Electrical Conductivities and Critical Micelle Concentrations (Determined by the Local Polynomial Regression Method) of Imipramine and Clomipramine Hydrochlorides from (283 to 313) K

José L. López Fontán,[†] Julián Costa,[‡] Juan M. Ruso,[†] Gerardo Prieto,[†] and Félix Sarmiento*,[†]

Group of Biophysics and Interfaces, Department of Applied Physics, Faculty of Physics, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain, and Department of Mathematics, Faculty of Informatics, University of A Coruña, 15071 A Coruña, Spain

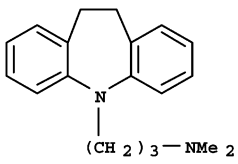
Electrical conductivity measurements for aqueous solutions of imipramine and clomipramine hydrochlorides have been carried out from (283 to 313) K. From these data, critical micelle concentrations (CMCs) have been obtained by application of the local polynomial regression method, which is based on a nonparametric estimation of the regression function. The method is extremely flexible because it does not impose any parametric model on the subjacent structure of the data but rather allows the data to speak for themselves. The variation of the CMC with temperature was a second-order polynomial, with different trends for imipramine (convex) and clomipramine (concave). This distinct behavior was analyzed by the effects of dehydration of the headgroups and thermal solubility of molecules.

Introduction

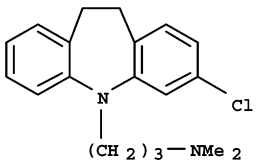
The physical properties of surfactant solutions such as electrical conductivities, surface tension, light-scattering, ultrasound velocity, osmotic pressure, etc. change in the neighborhood of the critical micelle concentration (CMC).[1] This change can be abrupt or slight. In the first case, the CMC is determined by the intersection between two straight lines above and below the CMC. In the second case, it is difficult to obtain a precise CMC as several straight lines can be obtained by fitting the experimental points. To solve this problem, recently we have reported a statistical method to determine CMCs with precision, the local polynomial regression method (LPRM).[2] The method is based on a nonparametric estimation of the regression function, which has the advantage of being extremely flexible given it does not impose any parametric model on the subjacent structure of the data but rather allows the data to speak for themselves. Hence, this methodology is applicable in practically all circumstances with good results.

The self-association of surface-active drugs of quite different chemical structures has been widely studied.[3] In general, these substances behave in solution as the second case previously indicated, i.e., the variation of the physical property observed against drug concentration is slow. On the other hand, to know the exact CMC of the drug is of paramount importance, because to obtain an optimal effect, the drug must be administrated at a low enough concentration at which the aggregation is negligible.[3]

In this article, we report results on electrical conductivities in the range (283 to 313) K and CMCs, determined by application of the LPRM, of imipramine and clomipramine hydrochlorides, two antidepressant surface-active drugs possessing an almost planar tryciclic ring system with a short hydrocarbon chain carrying a terminal N atom (see below for structures). In the absence of electrolyte, the micellar association pattern of these drugs in solution is characterized by a diffuse inflection in the physical properties at a critical concentration.[4] For this reason, the application of LPRM to determine the CMC is very suitable.



IMIPRAMINE



CLOMIPRAMINE

Materials and Methods

The hydrochlorides of clomipramine (3-chloro-5-(3dimethylamino)propyl)-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine) and imipramine (5-(3-(dimethylamino)propyl)-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine) (Sigma Chemical Co. Ltd., Nos. C-7291 and I-7379, respectively) were sufficiently well characterized and purified to be used as received. Both of the compounds conformed to the purity requirements of the British Pharmacoepia and as such contained not less than 98.5% of the specified compound. Water was double-distilled, deionzed, and degassed before use.

The conductance was measured in the temperature range (283 to 313) K using a conductivity meter (Kyoto Electronic C-117), the cell of which (Kyoto, type K-121), that measures temperature and conductivity simultaneously, was calibrated with KCl solutions in the appropriate concentration range. The cell constant was calculated using molar conductivity data published by Shedlovsky[5] and Chambers et al.[6] The precision of the cell is of 0.1 K.

The sample was introduced in a bath which was heating at a rate of 1 K per minute. This rate is enough to guarantee micelle monomers equilibrium, because the duration of the dynamic process may vary from 10^{-8} s (which is the time it takes a surfactant to leave or enter a micelle) to 10^{-2} s (the time scale of the fusion of micelles).[7]

* To whom correspondence may be addressed. Tel.: +34 981 563 100. Fax: +34 981 520 676. E-mail: fsarmi@usc.es.
[†] University of Santiago de Compostela.
[‡] University of A Coruña.

