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ANALYSIS

THE EXTRACTION OF AROMATIC CARBOXYLIC ACIDS BY THE COPPER COMPLEX WITH CURTIS MACROCYCLIC TETRAMINE AND ITS UTILIZATION FOR PHOTOMETRIC DETERMINATION OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

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Abstract: Copper complex with Curtis macrocyclic tetramine is offered as reagent for extraction-photometric determination of nonsteroidal anti-inflammatory drugs (NSAIDs), belonging to the class of aromatic carboxylic acids. The studies indicate that this method is suitable for quantitative determination of NSAIDs, which have the constant distribution in the system chloroform/water (log P) no less than 3 and dissolubility in chloroform (S) no less than 10 mg/mL. Under optimum conditions, there are liner relationships between the absorption of chloroform extracts and concentration of NSAID in the range of 0.2–4 mg/mL for indometacin (Ind), 0.2–3 mg/mL for mefenamic acid (Mef) and 0.5–3 mg/mL for diclofenac (Dic). The detection limits (S/N = 3) of Ind, Mef and Dic are 0.2, 0.1 and 0.15 mg/mL, respectively. With the help of calculating method (SPARC V4.2) it was predicted the possibility of utilization of this method for extractive-photometric determination of its detached specimen NSAID.

Keywords: nonsteroidal anti-inflammatory drugs; extractive-photometric method; copper complex

Some arylalkanoic and N-arylanthranilic acids have anti-inflammatory and analgesic effects and make an important group of nonsteroidal anti-inflammatory drugs (1). For their quantity determination usually is used a method of potentiometric titration in nonaqueous or mixed solvents, because in water they are completely insoluble. The mentioned method is precise but may be applied only to drug substances (2) as tablets and other dosage forms can contain auxiliary components of acid-basic character which can impede titration.

To determine milligram quantities of NSAID in dosed drug forms, spectrophotometry may be used, especially in combination with extraction for separation of special purpose component from main admixture. At the same time, one can use absorption spectra of individual species and their complexes with metal ions.

In the literature, several methods are described of extraction-photometric determination for several NSAIDs in a form of copper complexes (3–7). However, the optimum conditions for extraction must be kept in the narrow pH range, besides, the extracted complex has complicated chemical composition and presumably dimeric structure, which reduces sensitivity and reproduction of the assay.

The application of carbonic acids for extraction of metal ions, including copper, in organic phase is well known. As a rule, the effective copper(II) extraction occurs in the presence of rather big surplus of aromatic carboxylic acids (HR) (1000 and more). At the same time, substantial quantity of ligand, especially in alkaline medium, can be left in water phase. Nowadays, the conditions of settling inverse tasks (complete combination of carbonic acid in metal complex and its quantitative extraction in organic phase) can be find out empirically without taking into consideration the ligand and their physico-chemical characteristics and their complexes in two-phase systems. For the extraction of carboxylic acids (including NSAIDs) it may have prospects to use copper(II) complexes with the Curtis macrocyclic tetramines (8), particularly, with 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacy-

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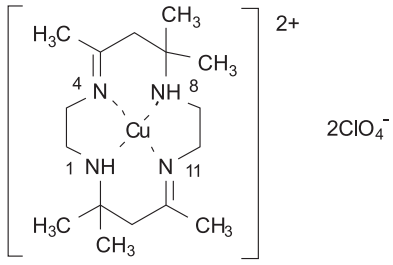
clotetradeca-4,1-diene (T). Its copper complex has the following structure:



CuT

is extremely steady (lg K ≈ 20), turns red (λ_{max} = 545 nm) and make with some organic acids ionic associates extracted with chloroform (9, 10). In case of HR, its combination can be described by the formula [CuTR](ClO_4), and possibility of its use in pharmaceutical analysis was shown by the example of quantitative determination of ibuprofen (11).

