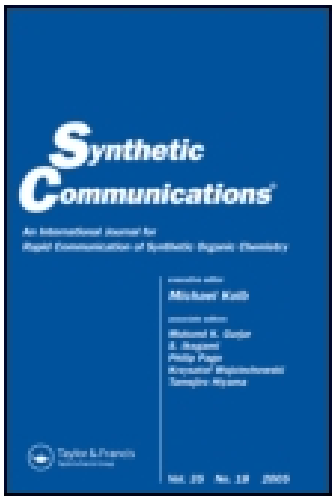


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

SYNTHESIS OF NEW CATIONICS, CARBOXYBETAINES, AND SULFOBETAINES BOLAAMPHIPHILES

Souad Souirti [a] & Michel Baboulè [b]

[a] Université Ibn Tofail , Laboratoire de Synthèse Organique et Réactivité, BP 133, Kenitra, Maroc, 14000

[b] Université Paul Sabatier , Laboratoire des Interactions Moléculaires et Réactivités Chimique et Photochimique (CNRS, UMR 5623), 118 route de Narbonne, Toulouse Cédex, 31062, France

Published online: 09 Nov 2006.

To cite this article: Souad Souirti & Michel Baboulè (2001) SYNTHESIS OF NEW CATIONICS, CARBOXYBETAINES, AND SULFOBETAINES BOLAAMPHIPHILES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:1, 9-18, DOI: 10.1081/SCC-100000173

To link to this article: http://dx.doi.org/10.1081/SCC-100000173

SYNTHETIC COMMUNICATIONS, 31(1), 9–18 (2001)

SYNTHESIS OF NEW CATIONICS, CARBOXYBETAINES, AND SULFOBETAINES BOLAAMPHIPHILES

Souad Souirti[1] and Michel Baboulène[2,*]

[1]Laboratoire de Synthèse Organique et Réactivité,
Université Ibn Tofail, BP 133, 14000 Kénitra, Maroc
[2]Laboratoire des Interactions Moléculaires et Réactivités
Chimique et Photochimique (CNRS, UMR 5623),
Université Paul Sabatier, 118 route de Narbonne,
31062 Toulouse Cédex, France

ABSTRACT

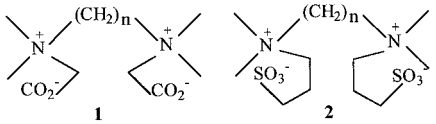
A new family of bolaform compounds with carboxybetaine or sulfobetaine heads was synthesized in excellent yield from a common intermediate: α,ω-bis-(N,N-dimethylamino)-alkane. Dicationic bolaforms bearing esters groups also were isolated.

There has been considerable interest in recent years in the synthesis and physico-chemical properties of bolaamphiphile compounds (1). This class of surfactants, characterized by the presence of two hydrophilic heads linked by a long hydrophobic chain, can now be prepared by "modular" synthesis. These compounds are of value for construction of model biological membranes and have applications in pharmacology (2–4) and chemical catalysis (5,6).

*To whom correspondence should be addressed. Fax: +33 5 61 25 17 33; E-mail: mbab@ramses.ups-tlse.fr

The diionic bolaforms (anionic and/or cationic) have been the first to exhibit self-association and now have industrial applications (7–10). These novel compounds have also been prepared with sugar (11) and non-ionic heads (12).

To our knowledge there are no reports on betaine bolaforms, although monozwitterionic amphiphiles have formed the subject of numerous studies and applications (13–15). Despite the presence of an electrically charged polar head, these surfactants are electrically neutral, which makes them compatible with biological systems and confers applications in biochemistry and cosmetology. As betaine bolaforms have interest from synthetic, fundamental and applied points of view, we describe here the synthesis of novel bolaforms **1** and **2** with carboxybetaine or sulfobetaine heads.



1 **2**

n = 8, 12

SYNTHESIS

Results and Discussion

Route to Carboxybetaine Bolaforms **1**

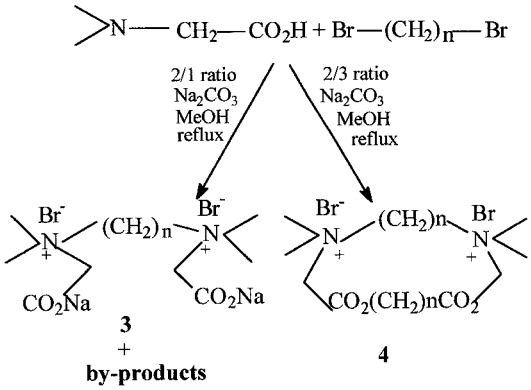
By analogy with previous methods of synthesis of monobetaine amphiphiles, two routes were selected. The first was a direct condensation of a long chain dihaloalkane with dimethyl glycine (Scheme 1).

After a number of attempts using different reaction conditions, we failed to obtain complete diquarternization of the nitrogen atoms. Various by-products were formed, hindering recovery of the major compounds **3**. It should be noted that the compounds **3** had a correct elemental analysis, provided they were associated with two equivalents of sodium bromide. Our attempts at separation were unsuccessful; the stoichiometry of compound **3**: NaBr was consistent at 1:2.