10.1021/je049954l CCC: $27.50
Published on Web 05/13/2004

Table 1. Electrical Conductivities of Imipramime Hydrochloride + Water at Different Temperatures

	κ/mS·cm^{-1}															
c/mol·kg^{-1}	283 K	284 K	285K	286 K	287 K	288 K	289 K	290 K	291 K	292 K	293 K	294 K	295 K	296 K	297 K	298 K
0.152	8.165	8.170	8.185	8.215	8.235	8.250	8.290	8.325	8.365	8.415	8.465	8.500	8.530	8.565	8.615	8.660
0.140	7.745	7.755	7.765	7.785	7.805	7.835	7.860	7.895	7.935	7.985	8.030	8.060	8.090	8.125	8.170	8.215
0.130	7.375	7.395	7.400	7.420	7.440	7.465	7.495	7.525	7.560	7.600	7.650	7.675	7.705	7.745	7.785	7.825
0.120	6.995	7.010	7.020	7.035	7.055	7.075	7.100	7.130	7.165	7.205	7.240	7.265	7.290	7.325	7.365	7.405
0.100	6.225	6.225	6.235	6.240	6.256	6.275	6.295	6.325	6.355	6.390	6.435	6.455	6.475	6.500	6.535	6.570
0.090	5.825	5.825	5.835	5.845	5.855	5.875	5.895	5.915	5.940	5.970	6.005	6.025	6.045	6.070	6.095	6.130
0.080	5.405	5.415	5.420	5.430	5.440	5.450	5.465	5.485	5.505	5.540	5.570	5.585	5.600	5.625	5.645	5.675
0.070	4.970	4.975	4.975	4.980	4.985	4.995	5.010	5.025	5.045	5.065	5.090	5.105	5.120	5.135	5.150	5.175
0.065	4.735	4.735	4.735	4.730	4.735	4.745	4.755	4.770	4.790	4.805	4.830	4.840	4.855	4.865	4.885	4.900
0.060	4.490	4.485	4.485	4.490	4.490	4.500	4.505	4.515	4.530	4.545	4.565	4.570	4.575	4.590	4.605	4.620
0.055	4.230	4.225	4.220	4.220	4.215	4.225	4.230	4.235	4.250	4.260	4.275	4.280	4.285	4.295	4.300	4.315
0.050	4.010	4.000	4.000	3.995	3.995	3.995	4.000	4.005	4.015	4.020	4.035	4.035	4.040	4.050	4.055	4.060
0.045	3.715	3.705	3.705	3.695	3.690	3.690	3.690	3.695	3.700	3.710	3.720	3.720	3.720	3.725	3.735	3.740
0.040	3.365	3.355	3.345	3.345	3.340	3.340	3.340	3.345	3.345	3.350	3.360	3.355	3.350	3.355	3.360	3.365
0.035	2.995	2.990	2.975	2.970	2.960	2.960	2.965	2.960	2.970	2.965	2.975	2.975	2.975	2.975	2.980	2.985
0.030	2.560	2.550	2.550	2.540	2.540	2.535	2.530	2.535	2.535	2.540	2.545	2.545	2.540	2.550	2.550	2.555
0.020	1.770	1.765	1.760	1.760	1.755	1.750	1.750	1.750	1.750	1.755	1.760	1.760	1.760	1.760	1.760	1.765
0.010	0.924	0.921	0.919	0.917	0.915	0.914	0.913	0.913	0.914	0.915	0.916	0.916	0.916	0.916	0.917	0.918
0.008	0.702	0.699	0.698	0.696	0.695	0.694	0.694	0.694	0.695	0.695	0.696	0.696	0.696	0.696	0.696	0.698

