Synthesis and Characterization of Chiral [3,22]-Ionenes

Reinaldo C. Bazito, Fernando L. Cássio, Frank H. Quina*

Summary: Two [3,22]-ionenes with pendent chiral groups, glucopyranosyl-[3,22]-ionene and β-cyclodextrin-[3,22]-ionene, were synthesized by the reaction between the tosyl derivatives of the carbohydrate (methyl alpha-glucopyranoside or beta-cyclodextrin) and the tertiary [3,22]-polyamine obtained by selective demethylation of [3,22]-ionene. The derivatives were characterized by ^{1}H NMR spectroscopy, presenting degrees of substitution of 30 and 45% for the glucosyl and cyclodextrin derivatives, respectively. It was shown by using pyrene as the fluorescent probe, that both polymers form hydrophobic domains, characteristic of micelle-mimetic polysoaps in aqueous solution.

Keywords: chiral; ionene; micelle-mimetic

Introduction

The [n,m]-ionenes are linear cationic polyelectrolytes consisting of dimethylammonium groups connected by aliphatic chain segments (Scheme 1).[1–4]

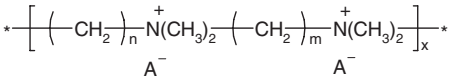
The length (n and m) of the methylene segments of [n,m]-ionenes can be controlled by the proper choice of the reagents used for their synthesis. Ionenes with short methylene segments, such as the [3,10]-ionene, exhibit behavior typical of linear polyelectrolytes, adopting an extended rod-like conformation in aqueous solution.[5] On the other hand, ionenes with at least one methylene segment longer than 14 carbons, present polysoaps or micelle-mimetic behavior, adopting globular conformations and forming hydrophobic microdomains in aqueous solution through intrapolymeric aggregation of the longer methylenic segments of the polymer chain.[4–7] Aqueous solutions of ionenes usually have much higher surface tensions and exhibit much lower foaming than typical surfactant solutions and do not emulsify in the presence of organic solvents.[4–7] In addition, they can be immobilized on solid supports (either electrostatically or covalently).[7] These properties have led to many applications of micelle-mimetic ionenes in analytical chemistry and chromatography.[7–13]

The first chiral ionene reported in the literature was a rod-like [3,6]-ionene with pendent l-menthoxymethyl groups.[14,15] This ionene has been used as a chiral selector in liquid membrane applications.[8] In this work, we describe the first synthesis of chiral micelle-mimetic ionenes containing pendent glucopyranosyl and β-cyclodextrin groups, the 6-O-methyl-α-glucopyranosyl-[3,22]-ionene and the mono-6^A-O-β-cyclodextrin-[3,22]-ionene, respectively. These chiral micelle-mimetic [3,22]-ionenes conjugate the interesting polysoap properties with the presence of chirality, resulting in compounds potentially useful as chiral selectors in analytical separations.[8,9]

Materials and Methods

All solvents and reagents were purified, when necessary, according to usual methods.[16,17] The [3,22]-ionene was

Instituto de Química, USP, C.P. 26077, CEP 05513-970, São Paulo, Brazil
Fax: (+55) 11 3091 2162
E-mail: bazito@iq.usp.br



Scheme 1.
Dimethylammonium groups connected by aliphatic chain segments.

synthesized as described elsewhere.[4,9] The melting points were determined in an Electrothermal IA 6304 melting point apparatus. ^{1}H NMR spectra were obtained in a Varian Innova-300 spectrometer, operating at 299.95 MHz for ^{1}H, at room temperature. Pyrene fluorescence spectra were obtained in a Hitachi F-4500 spectrofluorimeter, using a pyrene concentration of 1 μmol · L^{-1}, excitation at 337, 2.5 mm excitation and emission slits, in 1.00 cm path length quartz fluorescence cuvettes (Hellma).

