Journal of the Chilean Chemical Society
versión On-line ISSN 0717-9707

J. Chil. Chem. Soc. v.52 n.1 Concepción mar. 2007

doi: 10.4067/S0717-97072007000100014

J. Chil. Chem. Soc, 52, N° 1 (2007)

HYDROPHOBICALLY MODIFIED POLYELECTROLYTES AS POTENTIAL DRUGS RESERVOIRS OF N-ALKYL-NITROIMIDAZOLES

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ABSTRACT

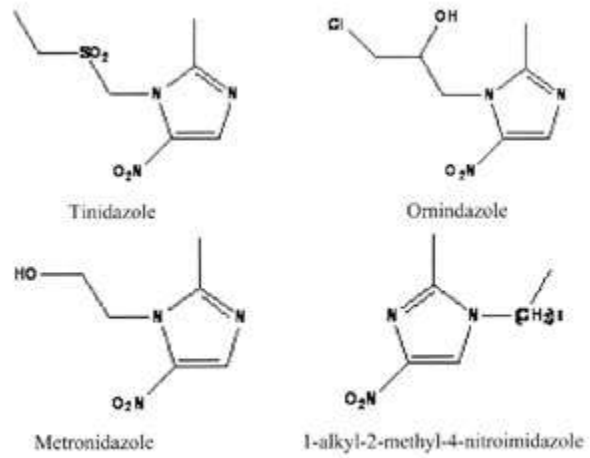
The solubilization of three commercial drugs (ornindazole, metronidazole and tinidazole) and model compounds (*N*-alkyl-2-methyl-4-nitroimidazoles) on aggregates formed by anionic polyelectrolytes, carrying alkyl side chains of different length, have been investigated in aqueous solution at pH 3.0, 7.0 and 11.0. Potassium salts of poly(maleic acid-*co*-1-olefins), PA-*n*K_2 with *n* ranging from 8 to 18, were used as micelle-forming polymers. The partition of these drugs between water and the hydrophobic microdomains provided by PA-*n*K_2 was studied by the pseudo-phase model to determinate the distribution coefficient K_S, and the standard free energy of transfer $\Delta\mu^o_t$. The results indicate that solubility of alkyl-nitroimidazoles on these polymer micelles depends moderately on the length of the alkyl chain, and therefore is mainly determined by the heterocyclic group. On the other hand, the solubilization of 1-hexyl-2-methyl-4-nitroimidazole increase with decreasing length of the side alkyl chain; i.e.K_S follows the order PA-8K_2 > PA-10K_2 > PA-12K_2 > PA-14K_2 > PA-16K_2 >PA-18K_2.

Keywords: Polyelectrolyte, maleic copolymers, *N*-alkyl-nitroimidazoles, partition, drugs reservoirs.

INTRODUCTION

In recent years considerable interest has developed in the search of adequate systems to be used as drug containers[1-4]. The concept is to introduce a micelle-like system where drugs, which generally are non-polar molecules, can be dissolved in aqueous solution. The substrate solubilized into the micelle is then released by a simple thermodynamic equilibrium with the medium, or by a drastic change of the external conditions, such as pH[5]. Therefore, micelles, vesicles, polyelectrolytes, block copolymers, and hydrophobically modified polyelectrolytes (HMP) can be considered as potential drugs reservoirs, from which drugs can be delivered over a certain period of time. The efficiency of this approach is dependent on the micelle stability, and the partitioning of the drugs into the micelles[6,7]. In addition the critical micelle concentration (cmc) of polymer micelles formed by block copolymers are one or two order of magnitude lower than those observed for regular surfactants[8]. In the case of HMP, it has been shown that only one □micelle□ is formed by each polymer chain, i.e. there is not cmc, and the micelle stability may be controlled by external factors such as pH or ionic strength. In other words, these polymer micelles can be designed in such a way that the hydrophobic microdomains are formed only under specific conditions. For example, it has been shown that alternate copolymers of maleic acid with olefins[9,10] and vinyl ethers[11]; and monoesters of poly(maleic acid-*co*-styrene)[12] perform a pH-induced conformational transition. At low pH values the polymer chains adopt a compact form, which becomes more extended as pH increases due to the increasing electrostatic repulsion between ionized carboxylic groups. The compact form has been called □polymer micelle□ because it presents a hydrophobic interior surrounded by an ionic corona. It has also been shown that this hydrophobic microdomain is able to dissolve organic molecules in aqueous solution[10,13].