	κ/(mS·cm^{-1})														
c/mol·kg^{-1}	299 K	300 K	301 K	302 K	303 K	304 K	305 K	306 K	307 K	308 K	309 K	310 K	311 K	312 K	313 K
0.152	8.695	8.730	8.775	8.825	8.875	8.900	8.925	8.955	8.995	9.045	9.095	9.145	9.215	9.270	9.345
0.140	8.245	8.280	8.325	8.370	8.425	8.445	8.470	8.500	8.540	8.580	8.620	8.675	8.730	8.795	8.865
0.130	7.850	7.880	7.915	7.965	8.015	8.030	8.060	8.090	8.125	8.160	8.200	8.250	8.300	8.360	8.425
0.120	7.435	7.465	7.505	7.540	7.585	7.605	7.630	7.655	7.690	7.730	7.770	7.810	7.860	7.925	7.970
0.100	6.595	6.620	6.650	6.685	6.715	6.740	6.755	6.785	6.805	6.835	6.875	6.910	6.955	6.995	7.045
0.090	6.150	6.175	6.200	6.230	6.260	6.275	6.290	6.310	6.330	6.355	6.380	6.415	6.455	6.495	6.535
0.080	5.690	5.710	5.735	5.755	5.785	5.795	5.805	5.820	5.840	5.860	5.880	5.910	5.940	5.980	6.015
0.070	5.185	5.195	5.215	5.235	5.260	5.265	5.275	5.280	5.295	5.310	5.330	5.350	5.375	5.400	5.430
0.065	4.910	4.920	4.935	4.945	4.965	4.970	4.980	4.990	4.995	5.010	5.030	5.045	5.065	5.090	5.115
0.060	4.630	4.635	4.650	4.665	4.680	4.680	4.680	4.690	4.700	4.705	4.720	4.735	4.755	4.770	4.795
0.055	4.320	4.330	4.335	4.345	4.360	4.360	4.365	4.365	4.375	4.380	4.390	4.405	4.415	4.430	4.450
0.050	4.065	4.070	4.075	4.085	4.095	4.095	4.100	4.100	4.100	4.115	4.120	4.130	4.140	4.155	4.170
0.045	3.740	3.745	3.750	3.760	3.765	3.765	3.760	3.765	3.770	3.775	3.780	3.790	3.805	3.815	3.830
0.040	3.370	3.370	3.375	3.380	3.390	3.385	3.380	3.385	3.385	3.390	3.395	3.400	3.410	3.420	3.430
0.035	2.985	2.985	2.990	2.995	3.005	3.000	3.000	3.000	3.000	3.005	3.010	3.015	3.025	3.030	3.045
0.030	2.555	2.555	2.560	2.560	2.560	2.570	2.570	2.570	2.575	2.580	2.580	2.580	2.585	2.595	2.600
0.020	1.760	1.765	1.770	1.770	1.770	1.770	1.770	1.770	1.770	1.775	1.780	1.780	1.785	1.790	1.800
0.010	0.918	0.919	0.919	0.920	0.922	0.922	0.920	0.921	0.921	0.922	0.923	0.925	0.928	0.930	0.934
0.008	0.697	0.698	0.698	0.699	0.700	0.700	0.699	0.699	0.700	0.700	0.701	0.703	0.705	0.707	0.709

Then the measurements were made at 1-K intervals. Concentrated drug solutions of known concentration were progressively added to water using an automatic pump (Dosimat 665 Method). To converge temperature, the samples were vigorously shaken.

Results and Discussion

Tables 1 and 2 show the specific conductivity values at each concentration and temperature. Figures 1 and 2 show the variation of these magnitudes for imipramine and clomipramine, respectively. From these data, the CMCs were obtained by applying the LPRM,[2,8−11] for which a brief explanation is given.

At our disposal is a series of observations from two variables, an independent variable X that in our case represents the concentration and a dependent variable Y that represents the measured conductivity. The objective is to establish the relationship between the two variables to study characteristics of interest, in particular, CMC.

The usual way one establishes the relationship between both variables is by means of a regression analysis. For given pairs of data (X_i,Y_i), $i = 1, 2, ..., n$, one attempts to fit a mathematical function through the data, the so-called regression function. The part that cannot be explained is the error (often treated as noise)

$$Y = m(X) + error \tag{1}$$

The statistical problem consists of estimating m and its jth derivative $m^{(j)}$, $j > 0$. Let $\hat{m}^{(j)}$ be the estimation of the jth derivative. The problem of calculating the CMC is related with the statistical problem of the regression where interest is in the location of a peak x_{CMC} of second derivative $m^{(2)}$

$$x_{CMC} = \arg\max|m^{(2)}(x)| \tag{2}$$

and the value of conductivity

$$m(x_{CMC}) \tag{3}$$

that will be estimated from

$$\hat{x}_{CMC} = \arg\max|\hat{m}^2(x)| \tag{4}$$

$$\hat{m}(\hat{x}_{CMC})$$

Noting our control over the variable X, two regression models are evident: fixed design and random design. In the random design regression model, we observe pairs of random variables (X_i,Y_i), $i = 1, 2, ..., n$, drawn independently from a bivariate distribution

$$m(x) = E(Y/X = x) \tag{5}$$

Table 2. Electrical Conductivities of Clomipramime Hydrochloride + Water at Different Temperatures

