COMPETITIVE EXTRACTION OF SOME BASES BY CARBOLLYL-COBALTATE ANION FROM WATER INTO CHLOROFORM

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The bis[undecahydro-7,8-dicarbaundecaborato(2–)]cobaltate(1–) (X^-) has been used for complementary study of its ionic associates with some cations of organic bases and quaternary salts. For the optimization of present analytical methods, quinuclidin-3-yl hydroxy(diphenyl)acetate, 1-(1-phenylcyclohexyl)piperidine, dibenzo[*b*,*f*][1,4]oxazepine and cocaine, were studied by competitive extraction method. X^- labelled with ^{60}Co was used as carrier anion, triphenylmethane and azo dyes as competitive anions. The aqueous phase was 0.1 and 0.01 M HCl, the organic phase was chloroform. A comparison was made with earlier results obtained by extraction spectrophotometry.

Key words: Competitive liquid extraction; Ionic associates; Nitrogen bases; Dicarbollylcobaltate anion; Alkaloids; Carboranes.

The bis[undecahydro-7,8-dicarbaundecaborato(2–)]cobaltate(1–), trivially the bis(1,2-dicarbollyl)cobaltate anion, $[Co(\eta^5\text{-}1,2\text{-}C_2B_9H_{11})_2]^-$ (henceforth X^-), was used in our earlier work[1] for the study of its ionic associates with some cations of organic bases and quaternary salts (B^+). We have determined appropriate extraction constants of twenty-two ionic associates and stated for further seven ones, that the use of X^- was limited because of its small specific activity.

The carrier system (B^+,X^-) can be used for the study of stability and partition of ionic associates (B^+,L^-), where HL is suitable monobasic acid on the base of coloured triphenylmethane and azo dyes, commonly used for extractive spectrophotometric determination of the concentration of bases[2–7].

The aim of the present communication is to complete our earlier results using the reagent X^- with specific activity higher by two orders. Thirteen new alkaloids and five other nitrogen bases were investigated. Also, four selected bases – quinuclidin-3-yl hydroxy(diphenyl)acetate, 1-(1-phenylcyclo-

hexyl)piperidine, dibenzo[*b*,*f*][1,4]oxazepine and cocaine – were studied by competitive extraction method and the results were compared with our earlier papers[2–7].

EXPERIMENTAL

Chemicals and Apparatus

Caesium bis(1,2-dicarbollyl)cobaltate labelled with ^{60}Co, Cs[^{60}Co(η^5-1,2-$C_2B_9H_{11}$)], was synthesized in Nuclear Research Institute, Řež. Their radiochemical purity was checked γ-spectrometrically, total activity being 9.4 MBq. The stock solutions were prepared by dissolving exact amounts of CsX in 0.1 and 0.01 M HCl; their concentrations were $1.0 \cdot 10^{-7}$ to $6.6 \cdot 10^{-6}$ mol l^{-1}, activities 65–3 000 Bq ml^{-1}.

More accurate measurements were made for quinuclidin-3-yl hydroxy(diphenyl)acetate (**1**), 1-(1-phenylcyclohexyl)piperidine (**2**), cocaine (**3**), physostigmine, lysergic acid *N*,*N*-diethylamide (LSD) and quaternary salts triphenylmethylphosphonium iodide, tetraphenylarsonium chloride, hexadecylpyridinium bromide and hexadecyltrimethylamonium bromide. New investigated bases were 1-methylpiperidin-3-one, quinuclidin-3-ol, 1-methyl-3-piperidylhydroxy(diphenyl)acetate, dibenzo[*b*,*f*][1,4]oxazepine (**4**), *N*-(1-naphthyl)ethane-1,2-diamine, histamine, caffeine, brucine, quinine, lobeline, papaverine, procaine, arecoline, adrenaline, choline, pilocarpine, yohimbine and homatropine. All the chemicals were of analytical grade (Aldrich, Merck, Fluka, Lachema, SPOFA, Zdravotnické zásobování, Farmakon, Military Factory 072 Zemianské Kostoľany, Slovakofarma).

As coloured reagents HL which form competitive anions were used: triphenylmethane dyes Bromocresol Green, Bromophenol Blue, Bromothymol Blue, Bromoxylenol Blue, p-Xylenol Blue, Bromopyrogallol Red, Eriochrome Cyanine R [C.I.43820], azo dyes Eriochrome Blue Black B, Orange II [C.I.15510], Amido Black 10 B [C.I.20470], Ponceau Xylidine [C.I.16150] and 2,6-dinitrophenol. Methyl Orange and Cresol Red were not suitable due to poor solubility in both water and organic phases. All the reagents were dissolved in water except 2,6-dinitrophenol, for which $CHCl_3$ was used.