Thus, the ability of polymer micelles to solubilize a wide variety of agents has led to their use as drug containers[2,14-16]. Many examples have been reported concerning to the potential application of these systems on biology and pharmacy, due to the possibility to develop biocompatible systems by choosing biodegradable monomers like amino acids, carboxylates or anhydride groups[17-19]. Therefore, it turns to be interesting to evaluate the drug solubilization capacity of these copolymers, and ideally to establish a relationship between the drug and polymer structure with this property. Thus, in the present study, we have assessed the ability of the aggregates formed by potassium salts of copolymers of poly(maleic acid-1-olefins), referred like PA-*n*K_2 with n = 8, 10, 12, 14, 16 and 18, to solubilize drugs in aqueous solution. As substrate we have used three commercial drugs: tinidazole, ornindazole and metronidazole (see Scheme I), which are antiparasitic and antibacterial agents, and a series of *N*-alkyl derivatives of 2-methyl-4-nitroimidazoles as model compounds.



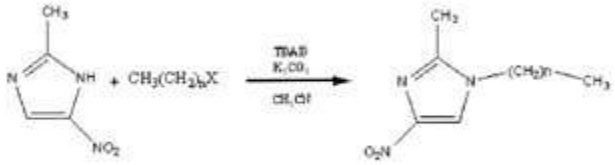
Scheme I

The distribution coefficients, and the free energy of transfer from the aqueous phase to the hydrophobic aggregates were determined for all these molecules. The results are discussed in terms of the polymer and drug structure.

EXPERIMENTAL

Materials.

Tinidazole and ornindazole were a gift from Laboratorios Bago, metronidazole was obtained from Laboratorios Chile, and they were used without further purification. The *N*-alkyl-2-methyl-4-nitroimidazoles were obtained by reaction of 2-methyl-5-itroimidazole (1 mol, Aldrich) with different alkylhalides (1.2 mol) (see table 1) in alkaline media, at reflux temperature in acetonitrile. All reactions were carried out in presence of tetrabutylammonium bromide (TBAB) 3%, as phase transfer catalyst (see Scheme II).



Scheme II

All products were purified by recrystallization from non-polar solvents, excepting *N*-hexyl-2-methyl-4-nitroimidazole, which was purified by column chromatography. ^{1}H-NMR was utilized to characterize the products.

Table 1. Alkylhalides used in the synthesis of alkyl-2-methyl-4-nitroimidazoles. Yields of reactions and ^{1}H-NMR of products.

N-Alkyl-2-methyl-4-NI	alkylhalides	Yield (%)	^{1}H-NMR ($CDHCl_3$)
1,2-dimethyl-4-NI	methyliodide	88	δ 2.43 (s, 3H, CH_3); δ 3.69 (s, 3H, N-CH_3); δ 7.68 (s, 1H)
1-ethyl-2-methyl-4-NI	ethylbromide	85	δ 1.49 (t, 3H, J = 7.4, CH_3); δ 2.44 (s, 3H, CH_3); δ 3.99(Q, 2H, N-CH_2); δ 7.72 (s, 1H)
1-propyl-2-methyl-4-NI	propyliodide	86	δ 1.00 (t, 3H, J = 7.6, CH3); δ 1.84 (m, 2H, J = 7.3, CH_2); δ 2.43 (s, 3H, CH_3); δ 3.89 (t, 2H, J = 7.3, N-CH_2). δ 7.68 (s, 1H)
1-butyl-2-methyl-4-NI	butylbromide	84	δ 0.99 (t, 3H, J = 7.3, CH_3); δ 1.40 (m, 2H, J = 7.4, CH_2); 1.78 (m, 2H, J = 7.3, CH_2); δ 2.44 (s, 3H, CH_3); 3.91 (t, 2H, J = 7.3, N-CH_2); 7.68 (s, 1H)
1-pentyl-2-methyl-4-NI	pentylbromide	77	δ 0.93 (t, 3H, J = 6.7, CH_3); δ 1.33 (m, 4H, CH_2); 1.80 (m, 2H, J = 7.3; CH_2); δ 2.43 (s, 3H, CH_3); δ 3.90 (t, 2H, J = 7.3; N-CH_2); δ 7.68 (s, 1H)
1-hexyl-2-methyl-4-NI	hexyliodide	65	δ 0.89 (s, 3H, CH_3); δ 1.33 (s, 6H, $(CH_2)_3$), δ 1.79 (m, 2H, J = 6.7, CH_2); δ 2.44 (s, 3H, CH_3); δ 3.93 (t, 2H, J = 7.2, N-CH_2); δ = 7.72 (s, 1H)