	κ/mS·cm^{-1}															
c/mol·kg^{-1}	283 K	284 K	285K	286 K	287 K	288 K	289 K	290 K	291 K	292 K	293 K	294 K	295 K	296 K	297 K	298 K
0.090	4.730	4.735	4.745	4.760	4.770	4.785	4.810	4.830	4.860	4.890	4.925	4.940	4.965	4.990	5.020	5.050
0.080	4.425	4.435	4.435	4.450	4.465	4.480	4.505	4.520	4.545	4.575	4.600	4.620	4.640	4.665	4.695	4.725
0.070	3.975	3.980	3.985	3.995	4.010	4.025	4.045	4.065	4.085	4.110	4.140	4.155	4.175	4.195	4.220	4.245
0.060	3.575	3.585	3.590	3.600	3.610	3.625	3.640	3.660	3.680	3.705	3.730	3.745	3.760	3.780	3.800	3.825
0.051	3.165	3.170	3.180	3.190	3.195	3.205	3.220	3.240	3.250	3.275	3.300	3.310	3.330	3.345	3.365	3.390
0.045	2.940	2.945	2.950	2.955	2.970	2.975	2.990	3.000	3.020	3.040	3.055	3.065	3.080	3.100	3.115	3.135
0.040	2.720	2.725	2.735	2.745	2.750	2.765	2.770	2.790	2.800	2.815	2.835	2.850	2.860	2.875	2.890	2.910
0.035	2.480	2.490	2.490	2.500	2.510	2.515	2.525	2.540	2.550	2.570	2.580	2.590	2.600	2.620	2.630	2.650
0.030	2.250	2.255	2.260	2.260	2.270	2.275	2.285	2.295	2.310	2.320	2.330	2.340	2.350	2.360	2.370	2.380
0.028	2.130	2.130	2.135	2.140	2.140	2.150	2.160	2.165	2.170	2.180	2.195	2.200	2.210	2.220	2.230	2.240
0.025	2.005	2.010	2.010	2.010	2.015	2.020	2.030	2.030	2.040	2.050	2.060	2.060	2.060	2.070	2.070	2.080
0.023	1.865	1.865	1.865	1.870	1.870	1.870	1.880	1.880	1.880	1.890	1.900	1.900	1.905	1.910	1.910	1.920
0.020	1.710	1.710	1.705	1.705	1.705	1.705	1.710	1.710	1.710	1.720	1.720	1.720	1.720	1.730	1.730	1.730
0.018	1.535	1.530	1.530	1.525	1.525	1.520	1.525	1.525	1.530	1.530	1.530	1.530	1.530	1.530	1.540	1.540
0.015	1.340	1.330	1.330	1.330	1.330	1.325	1.320	1.325	1.325	1.330	1.330	1.330	1.330	1.330	1.330	1.330
0.013	1.120	1.120	1.120	1.120	1.110	1.110	1.110	1.110	1.110	1.115	1.120	1.120	1.120	1.120	1.120	1.120
0.010	0.907	0.904	0.902	0.901	0.899	0.899	0.898	0.900	0.900	0.901	0.902	0.903	0.903	0.903	0.903	0.905
0.008	0.687	0.685	0.684	0.682	0.681	0.680	0.680	0.680	0.681	0.681	0.682	0.681	0.682	0.682	0.683	0.684
0.005	0.459	0.458	0.456	0.456	0.455	0.454	0.454	0.454	0.454	0.455	0.455	0.455	0.455	0.455	0.455	0.456
0.004	0.371	0.370	0.369	0.368	0.367	0.367	0.367	0.367	0.367	0.367	0.368	0.368	0.367	0.368	0.368	0.369