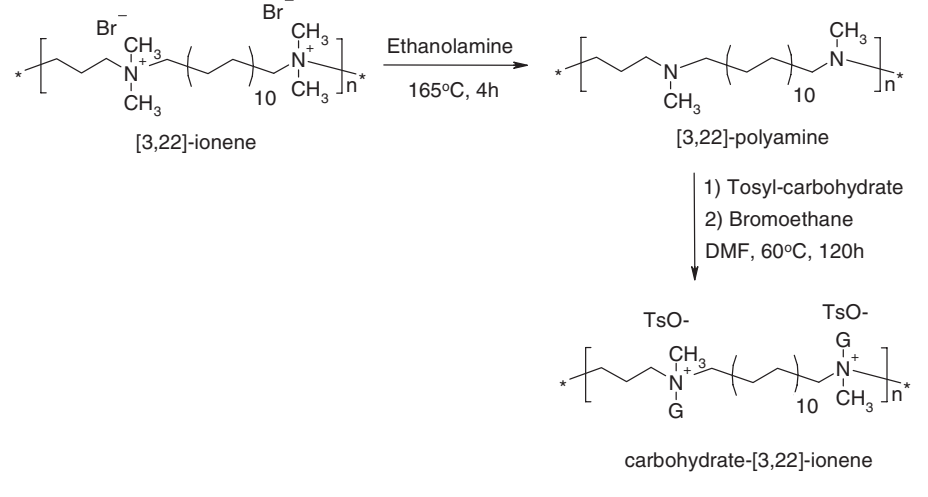
Results and Discussion

Chiral [3,22]-ionenes were obtained in three steps from [3,22]-ionene. These consisted of selective demethylation of the [3,22]-ionene, generating the corresponding tertiary polyamine; the reaction of this amine with the appropriate tosylated carbohydrate and, finally, the quaternization of the remaining tertiary amine groups of the polymer with bromoethane.

The tosylated carbohydrates employed were methyl 6-O-toluenesulfonyl-α-D-glucopyranoside, synthesized in two steps from D-glucose,[18,19] and mono-6-O-toluenesulfonyl-β-cyclodextrin, obtained from β-cyclodextrin in one step.[20]

[3,22]-Polyamine

The tertiary polyamine derived from the [3,22]-ionene, or poly[(methylimine) trimethylene-methylimine-docosane-1,22-diyl], from now on called [3,22]-polyamine, was obtained through the selective monodemethylation of the quaternary dimethylammonium groups of the [3,22]-ionene in ethanolamine.[21] Thus, 5 g of [3,22]-ionene were mixed with 20 mL of ethanolamine in a 100 mL round bottom flask equipped with a reflux condenser and drying tube with $CaCl_2$. The reaction mixture was heated to 165 °C for 4 h, cooled to room temperature and mixed with 80 mL of distilled water. The resulting mixture was extracted thrice with 80 mL of chloroform, the $CHCl_3$ fractions were mixed, dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure, resulting in 3.40 g of [3,22]-polyamine as a waxy yellow solid (97% yield). The polyamine was characterized by its ^{1}H NMR spectrum.



^{1}H NMR ($CDCl_3$): δ (ppm) = 1.25 (36H, N–CH_2–CH_2–($\underline{\mathbf{CH_2}}$)$_{18}$–), 1.44 (4H, N–$CH_2$–$\underline{\mathbf{CH_2}}$–$(CH_2)_{18}$–), 1.65 (2H, N–$CH_2$–$\underline{\mathbf{CH_2}}$–$CH_2$–N), 2.21 (6H, N($\underline{\mathbf{CH_3}}$)), 2.30 (8H, N–$\underline{\mathbf{CH_2}}$).

Glucopyranosyl-[3,22]-ionene

Methyl α-D-glucopyranoside

Methyl α-D-glucopyranoside was prepared from D-glucose, by the reaction with methanol catalyzed by acid (ion-exchange resin), as described in the literature.[18] Thus, 80.0 g of D-glucose (0.444 mol) resulted in 27.2 g (0.140 mol) of methyl α-D-glucopyranoside, MP 167–168 °C (lit. 167–169 °C),[18] with yield of 32%.