Poly(maleic anhydride-*co*-1-olefin) PA-« with *n* = 8, 10, 12, 14, and 16, were obtained by polymerizing maleic anhydride (1 mol) and 1-olefins (1.5 mol, octene to hexadecene) in 1,2-dichloroethane at 70 °C for 6 h and using benzoyl peroxide as initiator. The average molecular weights were determined by gel permeation chromatography, GPC, using poly(styrene) samples as standard, and ranges between 9000 and 20,000. Poly(maleic anhydride-*a*/f-1-octadecene) was obtained from Aldrich (M 30,000 - 50,000). The potassium salts of these copolymers, PA-«K□ were prepared by adding the polymers to an aqueous solution of KOH, while stirring, heated above 85 °C Further details have been given elsewhere[20]'. The degree of hydrolysis was complete, and it was determined by FTIR, measuring the disappearance of the absorption at 1779 cm"[1] that corresponds to the maleic anhydride residue.

Pyrene (Aldrich), used as fluorescent probé, was recrystallyzed twice from ethanol.

Measurement of Distribution Coefficients. The distribution coefficients were determined by ultrafiltration in an Amicon 202 cell with a PM 5000 membrane. Aqueous solutions of copolymer (2 g/L) at fixed pH, with different concentrations of nitroimidazoles NI were filtered, and the absorbance of filtrates was measured at 315 mu. The molar concentration of NI in the aqueous phase [NI_W] were obtained from a calibration curve and plotted against the molar concentration of NI in the polymer phase ÍNI 1 according to equation

1.

The equilibrium constants, K_s, were calculated from the initial slope where the activity coefficients can be assumed to be unity.

Fluorescence Probing. Fluorescence emission spectra were obtained with a SLM Aminco SPF-500C spectrophotofluorometer. The ratio I_3/I_1 corresponds to the ratio of intensities of peak three (384 nm) to peak one (373 nm) of the fluorescence spectrum of pyrene. The valué of this ratio is a function of the médium polarity, and an empirical

micropolarity scale has been proposed that it is widely used in the study of microheterogeneous systems[21,22]'. The fluorescence decay of the singlet excited pyrene was monitored at 400 nm, following excitation with pulses from a LSI nitrogen láser, model VSL-337ND-S (<4 ns fwhm, 300 uJ, 337.1 nm). The emission was detected with a Hamamatsu IP-28 photomultiplier tube through a grating monochromator (Oriel 77250). Signáis were digitized and stored with a TDS 430A digitizing oscilloscope (Tektronik). The data were analyzed in an IBM-compatible PC. A double exponential was fitted to the decay data. The concentrations used were 1 g/L and 2 *[íM* for the copolymers and pyrene, respectively. All samples were prepared with deionized water.

RESULTS AND DISCUSSION

The presence of hydrophobic aggregates in microheterogeneous systems can be detected by fluorescence probing through the measurement of the ratio I_3/I_1 and/or the lifetime of the pyrene fluorescence. In hydrophobically modified polyelectrolytes the change of these parameters has been used to monitor the conformational change induced by pH[12,23,24)]. Figure 1 shows the values of I_3/I_1 and τ as a function of pH for PA-nK_2 with n = 18, 12, and 8.