	κ/mS·cm^{-1}														
c/mol·kg^{-1}	299 K	300 K	301 K	302 K	303 K	304 K	305 K	306 K	307 K	308 K	309 K	310 K	311 K	312 K	313 K
0.090	5.070	5.100	5.110	5.130	5.155	5.170	5.190	5.215	5.240	5.275	5.310	5.340	5.385	5.430	5.480
0.080	4.745	4.770	4.795	4.820	4.855	4.870	4.885	4.910	4.935	4.960	4.995	5.025	5.060	5.100	5.150
0.070	4.265	4.285	4.310	4.340	4.370	4.385	4.400	4.425	4.445	4.470	4.500	4.530	4.565	4.600	4.640
0.060	3.845	3.860	3.885	3.910	3.935	3.950	3.965	3.980	4.000	4.025	4.050	4.080	4.110	4.140	4.175
0.051	3.400	3.415	3.440	3.455	3.480	3.490	3.505	3.520	3.540	3.560	3.580	3.605	3.630	3.660	3.690
0.045	3.150	3.165	3.180	3.205	3.220	3.235	3.250	3.260	3.280	3.295	3.315	3.340	3.360	3.380	3.410
0.040	2.920	2.935	2.950	2.970	2.990	3.000	3.010	3.020	3.035	3.050	3.070	3.090	3.110	3.125	3.155
0.035	2.660	2.670	2.695	2.710	2.725	2.735	2.740	2.750	2.760	2.778	2.790	2.810	2.825	2.845	2.865
0.030	2.390	2.400	2.410	2.420	2.430	2.440	2.440	2.460	2.470	2.475	2.480	2.490	2.505	2.520	2.535
0.028	2.240	2.250	2.260	2.270	2.280	2.280	2.290	2.290	2.295	2.300	2.310	2.330	2.340	2.350	2.360
0.025	2.090	2.090	2.100	2.105	2.110	2.120	2.120	2.125	2.130	2.130	2.140	2.150	2.160	2.165	2.170
0.023	1.920	1.920	1.930	1.930	1.940	1.940	1.940	1.940	1.940	1.940	1.945	1.950	1.955	1.960	1.970
0.020	1.730	1.730	1.735	1.740	1.740	1.740	1.740	1.740	1.740	1.740	1.750	1.750	1.750	1.760	1.760
0.018	1.540	1.540	1.540	1.540	1.540	1.540	1.540	1.540	1.540	1.540	1.550	1.550	1.555	1.560	1.565
0.015	1.330	1.335	1.340	1.340	1.340	1.340	1.340	1.340	1.340	1.340	1.340	1.345	1.350	1.355	1.360
0.013	1.120	1.120	1.120	1.120	1.125	1.120	1.120	1.120	1.120	1.125	1.130	1.130	1.130	1.135	1.140
0.010	0.905	0.905	0.907	0.907	0.909	0.909	0.909	0.908	0.909	0.910	0.911	0.913	0.916	0.919	0.922
0.008	0.684	0.684	0.685	0.686	0.687	0.686	0.686	0.686	0.686	0.687	0.688	0.689	0.690	0.692	0.695
0.005	0.456	0.456	0.457	0.457	0.458	0.458	0.457	0.457	0.457	0.457	0.458	0.459	0.460	0.461	0.463
0.004	0.368	0.369	0.369	0.369	0.370	0.369	0.369	0.368	0.369	0.369	0.369	0.370	0.370	0.371	0.372

In the fixed-design regression model, we assume that measurements of X are made at the fixed points x_1, x_2, ..., x_n (points chosen by the experimenter)

$$Y_i = m(x_i) + \epsilon_i, \qquad i = 1, 2, ..., n \tag{6}$$

where Y_1, Y_2, ..., Y_n are the measurements made at points x_1, x_2, ..., x_n and ϵ_i is the measurement error of the ith measurement.

We can assume the following structure in the errors: ϵ_i are independent; $E(\epsilon_i) = 0$, i.e., the errors are unbias (with null mean); $\mathrm{Var}(\epsilon_i) = \sigma^2 < \infty$, i.e., the errors are homoscedastic (with constant variances).

Noting the hypotheses assumed on the regression function m, we can differentiate between parametric regression and nonparametric regression. The classical regression methods are parametric models, where the type of regression function is specified depending on finitely many parameters. For example, the simplest case, and therefore most commonly used, is the simple linear regression (univariate linear first-order model), where we assume that the regression function corresponds to a straight line, hence called regression line, and the estimation of this straight line, for which different methods exist, is reduced to the estimation of two of its parameters, slope and intercept. The advantage of these parametric methods is that, when the functional model assumed for m is adequate, the estimation is reduced to a few parameters and, therefore, it is extremely efficient. However, when the model chosen is inadequate, the estimation will be invalid and in many cases of no use.

