlorcyclizine (CCH)	α	293	1420 ± 35	28 ± 2	-30 ± 18	5 ± 3
		298	1220 ± 30	28 ± 2		
		303	976 ± 30	28 ± 2		
		308	784 ± 33	27 ± 2		
	β	293	5750 ± 55	31 ± 3	-22 ± 14	8 ± 5
		298	4860 ± 60	31 ± 3		
		303	4160 ± 58	31 ± 3		
		308	3720 ± 52	31 ± 3		
Chlorpromazine* (CP)	α	298	120 ± 10	28 ± 3		
	β	298	11000 ± 1000	33 ± 3		
Dicyclomine* (DC)	α	298	280 ± 30	30 ± 3		
	β	298	95000 ± 9000	38 ± 4		

*Data taken from Ref. [7]

variations in the structures of the drugs used. Notwithstanding (i) and (ii) above the following trends are observed by inspection of Table III.

(a) The equilibrium constants of the 1 : 1 drug/α-CD complexes are a factor of 4–33 less than those of the corresponding drug/β-CD complexes.
(b) There are trends in the K values for the corresponding α- and β-CD complexes in the sense that for each drug both sets of equilibrium constants increase in the order: PH, DPHH, DPPH, CCH, CP and DC.
(c) The order of the drugs shown in (b) above is very close to their increasing molecular weights.

On the basis of some degree of order as exemplified in the above trends one expects some commonality of behaviour involving the formation of the inclusion compounds in the sense that either the heterocyclic moiety or the 'hydrophobic' part of the drug is included in the complex rather than random change from drug to drug. The structure of the heterocyclic bases for the various drugs listed in Table I are in some cases so different and in other cases so similar that it is impossible to draw any equilibrium constant/structure correlations which would confirm that the heterocyclic bases are involved in the inclusion phenomena. This means that the most likely mechanism for inclusion is associated with the charged 'hydrophobic' moieties, all of which are different and terminated by a positively charged nitrogen atom. In the complexation of CD with normal surfactants the first complex formed, S–CD also involves the charged end of the surfactant being included by the CD [12]. In the absence of direct structural data any further discussions would, at present, be premature.

Acknowledgements

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