Stock solutions of bases and quaternary salts were prepared by dissolving their exact amount in 0.1 M HCl (or 0.01 M HCl in the case of competitive extraction) so that their concentrations were $1 \cdot 10^{-4}$ to $5 \cdot 10^{-3}$ mol l^{-1}. Chloroform (Lachema Brno, Czech Pharmacopoeia ČsL 4 purity) was used as an organic phase without purification.

The γ activity of solutions was measured with an NA 3601 Gamaautomat (Tesla, Liberec) with a well-type NaI(TI) detector. Radiochemical purity of CsX was checked with a 4096-channel spectrometer Silena (Italy) with Ge detector.

Procedures

The extraction was carried out using a rotary extractor and test-tubes with glass stoppers. Organic and water phases (4 ml each) were shaken at 20 ± 1 °C for 1 h; this time period was sufficient for the extraction equilibrium to establish, even though preliminary experiments indicated that 10 min were sufficient. After separating the phases, 2 ml were withdrawn from each and placed into ampoules for the γ activity measurements. Such a frequency of activity measurement in the well-type detector was chosen to keep the mean quadratic error of each measurement below 5%.

From the experimental points, the equations of straight lines were calculated and appripriate regression coefficients were determined by means of the Adstat programme.

RESULTS AND DISCUSSION

Effect of Bases

Bases are converted in a 0.1 M HCl medium completely into their protonated form, denoted for simplicity B^+. Cations of quaternary salts are denoted in the same way. We must consider a double protonation for *N*-(1-naphtyl)ethane-1,2-diamine, pilocarpine, brucine and strychnine but the extractability of associates (B^{2+}, 2 X^-) is virtually negligible[8].

We have determined the dependence of the logarithm of equilibrium coefficient D_X on the logarithm of initial concentration of the protonated form of the studied bases or quaternary salts, B^+. The working conditions were analogous to those in our earlier paper[1].

Calculated values of $K_D K_{assoc}$, characterizing the equilibria

$$[B^+] + [X^-] \rightarrow [(B^+,X^-)] ; \qquad K_{assoc} = [(B^+,X^-)]/[B^+][X^-] \qquad (1)$$

$$[(B^+,X^-)] \rightarrow [(B^+,X^-)]_{OR} ; \qquad K_D = [(B^+,X^-)]_{OR}/[(B^+,X^-)] , \qquad (2)$$

where the subscript OR refers to the organic phase, are given in Table I. The values of the protonation constants are taken from[5,9,10,11]. Although we were working with reagent X^- containing specific activity higher by two orders than earlier[1], the extractability, or solubility of some ionic associates in the organic phase was so high that we were not able to determine the values of log D_X with sufficient accuracy. This is why the values of log $K_D K_{assoc}$ for lobeline, papaverine, triphenylmethylphosphonium iodide, tetraphenylarsonium chloride and hexadecyltrimethylammonium bromide are ≥8.2 in 0.1 M HCl medium. In constrast, it was found that histamine was extracted into chloroform very poorly even at its analytical concentration $5 \cdot 10^{-3}$ mol l^{-1}.

As the anion X^- is not hydrated in the water phase[12], its ionic associate must pass into the organic phase the better, the more hydrophobic is its cation and the more concentrated and minor is its positive charge. The structure of water also plays a decisive role due to hydrogen bridges[13]. The association constant will depend on the distance between the charge of

TABLE I
The values of logarithms of extraction constants $K_D K_{assoc}$ (water phase 0.1 M HCl, organic phase chloroform)