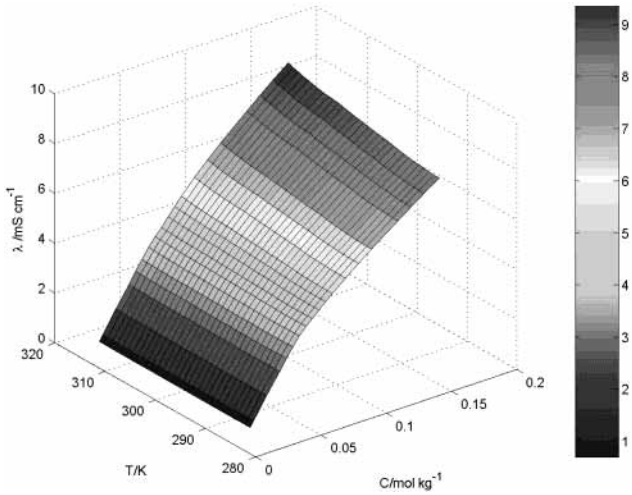


Figure 1. Electrical conductivities of imipramine hydrochloride + water as a function of molal concentration and temperature.

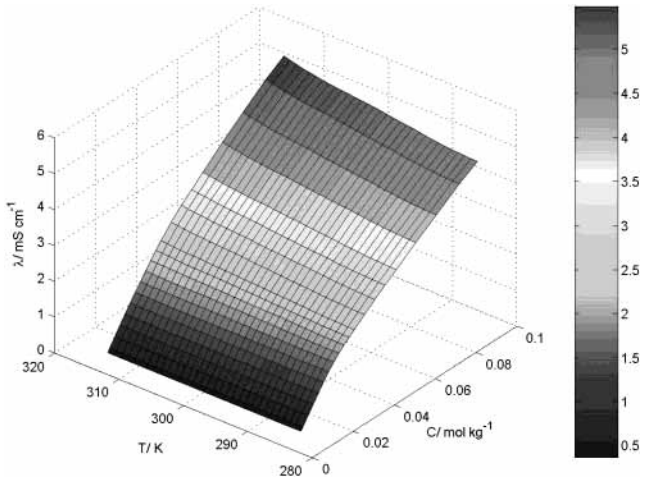


Figure 2. Electrical conductivities of clomipramine hydrochloride + water as a function of molal concentration and temperature.

To apply the method, we must perform weighted local fittings of polynomial functions by least squares. In our case, the estimation of the second derivative of the regression function using polynomials of odd order is necessary, at least a third order, because to compute CMC the Phillips definition[12] has been used

$$\left(\frac{d^3\kappa}{dc^3}\right)_{c=\mathrm{CMC}} = 0 \qquad (7)$$

where κ denotes the physical property (in our case, conductivity) and c the critical concentration.

The problem of estimating the derivatives of the regression curve has been resolved by implementing the local polynomial regression estimator in the programming language Matlab, using the quartic kernel and plug-in optimal the asymptotic mean squared error (AMSE)[10] bandwidth. The calculation of $h_j^{\mathrm{opt}}(x_0)$, the ideal optimal bandwidth, was achieved by estimating the variance of the errors, σ_ϵ^2, using a local polynomial regression with a pilot bandwidth; the Parzen−Rosenblatt[11] kernel estimator for $f(x_0)$ was also obtained by using a pilot bandwidth, and a parametric regression and a local polynomial regression were used for $m^{(p+1)}(x_0)$, ($(p + 1)$ derivative of function to fit at $x = x_0$). To avoid the problem of choosing an initial value h_0, an iterative approach was taken starting with a large h_0. This initial pilot bandwidth produces another bandwidth, and this last one produces another, and so on. The iteration is continued to convergence. The reason for using a local bandwidth, and therefore applying AMSE criteria to obtain the bandwidth parameter, is that the objective we are after is not as much to have an overall view of the regression function but more to locate the point that proves a particular condition (CMC point).

Figure 3 shows, as example, the application of the method to determine the CMC of imipramine at 288 K and Table 3 shows the obtained values for both drugs in all ranges of temepratures. Comparison with previously published data (Table 4) shows bigger discrepancies for imipramine than clomipramine. As possible causes of the discrepancies, the physical technique used to obtain the CMC (ultrasound velocity, osmotic coefficients, light scattering in the case of literature data) and the method to determine the CMC, by intersection of the fitting straight lines of experimental points above and below the CMC, can be noted. As it has been said, for systems with a slight variation of the physical property with concentration, this method induces to big errors.