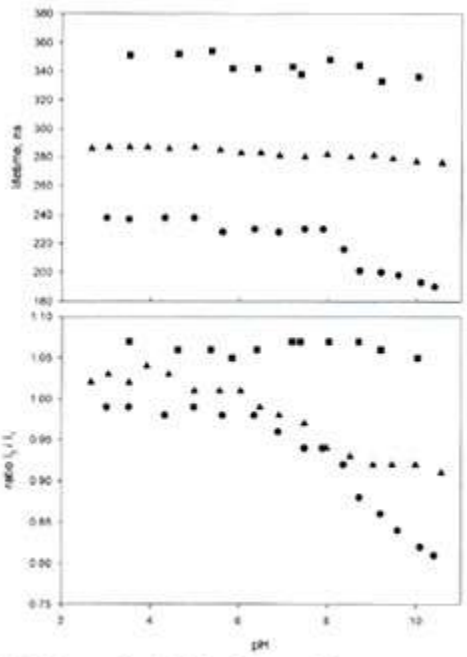


Figure1. Lifetime and ratio I_3/I_1 of pyrene fluorescence as a function of pH:■ PA-18K_2; ▲ PA-12K_2; ●PA-8K_2

The results are similar to those previously reported, i.e. both parameters remains almost constant in the whole range of pH, excepting the polymer with the shorter side alkyl chain, where an appreciable change is observed[10]'. However, even for n = 8 and at the higher pH used, the valúes of these parameters indícate that pyrene is always sensing a hydrophobic environment. For example, the ratio I_3/I_1 and the lifetime of pyrene fluorescence are 0.75 and 170 ns, respectively, which are higher than the corresponding valúes in aqueous solution (0.56 and 150 ns). Thus, the PA-

nK_2 copolymers in aqueous solution adopt a compact form in the whole range of pH, providing a hydrophobic microdomain, where organic molecules can be dissolved. It has also been shown that, for these copolymers, coiling of one polymer chain forms just one aggregate[9,10]. However, the hydrophobicity of the aggregates, as measured by the ratio I_3/I_1, varies with the number of carbon atoms in the side alkyl chain. Infigure 2 the ratio I_3/I_1 is given as a function of *n* at two different values of pH. In both cases the ratio increases with increasing *n*, indicating that the aggregates are becoming more and more hydrophobic as long as the side alkyl chain grows.

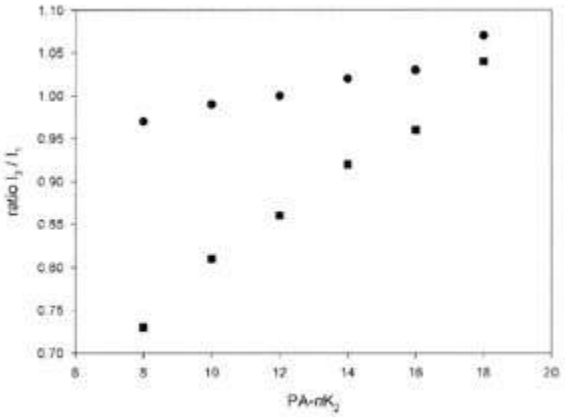


Figure 2. Ratio I_3/I_1 of pyrene fluorescence in the presence of PA-nK_2 at pH 3.0 (●) and pH 7.0 (■)

The distribution of nitroimidazoles derivatives, between the aqueous phase and the microdomains provided by the PA-nK_2 polymer chains, was analyzed in terms of the pseudo-phase model[25]. According to this model the distribution constant can be expressed on a molar concentration basis as:

$$K_S = \frac{[NI_M]}{[NI_W][P_M]}\frac{f_M}{f_W} \quad (1)$$

where $[NI_M]$ and $[NI_W]$ denote molar concentrations of imidazole derivatives in micellar and aqueous phases, respectively, $[P_M]$ is the concentration of repetitive units of PA-nK_2 forming part of the micellar pseudo-phase, $f_M$and f_W are the activity coefficients of the NI in the respective phase. From this experimental equilibrium constant, the thermodynamic distribution coefficient, written in a mole fraction basis, K_X, can be calculated through the relation $K_X = 55.5K_S$. Assuming ideal behavior of the NI in the micelles and in the aqueous phase, the molar standard free energy of transfer from aqueous solution to polymer micelles is obtained as $\Delta\mu^0_T = \Delta\mu^0_M - \Delta\mu^0_W = -RTlnK_X$.

Typical results of the distribution of *N*-alkyl-2-metlyl-4-nitroimidazoles between aqueous solution and the aggregates formed by PA-$18K_2$ at pH 7.0, are shown in Figure 3.