In this work we tried to determine some conditions of extraction of ionic associates [CuTR]ClO_4 and with their help to estimate perspective of usage for extraction-photometric determination of some NSAIDs representatives. Some other organic acids, namely: benzoic (Bz), *m*-toluic (*m*-Tol), anthranilic (Ant), salicylic (Sal) and acetylsalicylic (Asal), were also included to investigate intervals of pK_a and constants of distribution (log P).

EXPERIMENTAL

Chemicals

Deionized water was used to prepare all solutions and experiments. Copper complex CuT(ClO_4) was obtained and purified acc. to (12). Its initial 0.1 mol/L solution was prepared by dissolution of exactly weighed amount in water.

Benzoic, *m*-toluic, salicylic, acetylsalicylic and anthranilic acids were supplied by Aldrich and used without further purification. Drugs: diclofenac (Dic, 2-{2-[(2,6-dichlorophenyl)amino]-phenyl}acetic acid, CAS 15307-86-5) was obtained from its sodium salt by precipitation with hydrochloric acid and extraction with chloroform (13), ibuprofen (Ibu, 2-[4-(2-methylpropyl)phenyl]-propanoic acid, CAS 15687-27-1), naproxen (Nap, 2-(6-methoxynaphthalen-2-yl)propanoic acid, CAS 22204-53-1), indometacin (Ind, 2-[l-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid, CAS 53-86-1) and mefenamic acid (Mef, 2-[(2,3-dimethylphenyl) amino]benzoic acid, CAS 61-68-7) were kindly donated by pharmaceutical companies. In the work, we used 0.1 mol/L acid solutions in chloroform, which was purified by distillation.

Apparatus

The absorption spectra were recorded on Perkin-Elmer Lambda 9 spectrophotometr. The pH values of solutions were measured using OP- 211/1 laboratory digital pH-meter (Radelkis, Budapest, Hungary).

Procedure

Four milliliters of standard 0.01 mol/L chloroform acid solution and 6 mL of chloroform were placed in the separatory funnel and 5 ml 0.1 mol/L water solution of CuT and 5 ml of Britton-Robinson buffer of different pH values were added. After shaking for 5 min the phases were divided. The organic layer was filtered through filter paper with ca. 200 mg of anhydrous sodium sulfate and optical density of the extract was measured.

Analytical procedure

Ten tablets were weighed and pulverized. A weighed amount of the powder equivalent to 100–200 mg of the drug was transfered into a small flask, extracted with 3 × 10 mL of $CHCl_3$ and filtered in a 100 mL volumetric flask. The residue was washed with few mL of $CHCl_3$ and filtered washings were added to the same flask. The solution was completed to the mark with the same solvent. Suitable aliquots of the solution were transferred into a separatory funnel and shaked with 10 mL of saturated water solution of CuT under pH 9, adapted with the help of Na_2CO_3 solution. After phase separation, chloroform layer was filtered through paper filter with ~200 mg of anhydrous sodium sulfate. The absorbance of the organic phase was measured against a reagent blank prepared exactly like the procedure described above, but in absence of carboxylic acid. The content of the drug was determined either from the calibration graph or using the corresponding regression equation. For the calibration graph, a series of standards was prepared by dilution of corresponding stock solution to obtain the concentration range of 0.2–2.0 mg/mL NSAID in $CHCl_3$. Under optimized conditions for absorption, the analyte final concentration and optimal density were linear over the range $5.0 \times 10^{-4} – 1.2 \times 10^{-2}$ mol/L for Ind, $5.0 \times 10^{-4} – 1.0 \times 10^{-2}$ mol/L for Mef and $5.0 \times 10^{-5} – 1.0 \times 10^{-2}$ mol/L for Dic. The linearity of calibration graph was proved by the high values of the correlation coefficient (r = 0,9983; 0,9983 and 0.9990 for Ind, Mef and Dic, respectively). The detection limits, defined as the concentration corresponding to a signal equal to three times the standard deviation of the lowest concentration, were 0.12, 0.1 and 0.15 mg/mL for Ind, Mef and

Dic, respectively. The relative standard deviations (RSD), covering the range of interest varied from 0.8 to 1.0%.