Methyl 6-O-tosyl-α-D-glucopyranoside

Synthesized by the direct tosylation of methyl α-D-glucopyranoside, as described elsewhere.[19] Thus, 20.0 g (103 mmol) of methyl α-D-glucopyranoside provided in 17.3 g (49.7 mmol) of methyl 6-O-tosyl-α-D-glucopyranoside, MP 123–125 °C (lit. 124 °C),[19] in 48% yield. Its ^{1}H NMRspectrum (DMSO-d6) showed the following signals (δ in ppm): 2.43 (s, 3H, $\underline{\mathbf{CH_3}}$–$C_6H_4SO_3$), 3.00 (ddd, 1H, $J_{3\text{-OH}} = 5.6$ Hz, $J_{3\text{-}4} = 8.7$ Hz, $J_{2\text{-}3} = 9.8$ Hz, **H-3**), 3.15 (ddd, 1H, $J_{1\text{-}2} = 3.6$ Hz, $J_{2\text{-OH}} = 6.2$ Hz, $J_{2\text{-}3} = 9.8$ Hz, **H-2**); 3.20 (s, 3H, O$\underline{\mathbf{CH_3}}$), 3.33 (ddd, 1H, overlaps with HOD, **H-4**), 3.49 (ddd, 1H, $J_{5\text{-}6'} = 1.4$ Hz, $J_{5\text{-}6''} = 6.4$ Hz, $J_{4\text{-}5} = 8.1$ Hz, **H-5**), 4.06 (dd, 1H, $J_{5\text{-}6''} = 6.4$ Hz, $J_{6'\text{-}6''} = 10.6$ Hz, **H-6″**), 4.22 (dd, 1H, $J_{5\text{-}6'} = 1.7$ Hz, $J_{6'\text{-}6''} = 10.6$ Hz, **H-6′**), 4.48 (d, 1H, $J_{1\text{-}2} = 3.6$ Hz, **H-1**), 4.85 (d, 1H, $J_{2\text{-OH}} = 6.2$ Hz, **OH-2**), 4.95 (d, 1H, $J_{4\text{-OH}} = 4.9$ Hz, **OH-4**), 5.21 (d, 1H, $J_{3\text{-OH}} = 5.6$ Hz, **OH-3**), 7.49 (d, 2H, $J_o = 8.0$ Hz, **H-a**), 7.78 (d, 2H, $J_o = 8.0$ Hz, **H-b**).

Glucopyranosyl-[3,22]-ionene

The glucosylation of [3,22]-ionene was accomplished by the reaction of the [3,22]-polyamine and tosyl-glucoside,[22] followed by the exhaustive quaternization of the remaining tertiary amine groups with bromoethane. Thus, 300 mg of [3,22]-polyamine (1.47 mmol of amine groups), 512 mg (1.47 mmol) of methyl 6-O-tosyl-α-D-glucopyranoside and 20 mL of anhydrous DMF were mixed in a 50 mL round bottom flask equipped with a reflux condenser and drying tube. The mixture was heated at 60 °C for 120 h and cooled to room temperature. 300 mg (2.94 mmol) of bromoethane were added in a single portion and the mixture was stirred at room temperature for another 188 h, under inert atmosphere. The solvent was then removed under reduced pressure. The resulting solid was dissolved in 20 mL of 0.1 mol · L^{-1} NaCl and dialyzed against deionized water for 72 h. The resulting solution was lyophilized, resulting in 321 mg of glucopyranosyl-[3,22]-ionene, characterized by its ^{1}H NMR spectrum (D_2O), δ (ppm): 1.25–1.50 (40H, N–CH_2–($\underline{\mathbf{CH_2}}$)$_{20}$– + N–$CH_2$–$\underline{\mathbf{CH_3}}$), 2.20 (2H, N–$CH_2$–$\underline{\mathbf{CH_2}}$–$CH_2$–N), 2.81 (6H, N($\underline{\mathbf{CH_3}}$)), 3.15 (8H, N–$\underline{\mathbf{CH_2}}$). Besides these signals, those corresponding to the glucosyl portion and to residual toluenesulfonate counterions could also be seen: 3.16 (O$\underline{\mathbf{CH_3}}$); 2.30 ($\underline{\mathbf{CH_3}}$–$C_6H_4SO_3^-$); 3.26 (H2), 3.48 (H4); 3.56 (H5); 4.16 (H6″), 4.24 (H6′); 4.50 (H1), 7.31 e 7.71 (CH_3–$\underline{\mathbf{C_6H_4}}SO_3^-$). The ratio of the integrals of the signals at 2.81 ppm [6H of polyamine N($\underline{\mathbf{CH_3}}$)] and at 3.16 ppm (3H of the glucosyl O$\underline{\mathbf{CH_3}}$) indicated that 30% of the nitrogen atoms of the polymer (or 60% of the repeat units) contain a pendant glucopyranosyl group.