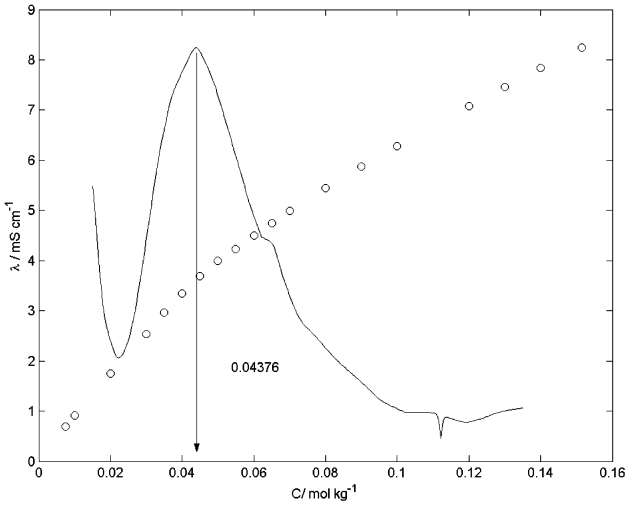


Figure 3. Electrical conductivity of imipramine hydrochloride in water as a function of molal concentration at 288 K. (○) Experimental points. The solid line represents the absolute value of the second derivative obtained with the LPRM method, global bandwidth. The arrow indicates the CMC obtained.

Table 3. CMCs of Imipramine (IMP) and Clomipramine (ClPM) Hydrochlorides at Different Temperatures, Obtained by the LPRM

	CMC/mol·kg^{-1}				
T/K	IMP	ClMP	T/K	IMP	ClMP
283	0.043 09	0.018 64	299	0.044 55	0.021 16
284	0.043 07	0.019 01	300	0.044 46	0.021 19
285	0.043 35	0.019 37	301	0.044 06	0.021 37
286	0.043 70	0.019 33	302	0.044 14	0.024 31
287	0.043 68	0.019 65	303	0.044 08	0.024 37
288	0.043 76	0.020 04	304	0.043 77	0.024 64
289	0.043 66	0.020 45	305	0.043 72	0.024 54
290	0.043 71	0.020 33	306	0.043 57	0.025 29
291	0.043 66	0.020 5	307	0.043 41	0.028 00
292	0.044 39	0.020 45	308	0.043 11	0.028 09
293	0.044 59	0.020 78	309	0.043 09	0.028 04
294	0.044 63	0.020 74	310	0.042 95	0.028 27
295	0.044 62	0.020 82	311	0.042 62	0.028 43
296	0.044 64	0.020 99	312	0.042 11	0.028 41
297	0.044 65	0.020 91	313	0.041 18	0.031 82
298	0.044 42	0.020 98			

Table 4. Values of the CMCs of Imipramine Hydrochloride (IMP) and Clomipramine Hydrochloride (ClMP) from Different Sources

CMC/mol·kg^{-1}				
IMP	ClMP	T/K	method	ref
0.060	0.026	288	ultrasound velocity	4
0.052		293	ultrasound velocity	13
0.049	0.024	293	ultrasound velocity	4
0.051	0.023	298	ultrasound velocity	4
0.054		298	ultrasound velocity	13
0.066	0.024	303	ultrasound velocity	4
0.065		303	ultrasound velocity	13
0.048		303	conductivity	14
0.050		303	light scattering	14
0.042	0.027	303	osmotic coefficient	15
0.094	0.027	308	ultrasound velocity	4, 13
0.056		308	osmotic coefficient	15
0.071		313	osmotic coefficient	15
	0.031	313	ultrasound velocity	4

The variation of the CMC with temperature was a second-order polynomial according to the equation

$$\mathrm{CMC} = a + b(T/\mathrm{K}) + c(T/\mathrm{K})^2 \qquad (8)$$

with coefficients given in Table 5. Agreement with the

Table 5. Coefficients *a*, *b*, and *c* for Fits of Equation 8

CMC/ mol·kg^{-1}	*a*	*b*/K^{-1}	*c*/K^{-2}
IMP	-0.08 ± 0.05	0.0057 ± 0.0003	$-9.7 \times 10^{-6} \pm 5 \times 10^{-7}$
ClMP	1.2 ± 0.2	-0.009 ± 0.001	$1.5 \times 10^{-5} \pm 2 \times 10^{-6}$

values of the *c* coefficient in this variation appears as slightly convex for imipramine and slightly concave for clomipramine. The increase in the CMC is the result of the predominance of the thermal solubility over the hydration effect of the hydrophilic headgroup with increasing temperature.[16] Clomipramine with a Cl atom at position 3 is twice as surface active as the unsubstituted imipramine.[17] Thus, it seems that imipramine micelles are less hydrated than clomipramine micelles and that the substitution is enough to change the CMC temperature behavior.