The effects of common additives, adjuvants and excipients (glucose, magnesium stearate, starch, methylparaben, gum acacia) were studied, and it was found that there were no interferences. Therefore, indometacin, mefenamic acid and diclofenac can be determined directly in their dosage forms by the suggested method without previous separation.

RESULTS AND DISCUSSION

Influence of pH

Molar absorptivity (ε) of ionic associate $[CuTR](ClO_4)$ in $CHCl_3$ doesn't depend upon the nature of R and equals 150 ± 10 M^{-1} at 545 nm. As it is shown in Figure1, practically for all investigated combinations there are increasing optical density of extracts with decreasing acidity of water phase. Light absorption reaches maximum with an increase of pH and doesn't change till pH ~11 in equal ratio of components (C_{Cut}/C_{HR} = 125/1) and in only one extraction the output on the "plateau" maximum optical density of chloroform extracts is different and depends upon the nature of carboxylic acid. For presentation in the Figure, corresponding results of the carboxylic associates 4, 6 and 9 which have similar character are not presented. For diclofenac, indometacin and mephenamic acid the absorption of copper complex from water phase is the best, less good is for ibuprofen, naproxen, antranilic, salicylic, benzoic and acetylsalicylic acids, which under these conditions insignificantly make ionic associates with CuT in chloroform. It results from the fact that during the extraction of associates the main parts of the indicated acids are left in water phase, and also with low degree of extraction of ionic associates. The process of their formation can be described by equation:

$(CuT)_w + (HR)_o = (CuTR)_o + (H)_w$

with appropriate constant:

$$K_e = \frac{[CuTR]_o[H]}{[CuT]_w[HR]_o} \quad (1)$$

where indexes *o* and *w* refer to organic and water phases, respectively. For ease, the ionic charges are not mentioned.

Taking into consideration the constant of dissociation of organic acids in water phase $K_a = \frac{[H][R]_w}{[HR]_w}$ and the constant of its distribution between water and organic phase $P = \frac{[HR]_o}{[HR]_w}$, we have:

$$K_e = \frac{[CuTR]_o[H](1+1/P+K_a/P[H])}{(C_{Cu} - [CuTR]_o)(C_R - [CuTR]_o} \quad (2)$$

where C_{Cu} and C_R – are common analytical concentrations of metal and ligand bound with equilibrium concentration equations of material balance:

$$C_{Cu} = [CuT]_w + [CuTR]_o \quad (3)$$

$$C_R = [HR]_w + [HR]_o + [R]_w + [CuTR]_o \quad (4)$$

Before we turn to the next interpretation of the obtained results, let's determine more exactly some definition of terms, relevant to the process of extraction. In classical variant (the extraction with the aim of isolation, separation, concentration metal ions), there is an interphase transfer of metal ions from water into organic phase. The effectiveness of this process is defined by term $R_{Cu} = \frac{[CuTR]_o}{C_{Cu}}$ and is characterized by degree of extraction (14). In context of this investigation, the notion "effectiveness" is defined by term $R_R = \frac{[CuTR]_o}{C_R}$ and is not related to metal ions, but to ligand, which is in the organic phase before the process of extraction. That's why R_R is more accurate to name the degree of association. This quantity is well correlated with the log P value of the investigated acids. As it is shown in Figure 2, the more higher is the degree of combination of carboxylic acid in ionic associate with CuT, when it is once extracted, the bigger is its constant of distribution in the system chloroform–water. With the values of logP ≥ 3, the degree of combination HR is higher than 90%, which is quite sufficient for analytical purposes.