Synthesis of Cyclodextrin-[3,22]-ionene

Mono-6^A-O-tosyl-β-cyclodextrin

The mono-tosyl-cyclodextrin was prepared by the reaction of tosyl-imidazole and cyclodextrin in water, according to the procedure described in the literature.[20] Thus, 40.0 g (35.2mmol) of β-cyclodextrin resulted in 17.2 g of mono-6^A-O-toluenesulfonyl-β-cyclodextrin, in 38% yield. The ^{1}H NMR spectrum of the product (DMSO-d6) showed the following signals (δ in ppm), in agreement with the literature:[20,23] 2.49 (3H, $\underline{\mathbf{CH_3}}$–$C_6H_4SO_3$); 3.20–3.65 (m, 40H, overlaps with HOD); 4.15–4.20 (m, 1H), 4.31–4.35 (m, 2H); 4.51 (s, 3H); 4.78 (s, 2H); 4.84 (s, 4H), 5.62–5.83 (m, 14H), 7.43 (d, 2H, tosyl), 7.75 (d, 2H, tosyl).

β-cyclodextrin-[3,22]-ionene

The compound was synthesized by the reaction between the [3,22]-polyamine and mono-6^{A}-O-toluenesulfonyl-β-cyclodextrin. Thus, 200 mg of [3,22]-polyamine (0.98 mmol of amine groups), 630 mg (0.49 mmol) of mono-6^{A}-O-toluenesulfonyl-β-cyclodextrin and 20 mL of anhydrous DMF were mixed in a 50 mL round bottom flask equipped with a reflux condenser and drying tube. The mixture was heated to 60 °C for 120 h, cooled to room temperature and 200 mg (2.00 mmol) of bromoethane were added in a single portion. The mixture was stirred for another 188 h and the solvent was removed under reduced pressure. The residue was dissolved in 20 mL of 0.1 mol · L^{-1} NaCl and dialyzed against deionized water for 72 h. The resulting solution was lyophilized, producing 210 mg of glucopyranosyl-[3,22]-ionene. The ^{1}H NMR spectrum (D_2O) showed the following signals (δ in ppm): 1.25 (m, 36H, N–CH_2–CH_2–(**CH_2**)$_{18}$– + N–CH_2–**CH_3**), 1.71 (4H, N^{+}–CH_2–**CH_2**–$(CH_2)_{18}$–), 2.20 (2H, N–CH_2–**CH_2**–CH_2–N), 2.97 (6H, N(**CH_3**)), 3.15 (8H, overlaps with cyclodextrin signals, N–**CH_2**). Signals of the cyclodextrin group and of residual toluenesulfonate counterions were also present: 2.47 (**CH_3**–$C_6H_4SO_3^{-}$), 3.10–4.00 (m, 40H, overlaps with N–**CH_2**), 4.10–4.30 (m, 3H), 7.31 e 7.71 (CH_3–**C_6H_4**SO_3^{-}). The ratio of the integrals of the signals at 2.97 ppm (6H of polyamine N(**CH_3**)) and at 4.10–4.20 ppm (3H of cyclodextrin) showed that 45% of the nitrogen atoms of the polymer (90% of the repeat units) contain a pendent cyclodextrin group.

Micelle-Mimetic Properties of the Chiral [3,22]-Ionenes

Pyrene was employed as a fluorescence probe to demonstrate the formation of hydrophobic microdomains in aqueous solutions of the chiral [3,22]-ionenes, because pyrene has a high affinity for hydrophobic domains and is too large to be included into the cavity of β-cyclodextrin.[24] The pyrene fluorescence spectrum