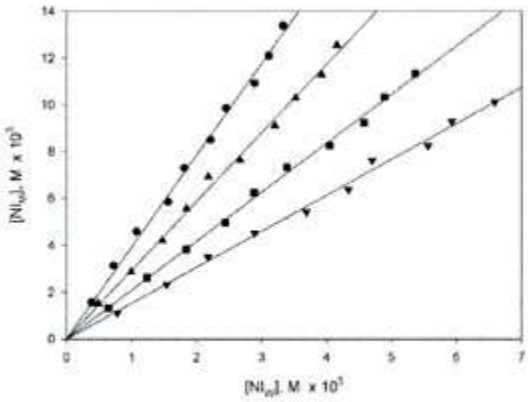


Figure 3. Partition of alkyl-2-methyl-4-nitroimidazoles between aqueous phase and aggregates formed by PA-18K$_2$ at pH 7.0. ▼ methyl, ■ ethyl, ▲ butyl, ● hexyl.

The plots are all linear, and the values of K_S and K_X are collected in Table 2, where the results obtained for the commercial drugs have also been included. The data indicate that, for the *N*-alkyl-2-methyl-4-nitroimidazoles, the solubilization into the polymer aggregates increases with increasing length of the alkyl chain.

Table 2. Distribution constants, K_s and K_X, and the standard free energy of transfer $\Delta\mu^0_T$ of *N*-alkyl-2-methyl-4-nitroimidazoles and commercial drugs, from the aqueous solution to the aggregates formed by PA-18K$_2$.

N-alkyl-2-M-4-NI	K_s	K_X x 10^{-3}	$-\Delta\mu^0_T$, kJ mol^{-1}
methyl	340.0	18.9	24.4
ethyl	464.4	25.8	25.2
propyl	573.3	31.8	25.7
butyl	651.1	36.1	26.0
pentyl	766.7	42.6	26.4
hexyl	871.1	48.3	26.7
ornidazole	325.6	18.1	24.3
tinidazole	160.6	8.9	22.5
metronidazole	395.1	21.9	24.8

To get an insight on the nature of the forces that determine the incorporation of NI into the hydrophobic polymer aggregates, we have used the assumption that $\Delta\mu^0_T$ can be written as

$$\Delta\mu^0_T = \Delta\mu^0_{NI} + n_C\Delta\mu^0_C \quad (2)$$

where $\Delta\mu^0_{NI}$ and $\Delta\mu^0_C$ are the contributions to the free energy of transfer of the heterocycle ring (2-methyl-4-nitroimidazole group) and each methylene group, respectively, n_C is the number of carbon atoms in the alkyl group[26]. This free energy relationship has been widely used for the partitioning of solutes between two

immiscible solvents[26], transfer of organic molecules from water to micelles[25], and water to polymer micelles[10]. A plot of $\Delta\mu^0_T$ against n_C is shown in Figure 4.

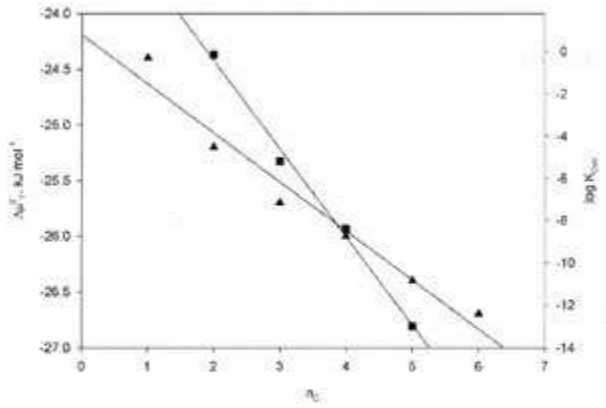


Figure 4. Free energy of transfer, from the aqueous solution to the aggregates formed by PA-18K, at pH 7.0, (▲) and octanol index (!) of alkyl-2-methyl-4-nitroimidazoles as a function of the number of carbon atoms in alkyl chain.