Literature Cited

(1) Rosen, M. J. *Surfactants and Interfacial Phenomena*; Wiley & Sons: New York, 1989.

(2) López-Fontán, J. L.; Costa, J.; Ruso, J. M.; Prieto, G.; Sarmiento, F. A Nonparametric Approach to Calculate Critical Micelle Concentrations: The Local Polynomial Regression Method. *Eur. Phys. J. E* **2004**, *13*, 133−140.

(3) Attwood, D.; Florence, A. T. *Surfactant Systems, Their Chemistry, Pharmacy and Biology*; Chapman and Hall: New York, 1983.

(4) Attwood, D.; Mosquera, V.; García, M.; Suarez, M. J.; Sarmiento, F. A Comparison of the Micellar Properties of Structurally Related Antidepressant Drugs. *J. Colloid Interface Sci.* **1995**, *175*, 201−206.

(5) Shedlovsky, T. An Equation for Electrolytic Conductance. *J. Am. Chem Soc.* **1932**, *54*, 1405−1411.

(6) Chambers, J. F.; Stokes, J. M.; Stokes, R. H. Conductances of Concentrated Aqueous Sodium and Potassium Chloride Solutions at 25 °C. *J. Phys. Chem.* **1956**, *60*, 985−986.

(7) Smit, B.; Essenlink, K.; Hilbers, P. A. J.; van Os, N. M.; Rupert, L. A. M.; Szleifer, I. Computer Simulations of Surfactants Self-Assembly. *Langmuir* **1993**, *9*, 9−11.

(8) Nadaraya, E. A. On Estimating Regresión. *Theory Probab. Appl.* **1964**, *15*, 141−142.

(9) Watson, G. S. Smooth Regression Analysis. *Sankhya, Ser. A* **1964**, *26*, 359−372.

(10) Fan, J.; Gijbels, I.; Hu, T.-C.; Huang, L.-S. A Study of Variable Bandwidth Selection for Local Polynomial Regression. *Statistica Sinica* **1996**, *6*, 113−127.

(11) Silverman, B. W. *Density Estimation for Statistics and Data Analysis;* Chapman and Hall: New York, 1986.

(12) Phillips, J. N. Energetics of Micelle Formation. *Trans. Faraday Soc.* **1955**, *51*, 561−569.

(13) Attwood, D.; Blundell, R.; Mosquera, V.; García, M.; Rodriguez, J. Apparent Molar Volumes and Adiabatic Compressibilities of Aqueous Solutions of Amphiphilic Drugs. *Colloid Polym. Sci.* **1994**, *272*, 108−114.

(14) Attwood, D.; Gibson, J. Aggregation of Antidepressant Drugs in Aqueous Solution. *J. Pharm. Pharmacol.* **1978**, *30*, 176−180.

(15) Taboada, P.; Attwood, D.; Ruso, J. M.; Suárez, M. J. Sarmiento, F.; Mosquera, V. Concentration Dependence of the Osmotic and Activity Coefficients of Imipramine and Clomipramine Hydrochlorides in Aqueous Solution. *J. Chem. Eng. Data* **1999**, *44*, 820−822.

(16) Islam, Md. N.; Kato, T. Temperature Dependence of the Surface Behavior and Micelle Formation of Some Nonionic Surfactants. *J. Phys. Chem.* **2003**, *107*, 965−971.

(17) Thoma, K.; Albert, K. Colloidal Association of Tri and Tetracyclic Antidepressants and Neurologicals. *Pharm. Acta Helv.* **1979**, *54*, 965−971.

Received for review January 26, 2004. Accepted April 13, 2004. This research was funded in part by Spanish Ministry of Science and Technology (Projects BFM2002-00265 and MAT2002-00608, European FEDER support included) and by Xunta de Galicia (Projects PGIDIT03PXIC10505PN and PGIDIT03PXIC20615PN).

JE049954L