Base	log $K_D K_{assoc}$	pK_{BH^+}	p$K_{BH_2^+}$
Histamine	[a]		
Adrenaline	2.0	9.39[d]	
Caffeine	2.6	10.4[d]	
1-Methylpiperidin-3-ol	3.1	10.19[d]	
Quinuclidin-3-ol	3.2		
Choline	3.4	8.94[d]	
Arecoline	4.9	6.84[e]	
N-(1-Naphtyl)ethane-1,2-diamine	4.9		
Pilocarpine	5.1	12.57[e]	7.15[e]
Procaine	5.3	8.85[d]	
Dibenzo[*b*,*f*][1,4]oxazepine (**4**)	5.6	3.0[b]	
Homatropine	5.6	9.7[d]	
Quinine	6.1	4.11[d]	
Yohimbine	6.7	7.66[e]	
Physostigmine	6.7	1.76[d]	
1-Methyl-3-piperidylhydroxy(diphenyl)acetate	7.2		
Quinuclidin-3-yl hydroxy(diphenyl)acetate (**1**)	7.5	8.74[b]	
Brucine	7.9	8.16[d]	2.50[d]
Strychnine	7.9	8.20[d]	2.50[d]
1-(1-Phenylcyclohexyl)piperidine (**2**)	7.9	7.98[b]	
Hexadecylpyridinium bromide	7.9		
LSD	8.1	7.68[e]	
Cocaine (**3**)	8.0	8.41[d]	
Triphenylmethylphosphonium iodide	≥8.2		
Tetraphenylarsenium chloride	≥8.2		
Hexadecyltrimethylammonium bromide	≥8.2		
Lobeline	≥8.2		
Papaverine	≥8.2	5.90[d]	

[a] Not determined for too low values of D_X; [b] ref.[5]; [c] ref.[9]; [d] ref.[10], [e] ref.[11]

ions in the ionic associates and on the structure of the cations. The highest values of $K_D K_{assoc}$ are shown for nonhydrated hexadecyltrimethylammonium, tetraphenylarsonium, triphenylmethylphosphonium and hexadecylpyridinium ions, in the alkaloid series then by the cations of papaverine, lobeline, cocaine, brucine and for LSD and **2**. On the contrary, low values of $K_D K_{assoc}$ were found for adrenaline with three functional hydroxy groups or histamine, caffeine, arecoline and pilocarpine which contain nitrogen heterocycles but not aromatic groups.

Competitive Extraction

For the distribution of anion X^- in the presence of a competing HL system, we have[1]:

$$D_X = K_D K_{assoc} [(B^+,L^-)]_{OR} / K_D' K_{assoc}' [L^-] \qquad (3)$$

and for 50% extraction of X^-

$$K_D' K_{assoc}' = K_D K_{assoc} [(B^+,L^-)]_{OR} / [L^-] \, . \qquad (4)$$

$$[B^+] + [L^-] \rightarrow [(B^+,L^-)] \, ; \qquad K_{assoc}' = [(B^+,L^-)] / [B^+][L^-] \, , \qquad (5)$$

where

$$[(B^+,L^-)] \rightarrow [(B^+,L^-)]_{OR} \, ; \qquad K_D' = [(B^+,L^-)]_{OR} / [(B^+,L^-)] \, . \qquad (6)$$

Thus, for the particular system the $K_D' K_{assoc}'$ product can be determined if the $K_D K_{assoc}$ product is known and if B^+ is virtually present solely in the organic phase as ion associates $(B^+,X^-)_{OR}$ and $(B^+,L^-)_{OR}$.

The subject of our interest is four selected bases which play a role as compounds with psychic effect on human organism: **1**–**4**. In determination of these compounds spectrophotometry has so far predominated.

The extractions in the presence of HL were accomplished at the starting concentration of carrier (B^+,X^-) of $5 \cdot 10^{-6}$ mol l^{-1} for **1**–**3** and $1 \cdot 10^{-5}$ mol l^{-1} for **4**. Figures 1 and 2 will display the dependences $\log D_X = f(\log[L^-])$ for typical reagents, where the slopes are -1 ± 0.2 in all experiments. The calculated values of the $K_D' K_{assoc}'$ products are given in Table II.

It is evident that the dyes can be classified according to the extractability of their ionic associates into chloroform; the order of the $K'_D K'_{assoc}$ products is the same: **1** = **2** > **3** > **4**, except for Eriochrome Blue Black B and Bromopyrogallol Red complex with cocaine. For practical use bromo derivatives of phenol-, cresol- and thymolphthaleins are more suitable; in contrast, Methyl Orange and Cresol Red are unsuitable for their poor solubility in both phases. The determination of the $K'_D K'_{assoc}$ values is the more accurate, the higher the values of $K_D K_{assoc}$ are because of limits in the highest starting concentrations of the competing anions L^-.