The standard free energy of transfer by methylene group is-0.44 kJ mol"[1]. This figure is lower than that obtained with n-alkylphenols distributing in the same system, or SDS micelles. However, the valué of A|x°$_{NI}$ (-24.2 kJ mol"[1]) is similar to that found for the phenol group, indicating that also in this case the main contribution to the free energy of transfer is made by the parent heterocyclic ring. The effect of the hydroxyl group can be evaluated by comparing the results obtained for W-propyl-2-methyl-4-nitroimidazole and metronidazole. The addition of a hydroxyl group to the propyl chain decreases the distribution constant from 573 to 395, and therefore Ali° is equal to +0.09 kJ mol"[1]. On the other hand, the addition of a chlorine atom (compares metronidazole and ornindazole data) reduces slightly the solubility into the polymer aggregates (K_S changes from 395 to 326). The contribution of the Cl atom to $\Delta\mu^0_T$ is just +0.05 kJ mol^{-1}. Finally, the presence of a SO_2 group in the alkyl chain produces even a largest decrease on the solubility of the propyl derivative into the polymeric aggregates. The distribution constant decreases from 573 to 161, and the contribution to the free energy of transfer of the $-SO_2$ group is +0.33 kJ mol^{-1}. It is interesting to note that the $-SO_2$ group has a bigger effect than the hydroxyl group in reducing the K_S value. This is the first value reported for the free energy of transfer of the $-SO_2$ group.

The decimal logarithm of the partition coefficient of alkylmethylnitroimida zoles between 1-octanol and water logK_{OW} were also determined. This parameter is largely used as an empirical measure for lipophilicity in pharmacological and toxicological studies[27-29]. The results, shown in Figure 4, indicate that this parameter and $-\Delta\mu^0_T$ follow a similar trend, i.e. their values increase linearly with increasing length of the 1-alkyl substitution. However, the contribution by methylene group to the free energy is one order of magnitude higher for the transfer to octanol (–4.17 kJ mol^{-1}) than to the transfer into the polymer micelles. This means that the effect of NI structure, predicted by logK_{OW}, on the solubility into the polymer aggregates is much stronger than the real one. Probably, the solubilization into a hydrophobic aggregate and the partition between two immiscible phases involve different entropic factors,

which makes that the distribution constants, K_S and K_{OW}, varies with the substrate structure in a different way.

The effect of pH was determined by measuring the distribution constants for hexyl-2-methyl-4-nitroimidazole at pH 3.0, 7.0, and 11.0 in PA-8K_2 and PA-18K_2. The results are shown in Figure 5, where for comparison the values of the ratio III/I have also been included.

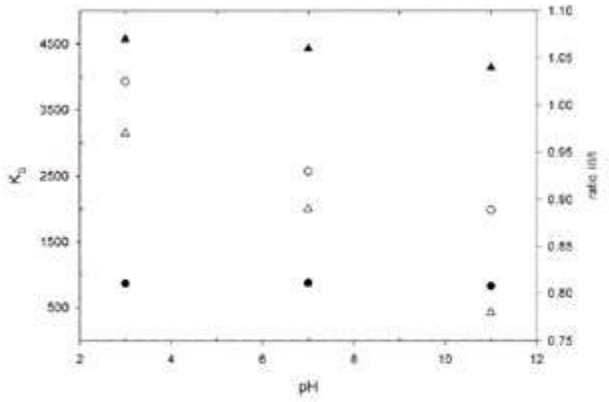


Figure 5. Distribution coefficients of hexyl-2-methyl-4-nitroimidazole at pH 3.0, 7.0, and 11.0 in PA-8K_2 (□) and PA-18K_2 (○). For comparison the ratio I_3/I_1 of pyrene in presence of PA-8K_2 (Δ) and PA-18K_2 (□) have been included.

The distribution constants and the ratio III/I show the same dependence with pH, confirming that the NI is solubilized into the polymer aggregates. PA-18K_2 form aggregates in the whole range of pH, and therefore the valúes of K_s are almost independent of pH. On the other hand, for PA-8K_2 the ratio III/I indicates a pH-induced transition from a compact to a random form, and consequently K_s decreases with increasing pH. In other words, increasing pH drastically reduces the polymer micelle stability, and consequently most of the drug is released to the aqueous phase when the pH is increased.

Another interesting point arises from these results, unexpectedly the distribution constants are higher for PA-8K_2than in PA-18K_2, despite that the aggregates formed by the latter are more hydrophobic. The effect of polymer structure on the distribution coefficients was determined for tinidazole, ornindazole and W-hexyl-2-methyl-4-nitroimidazole. The results obtained for tinidazole are collected in Table 3.