Determination of the extraction constant

After finding the logarithm form of eq. (2) and changing signs we are getting the equation:

$$\lg \frac{[CuTR]_o}{C_{cu} - [CuTR]_o} = \lg \frac{C_R - [CuTR]_o}{1+1/P+K_o/P[H]} + pH + \lg K_e \quad (5)$$

from which the value lg K_e can be defined graphically. To obtain this, one should construct the correlation in coordinates $X = \lg \frac{C_R - [CuTR]_o[H]}{1+1/P+K_a/P[H]} + pH$, $Y = \lg \frac{[CuTR]_o}{C_{Cu} - [CuTR]_o}$, using points in the lines of ascent in diagrams (Fig.1), where experimentally defined parameters are pH and balanced concentration of ionic associate $[CuTR]_o$ in organic phase. The last one was calculated from the definition of optical density and the value of molar absorptivity. The values for calculations of K_a and P can be taken from the literature, but as it was revealed in their analyses (cf. Table 1), the published values of pK_a for many acids are significantly different and the constants of distribution in the system chloroform–water are known only for some acids. To obtain comparable

Table 1. The comparison of theoretically calculated values and literature data of pK_a and LogP of the carboxylic acids and parameters of extraction (pK_e, R_R%) of their ionic associates with CuT in the system chloroform–water.

No.	Name	pK_α lit.[a)]	pK_α SPARC	Log P Lit.[b)]	Log P SPARC	pK_e	R_R, %
1	Benzoic acid	3.98–4.21	4.02	0.30–0.71	1.05	3.94	21.3
2	*m*-Toluic acid		4.1		1.56	4.1	42.5
3	Salicylic acid	2.75–3.29	3.08	0.34–0.5	1.27	2.96	31.3
4	Acetylsalicylic acid	3.41–3.57	3.49	0.26–0.30	0.5	-	< 1
5	Anthranilic acid		4.64	–1.15–0.57	1.05	4.74	16.3
6	Mefenamic acid	4.33–4.55	4.20		4.85	4.34	99.7
7	Naproxen	4.10–4.28	4.50		2.23	4.67	67.5
8	Ibuprofen	4.13–5.3	4.50		3.01	4.62	90.0
9	Indometacin	4.14–5.30	4.66		3.61	4.89	96.3
10	Diclofenac	3.99–4.20	4.15		4.95	4.2	99.8

[a)]Ref. (15), [b)]Ref. (16).

Table 2. Determination of indometacin, mefenamic acid and diclofenac by the proposed method compared with the titrimetric method.

Titrimetric method[a]			Proposed method		
Amount taken [mg]	Found [mg]	Recovery %[b]	Amount taken [mg]	Found [mg]	Recovery %[b]
Indometacin					
100	101	101.0	100	100	100.0
150	148	98.7	150	149	99.3
200	204	102.0	200	202	101.0
250	247	98.8	250	252	100.8
300	298	99.3	300	298	99.3
Mean recovery		99.96 ± 1.82			100.08 ± 1.00
RSD		1.47			0.8
Mefenamic acid					
100	99	99.0	100	99	99.0
150	147	98.0	150	152	101.3
200	204	102.0	200	202	101.0
250	253	101.2	250	252	100.8
300	302	100.7	300	300	100.0
Mean recovery		100.18 ± 2.04			100.4 ± 1.15
RSD		1.64			0.92
Diclofenac					
100	102	102.0	100	99	99.0
150	147	98.0	150	152	101.3
200	198	99.0	200	203	101.5
250	254	101.6	250	252	100.8
300	302	100.7	300	303	101.1
Mean recovery		100.26 ± 2.13			100.7 ± 1.25
RSD		1.7			1.0

[a]Ref (2). [b]Average of three determinations.

results in such cases, computer programs are often used, which can give a possibility to calculate different physico-chemical parameters of organic combinations on the bases of their molecular descriptors (17). In this article, we used the program SPARC (18), which gave good results when we calculated acids characteristics of different classes combinations and also their lipophilicity (20). It is one of a few, which gives a possibility to calculate theoretically a wide range of parameters, including ionic constants, distribution and also dissolution in single and combined solvents. The comparison of the data

Table 3. Physico-chemical constants of some commercial NSAIDs.