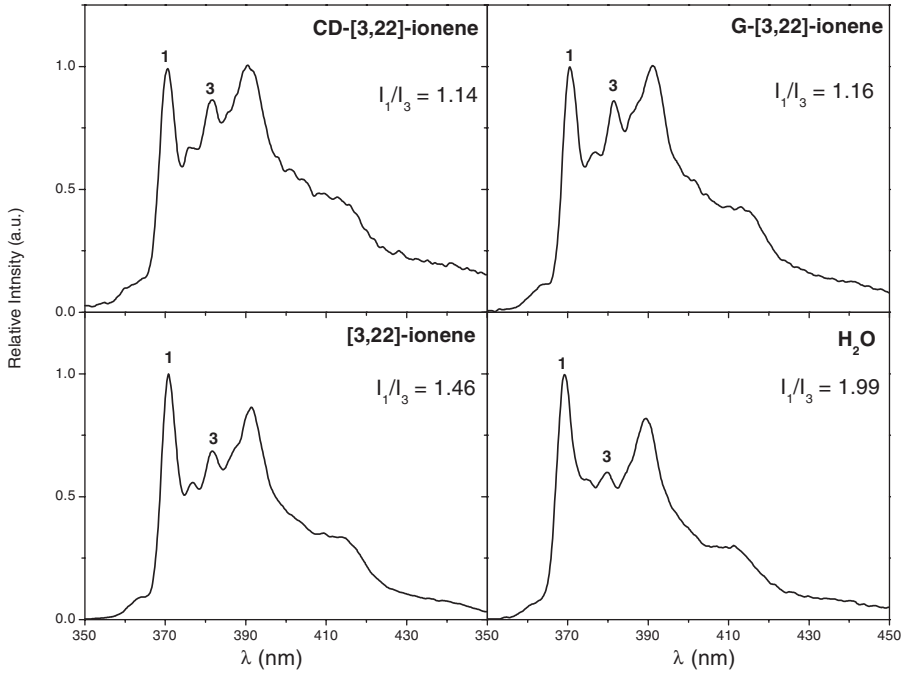


Figure 1.
Pyrene fluorescence spectra in aqueous solutions of the ionenes and in water.

exhibits five major vibronic bands. There is an intensification of band I relative to band III in polar solvents due to the reduction of the local symmetry of pyrene.[25] The ratio of the intensities of bands I and III (I_1/I_3) is, therefore, an empirical measure of the polarity of the solubilization site of pyrene.[25]

Pyrene fluorescence spectra in aqueous solutions of cyclodextrin-[3,22]-ionene (CD-[3,22]-ionene), glucopyranosyl-[3,22]-ionene (G-[3,22]-ionene), [3,22]-ionene and in water are shown in Figure 1. The values of I_1/I_3 obtained for pyrene in a series of pure solvents and in aqueous solutions of the [3,22]-ionenes are collected in Table 1.

Ionene polysoaps with pendent glucose and cyclodextrin groups show micelle-mimetic behavior in aqueous solutions, as indicated by the fact that pyrene solubilized in these solutions senses a more hydrophobic environment than water (polarity similar to 1-propanol). This polarity is similar to that observed for pyrene in aqueous solutions of anionic surfactants such as sodium dodecyl sulfate ($I_1/I_3 = 1.15$)[25] and of methyl 2-hexadecanoylamide-2-deoxy-6-trimethylammonium-D-glucopyranoside chloride ($I_1/I_3 = 1.13$)[26] and similar sugar-derived surfactants.[27]

Table 1.
I_1/I_3 for pyrene in various pure solvents and aqueous solutions of [3,22]-ionenes.

Solvent	I_1/I_3
Water	1.99
Ethylene glycol	1.67
Methanol	1.46
Ethanol	1.32
1-Propanol	1.14
1-Octanol	0.93
1-Decanol	0.86
1-Dodecanol	0.87
Dodecane	0.60
[3,22]-Ionene (1 g · L^{-1})	1.46
G-[3,22]-Ionene[a)]	
0.5 g · L^{-1}	1.21
1 g · L^{-1}	1.16
CD-[3,22]-ionene[b)]	
0.5 g · L^{-1}	1.22
1 g · L^{-1}	1.14

[a)] G-[3,22]-ionene: glucopyranosyl-[3,22]-ionene.
[b)] CD-[3,22]-ionene: β-cyclodextrin-[3,22]-ionene.

Interestingly, there is practically no difference between the polarity of the microdomains of the cyclodextrin and the glucose-derivatized ionenes and both are more hydrophobic than the parent [3,22]-ionene. Presumably the large size and hydration of the carbohydrate moiety imparts a certain steric rigidity to the global conformation of the chiral polysoap molecule, reducing water penetration in the hydrophobic domains.

Conclusion

Methyl α-glucopyranoside-[3,22]-ionene (35% of the amino groups quaternized with glucosyl groups) and β-cyclodextrin-[3,22]-ionene (45% of the amino groups quaternized with β-cyclodextrin groups) were synthesized in good yields and characterized. These polymers behave as polysoaps in aqueous solutions, forming hydrophobic domains that are less polar than those of the parent [3,22]-ionene. Preliminary studies of the application of these polymers as chiral selectors are currently underway.