Table 3. Distribution constants, K_s and $K_{x'}$ and the standard free energy of transfer $\Delta\mu^0_T$ of tinidazole from the aqueous solution to the aggregates formed by PA-nK_2 at pH 7.0.

n	K_s	$K_x \times 10^{-3}$	$-\Delta\mu^0_T$, kJ mol^{-1}
8	844	46.40	26.6
10	523	29.58	25.5
12	346	18.76	24.4
14	253	13.94	23.6
16	197	16.85	23.0
18	153	8.91	22.5

Interestingly, the transfer from water to the polymeric micelles, as measured by the distribution constant, decreases with increasing length of the side alkyl chain. This unexpected behavior is observed for the three NI compounds analyzed, even though in the case of ornindazole the effect is minimal.

Using a free energy linear relationship of the same kind of that given in equation 2, it is possible to obtain the contribution of each methylene group, in the polymer side chain, to the standard free energy of transfer. Thus, from a plot of $\Delta\mu^0_T$ against *n* (figure 6) the following values of $\Delta\mu^0_C$ were obtained +0.41 kJ mol^{-1}, +0.26 kJ mol^{-1}, and +0.018 kJ mol^{-1} for tinidazole, 2-hexyl-4-methyl-nitroimidazole, and ornindazole respectively.

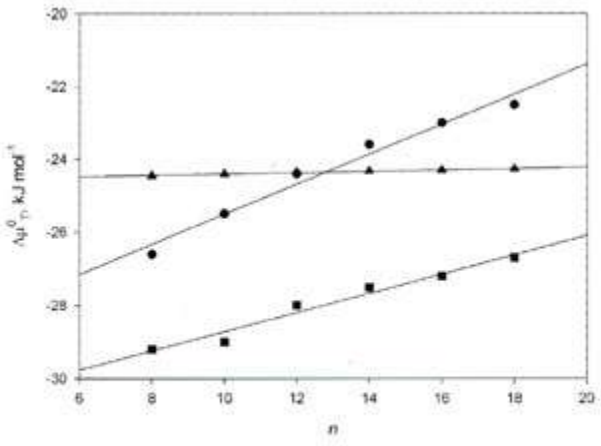


Figure 6. Free energy of transfer of (□) tinidazole, (○) 2-hexyl-4-methyl-nitroimidazole, and (△) ornindazole as a function of the number of carbon atoms in the side alkyl chain.

Therefore, the increase in the length of the alkyl chain that forms the nucleus of the polymer aggregate decreases the solubility of the NI derivatives into the polymer microdomain. This behavior suggests that the solubilization of the NI compounds into the polymer aggregates is not determined by the hydrophobicity of the polymer microdomain.

CONCLUSIONS

The ability of PA-nK_2 copolymers to solubilize drugs, derived from the nitroimidazole ring, has been evaluated. The distribution coefficients of three commercial drugs and a family of W-alkyl-2-methyl-4-nitroimidazole derivatives were determined. From the data the free energy of transfer was obtained as a function of the number of carbón atoms in the alkyl chain of nitroimidazole, and the contribution by methylene group was found to be -0.44 kJ mol"[1]. The contributions of the parent ring, and other constituent groups were also determined. The logK_{ow}parameter was measured forAí-alkyl-2-methyl-4-nitroimidazole, and the results show a similar trend than □Ají[0] . However, the dependence with *n* of logK_{ow} is higher than that of □Ají[0] . The stability of the polymer micelles increases with increasing length of the side alkyl chain, and only PA-8K_2 exhibits a pH-induced conformational transition. Therefore, PA-nK_2 copolymers with n>8 can be used as drugs reservoirs in the whole range of pH. In the case of PA-8K an important amount of the drug can be released by changing the pH from 3.0 to 7.0.

ACKNOWLEDGMENTS

This work was supported by FONDECYT 1030526, and Universidad Andrés Bello DI 14-04. C.H.S. acknowledges a Ph.D. fellowship from the Deutscher Akademischer Austauschdienst-DAAD.

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Received: August 21, 2006 - Accepted: January 8, 2007)