NSAID	Formula	Mol. weight	pK_α Lit.	pK_α calcd. by SPARC	Log P calcd. by SPARC	S in $CHCl_3$ mg/mL calcd. by SPARC
Aceclofenac	$C_{16}H_{13}Cl_2NO_4$	354.2		3.49	3.04	0.22
Acemetacin	$C_{21}H_{18}ClNO_6$	415.8		3.61	3.36	0.12
Alclofenac	$C_{11}H_{11}ClO_3$	226.7		4.40	2.16	11.6
Alminoprofen	$C_{13}H_{17}NO_2$	219.3		5.12	1.22	4.18
Benoxaprofen	$C_{16}H_{12}ClNO_3$	301.7		4.51	2.99	4.89
Butibufen	$C_{14}H_{20}O_2$	220.3	(4.43–4.64)[b]	4.53	3.33	126.8
Carprofen	$C_{15}H_{12}ClNO_2$	273.7	(4.33–4.63)[b]	4.24	2.06	0.66
Etodolac	$C_{17}H_{21}NO_3$	287.4		4.44	1.14	0.81
Fenbufen	$C_{16}H_{14}O_3$	254.3	(4.3–4.56)[a, b]	4.41	1.83	0.24
Fenoprofen	$C_{15}H_{14}O_3$	242.3	(4.5)[a]	4.18	2.97	9.65
Flufenamic acid	$C_{14}H_{10}F_3NO_2$	281.2	(3.85–5.95)[a]	4.51	3.86	51.2
Flurbiprofen	$C_{15}H_{13}FO_2$	244.3	(4.13–4.9)[b]	4.24	3.07	25.0
Indoprofen	$C_{17}H_{15}NO_3$	281.3	(4.60)[c]	4.41	1.05	0.51
Ketoprofen	$C_{16}H_{14}O_3$	254.3	(3.7–5.94)[a]	4.28	2.34	11.6
Ketorolac	$C_{15}H_{13}NO_3$	255.3		4.07	2.52	3.96
Niflumic acid	$C_{13}H_9F_3N_2O_2$	282.2	(4.44–5.07)[a]	4.77	1.90	4.9
Sulindac	$C_{20}H_{17}FO_3S$	356.4	(4.50)[c]	4.22	1.73	0.17
Suprofen	$C_{14}H_{12}O_3S$	260.3		4.26	2.19	4.0
Tolmetin	$C_{15}H_{15}NO_3$	257.3	(3.5)[a]	4.20	0.9	0.38

[a]Ref. (15), [b]Ref. (19), [c]Ref. (20).

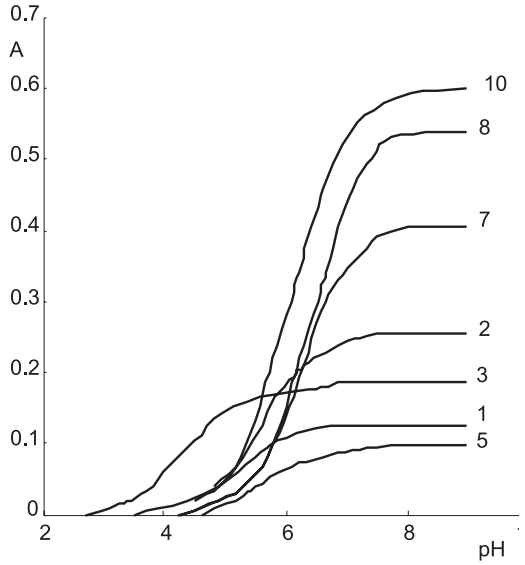


Figure 1. The dependence of optical density of chloroform extracts of the carboxylic associates with CuT on water pH (number of curve lines are corresponding to the acids' numbers in Table 1) (C_{HR} = 0.004 mol/L, C_{CuT} = 0.05 mol/L^1, l = 1 cm)