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[1] H. Noguchi, A. Rembaum, *Macromolecules* **1972**, *5*, 253.
[2] A. Rembaum, W. Baumgart, A. Eisenber, *J. Polym. Sci., Part C: Polym. Lett.* **1968**, *6*, 159.
[3] A. Rembaum, H. Noguchi, *Macromolecules* **1972**, *5*, 261.
[4] V. Soldi, N. D. Erismann, F. H. Quina, *J. Am. Chem. Soc.* **1988**, *110*, 5137.
[5] V. E. R. Nieves, E. J. Ribaldo, R. Baroud, F. H. Quina, *J. Polym. Sci., Part C: Polym. Lett.* **1982**, *20*, 433.
[6] P. Balbuena, E. Campanella, L. Gribaudo, *Fluid Phase Equilib.* **1991**, *62*, 225.
[7] Y. Suzuki, F. H. Quina, A. Berthod, R. W. Williams, Jr., M. Culha, I. U. Mohammadzai, W. L. Hinze, *Anal. Chem.* **2001**, *73*, 1754.
[8] W. L. Hinze, R. W. Williams, Jr., Z. Fu, Y. Suzuki, F. H. Quina, *Colloids Surf.* **1990**, *48*, 79.
[9] W. L. Hinze, B. Moreno, F. H. Quina, Y. Suzuki, H. Wang, *Anal. Chem.* **1994**, *66*, 3449.
[10] W. L. Hinze, L.-W. Feng, B. Moreno, F. H. Quina, Y. Suzuki, H. Wang, *Anal. Sci.* **1995**, *11*, 183.

[11] A. V. Pirogov, W. Buchberger, *J. Chromatogr. A* **2001**, *916*, 51.
[12] A. V. Pirogov, O. V. Krokhin, M. M. Platonov, Y. I. Deryugina, O. A. Shpigun, *J. Chromatogr. A* **2000**, *884*, 31.
[13] A. V. Pirogov, M. M. Platonov, O. A. Shpigun, *J. Chromatogr. A* **1999**, *850*, 53.
[14] Y. Suzuki, S. Tazuke, *J. Polym. Sci., Polym. Lett. Ed.* **1982**, *20*, 259.
[15] Y. Suzuki, S. Tazuke, *Makromol. Chem.* **1984**, *185*, 521.
[16] D. D. Perrin, W. L. F. Armarego, "*Purification of Laboratory Chemicals*", 3rd edition, Pergamon Press, Oxford 1988.
[17] M. Casey, J. Leonard, B. Lygo, G. Procter, "*Advanced Practical Organic Chemistry*", 1st edition, Blackie, London 1990.
[18] G. N. Bollenback, in: "*Methods in Carbohydrate Chemistry*", R. L. Whistler, M. L. Wolfrom, Eds., Academic Press, New York **1963**, p. 326.
[19] F. D. Cramer, in: "*Methods in Carbohydrate Chemistry*", R. L. Whistler, M. L. Wolfrom, Eds., Academic Press, New York **1963**, p. 244.
[20] H.-S. Byun, N. Zhong, R. Bittman, *Org. Synth.* **2000**, *77*, 225.
[21] H. Hagi, O. Ooishi, R. Tanaka, in: "*Polymeric Amines and Ammonium Salts*", E. J. Goethals, Ed., Pergamon Press, Oxford **1980**, p. 31.
[22] R. C. Bazito, O. A. El Seoud, *J. Surfact. Deterg.* **2001**, *4*, 395.
[23] R. C. Petter, J. S. Salek, C. T. Sikorski, G. Kumaravel, F. T. Lin, *J. Am. Chem. Soc.* **1990**, *112*, 3860.
[24] T. C. Werner, K. J. Forrestall, S. L. Mcintosh, J. Pitha, *Appl. Spectroscop.* **2000**, *54*, 560.
[25] K. Kalyanasundaram, J. K. Thomas, *J. Amer. Chem. Soc.* **1977**, *99*, 2039.
[26] R. C. Bazito, Ph.D. thesis, Instituto de Química—USP **2001**.
[27] R. C. Bazito, O. A. El Seoud, *Langmuir* **2002**, *18*, 4362.