Comparing our $K'_D K'_{assoc}$ values with those in papers[2–7], we notice that they differ usually by ±1 logarithmic unit. Higher differences can be explained by the fact that the water phase in our experiments contains strong acids HCl and HX only but pH values in papers[2–7] were adjusted by citrate buffers which contain competing citrate anions. Also HL are weak acids and dissociate to higher degrees in neutral and alkaline media. Thus the values

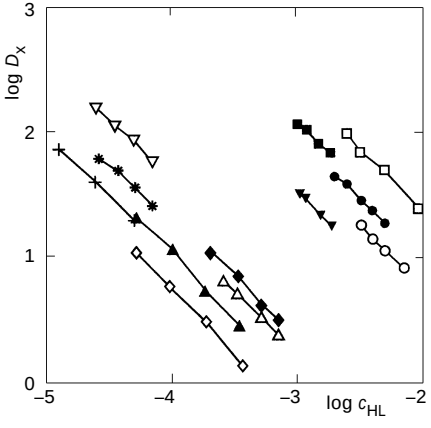

FIG. 1

Effect of initial concentration of competing reagent HL on distribution of X^- between solutions of $5 \cdot 10^{-6}$ mol l^{-1} **1** and **2** in 0.01 M HCl and chloroform. $c_X = 1.09 \cdot 10^{-6}$ mol l^{-1}. **1**: ✧ Bromocresol Green, ❍ Eriochrome Cyanine R, ● Amido Black 10 B, ▼ Bromopyrogallol Red, ∇ p-Xylenol Blue, + Eriochrome Blue Black B; **2**: ▲ Bromocresol Green, Δ Bromophenol Blue, ■ Bromopyrogallol Red, ◆ Orange II, ❒ 2,6-dinitrophenol, * Bromoxylenol Blue

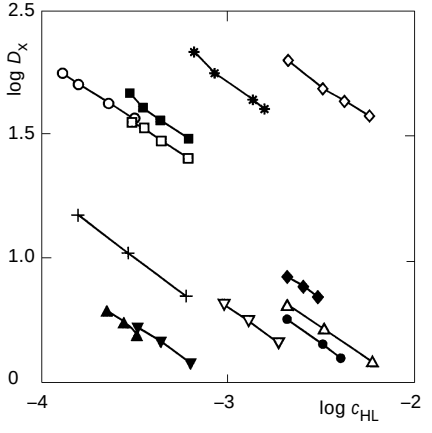

FIG. 2

Effect of initial concentration of competing reagent HL on distribution of X^- between solutions of $5 \cdot 10^{-6}$ mol l^{-1} **3** and $1 \cdot 10^{-5}$ mol l^{-1} **4** in 0.01 M HCl and chloroform. $c_X = 1.09 \cdot 10^{-6}$ mol l^{-1}. **3**: ❍ Bromocresol Green, * Bromopyrogallol Red, ✧ Eriochrome Cyanine R, ■ Orange II, + Eriochrome Blue Black B, ❒ Bromophenol Blue; **4**: ▼ Bromothymol Blue, ▲ Bromoxylenol Blue, Δ Eriochrome Cyanine R, ∇ Orange II, ● Amido Black 10 B, ◆ Ponceau Xylidine

TABLE II
The values of logarithms of extraction constants $K_D' K_{assoc}'$ (water phase 0.01 M HCl, organic phase chloroform)

Agent	$\log K_D' K_{assoc}'$			
	1	**2**	**3**	**4**
Bromocresol Green	5.4	5.5	4.5	3.8
Bromophenol Blue	5.2	5.3	4.5	3.2
Bromothymol Blue	5.3	5.2	4.5	4.0
Bromoxylenol Blue	5.3	5.3	4.3	4.0
Orange II	5.0	5.2	4.3	3.3
Eriochrome Blue Black B	5.1	5.0	5.6	3.7
Ponceau Xylidine	4.9	5.0	4.3	2.7
p-Xylenol Blue	4.5	4.4	4.2	3.2
Bromopyrogallol Red	3.6	3.4	3.7	3.2
Eriochrome Cyanine R	3.4	3.4	3.1	2.9
Amido Black 10 B	3.3	3.3	3.3	3.1
2,6-Dinitrophenol	3.2	3.2	2.8	2.6

of conditional extraction constants are very dependent on pH values of the water phase.

The conditions for the separation and analytical determination of some bases by the solvent extraction method depend on the knowledge of their protonation constants pK_{BH^+} and values of $K_D K_{assoc}$ and $K_D' K_{assoc}'$. For instance, the substance **4** cannot interfere in the determination of **1–3** at pH 6.

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