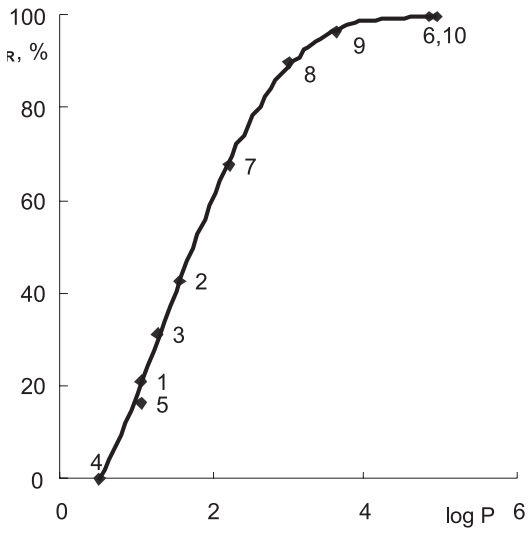


Figure 2. The dependence of extraction degree in chloroform phase of the carboxylic acids in the form of ionic associates with CuT on the distribution constants of HR (the number near points are corresponding to the number of the acids in Table 1)

in Table 1 shows that calculated with the help of SPARC pK_a and log P values are well correlated with the data published in the literature. The diagrams of equation (5) which were got with the help of the calculated values pK_a and log P are shown in Figure 3. They are straight lines with angle tangent of the slope equal one, which proves correlation CuT/HR in ionic associate equal 1:1. Straight lines cross Y axis in the point equal lg K_e. The similar data are received for carboxylic acids 4, 5 and 7. The results obtained are shown in Table 1. As it was anticipated, the constants of extraction grow within

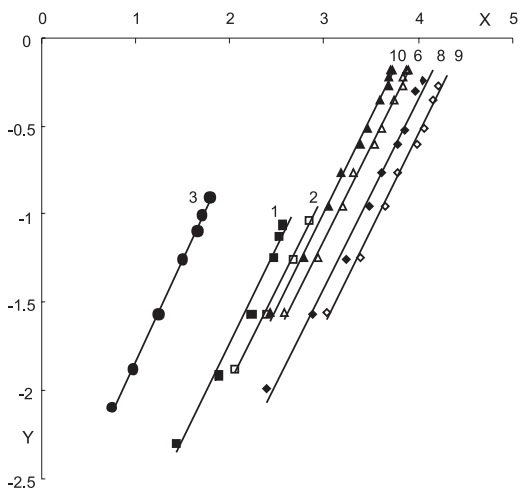


Figure 3. The determination of the extraction constants of carboxylic acids ionic associates with CuT (the number of lines are corresponding to the number of acids in Table 1). C_{HR} = 0.004 mol L^{-1}, C_{CuT} = 0.05 mol L^{-1}.

$$X = \lg \frac{C_R - [CuTR]}{(1 + 1/P + K_\alpha/P[H])} + pH;\ Y = \lg \frac{[CuTR]}{C_{cu} - [CuTR]}$$

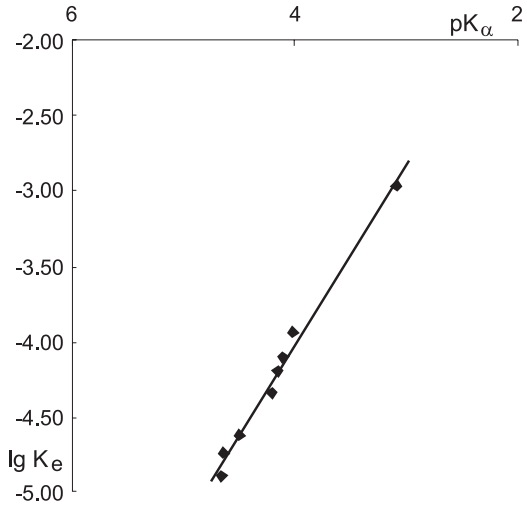


Figure 4. The dependence of extraction constants of ionic associates CuT with the carboxylic acids on their pK_a values.

the limits of intensification of acidity of the carboxylic acid (Fig. 4). Nevertheless, there is no correlation between pK_a (or lg K_e) and a degree of formation of ionic associate in organic phase. It should be noted that there is no combination between constants of distribution of substituted aromatic acids and indices of their dissociation.

The optimization of extraction conditions

Ionic associates are well extracted in neutral and alkaline medium. The hydrolysis of copper ions do not occur because of the high stability of microcyclic complex CuT. The possibility to use of this complex in wide pH intervals shows the best advantage of this reaction in the methodologies (3–6), where as analytical forms are used chelate combinations of copper. Nevertheless, the rise of pH above 9 is unsuitable, because of the worsening exfoliation of water and organic phases.

As it follows from eq. (1), the growth of the concentration of complex [CuT] in water phase should lead to improvement of extraction and increase the concentration of ionic associate [CuTR] in organic phase. However, due to limited dissolubility of [CuT] in water, it is impossible to make its concentration higher than 0.15 mol/L.

Penicillinic and cefalosporinic antibiotics, tetracyclines and chinolonocarboxylic acids with low values of log P do not produce chloroform extracts of ionic associates with CuT.

General analytical characteristics

The proposed method was successively applied to the determination of indometacin, mefenamic acid and diclofenac. The results shown in Table 2 suggest that the proposed method is more precise and sensitive than the titrimetric method (2).

The prediction of the possible formation of extracted ionic associate with other NSAIDs

As it was mentioned above, the decisive criterion, which defines suitability of this reaction for the analytical aims is high distribution coefficients of determined acids in the system chloroform–water. With the help of this parameter, one can predict the advisability of extraction-photometric methodology for determination of organic acid with the help of CuT. Below, there is a list the most popular commercial NSAIDs: Aceclofenac, Alclofenac, Alminoprofen, Benoxaprofen, Butibufen, Carprofen, Etodolac, Fenbufen, Fenoprofen**,** Flufenamic Acid, Flurbiprofen, Indoprofen, Ketoprofen, Ketorolac, Niflumic Acid, Sulindac, Suprofen, Tolmetin. On the basis of calculated log P values (Table 3) we can conclude that only Aceclofenac, Acemetacin, Benoxaprofen, Butibufen, Fenoprofen, Flurbiprofen and Flufenamic Acid have sufficiently high coefficients of distribution (log P = 3) and will well extract CuT in organic phase. The rest of NSAIDs should insignificantly form ionic associates in chloroform. It must be noted that rather high log P for

Aceclofenac and Acemetacin is not sufficient condition for their determination in the form of ionic associate. One can see from Table 3 that they have insignificant dissolution in chloroform (S ≈ 0.1–0.2 mg/L). With such concentrations ionic associate will have very insignificant absorption, which won't give a possibility to define these substances with rather sufficient sensitivity and precision.

CONCLUSIONS

Macrocyclic copper (II) complex with 5,7,7,12,14,14-hexamethyl-1,4,8,11–tetraazacyclotetradeca-4,11-diene can be successfully used for extraction-photometric determination of organic acids which have high coefficients of distribution in the system chloroform–water. This method significantly rises selectivity of the reaction, as it allows to determine hydrophobic acids in the presence of hydrophilic ones. For the direct task (extraction of copper(II) with the help of the carboxylic acids) (7) this case do not have decisive importance. Even for rather hydrophilic acids it is often managed to create very high concentration of them in organic phase, which is sufficient for complete extraction of ion metal from water phase.

The conclusion which was made, possibly, have common character for extraction systems with the help NSAIDs. Thus, under formation of ionic associate with cation dyestuff, diclofenac (21–23), ibuprofen (21) and mefenamic acid (21, 24) can be determined effectively, whereas for other representatives of NSAIDs such methodology is unknown.

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