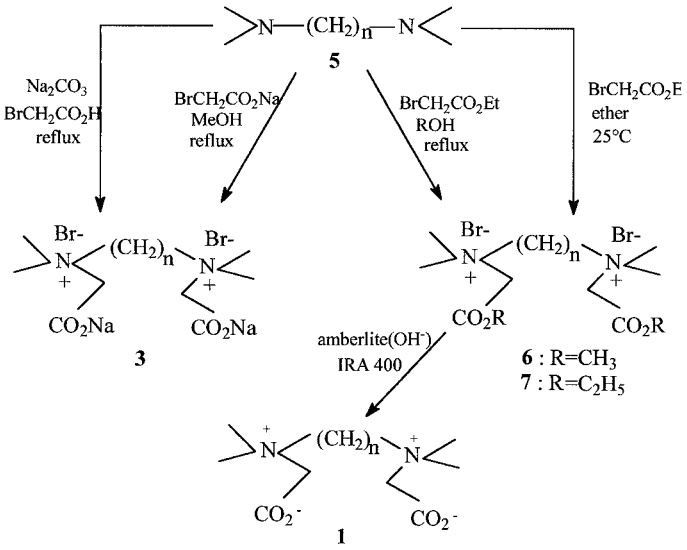
On the other hand, excellent yields of the novel bicatenary cationic bolaforms **4** were obtained (Scheme 1) by heating with an excess of the dihalogenated derivatives. Their properties are currently under investigation.

To avoid these difficulties, a two-stage process was studied starting from dimethylamine via α,ω bis-(N,N-dimethylamino) alkane **5** (Scheme 2).

We obtained an almost quantitative quaternization of the two nitrogen atoms of the diamine **5** by bromoacetic acid in basic medium. The compounds isolated were identical to the compounds **3** prepared by the first method described above.



Scheme 1. Synthetic Route to Compounds **3**.



Scheme 2. Synthetic Route to Compounds **1**, **3**, **6**, and **7**.

For synthesis of amphiphilic monocarboxybetaines, the presence of a sodium salt in various stoichiometries ranging from 1 to 2.5 equivalents/mole has been reported as a difficulty (16–21). A reaction in neutral medium can be obtained by the use of ethyl bromoacetate as alkylating agent. In ether in the cold, diquaternization was total for one hour reaction. By to warm to reflux, we observed a transesterification process. The novel dicationic bolaforms **6** and **7** were readily isolated in good yield (Table 1).

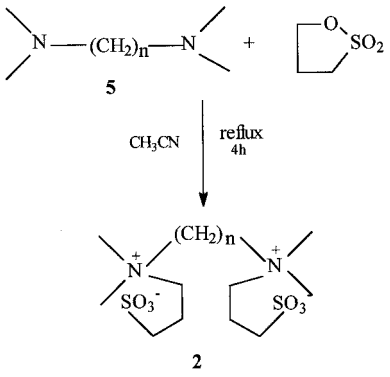
Table 1. Yields and Melting Points for Compounds Prepared

Products	**1a**	**1b**	**2a**	**2b**	**3a**	**3b**	**6a**	**6b**	**7a**	**7b**
n	8	12	8	12	8	12	8	12	8	12
yield (%)	95	92	95	95	94	88	98	98	98	98
mp (°C)	260	180	210	215	220	170	180	140	197	145

They were employed as intermediates to afford the carboxybetaine bolaforms **1** in quantitative yield. Simple reaction in alcoholic medium in the presence of a strongly basic ion exchange resin produced the carboxybetaine structure directly (20) devoid of sodium salt. Table 1 lists details of the two series of bolaforms (n = 8 or 12) prepared by this method.

Route to the Sulfobetaine Bolaforms **2**

We employed a procedure based on that of Fendler et al. (22) for the synthesis of amphiphilic monosulfobetaines. The diamine **5** prepared as described above was the main reactant (Scheme 3). The disulfobetaines **2** were obtained in quantitative yield on heating the reaction mixture (Table 1). However, we noted that in the cold and even with excess sultone, only the monosulfobetaine was obtained in quantitative yield. The disulfobetaine **2** was obtained by heating the mixture with a further equivalent of sultone. Apart from their interest as surfactants, these compounds offer a convenient route to novel disymmetric bolaforms, which are under investigation in our laboratory. The recent report of Spencer et al. (23) on the synthesis of N,N′-bis(trimethylammonium-1)-4-butylsulfonyl dodecane (yield around 18%), which has inhibitory activity towards squalene synthetase, indicates the potential biological applications of betaine bolaforms.



Scheme 3. Synthetic Route to Compounds **2**.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

CONCLUSION

We describe here the synthesis of novel betaine bolaform derivatives. Series of carboxybetaine, sulfobetaine, and cationic bolaforms were prepared in excellent yield using the synthon α,ω-bis-(N,N-dimethylamino) alkane. The process is easy and could be scaled up for industrial applications. The method permits access to a wide range of bolaform derivatives, opening new fields of investigation of both fundamental and applied interest.

EXPERIMENTAL

General

Commercial quality reagents were used without purification. Melting points (uncorrected) were obtained on a Kofler Prolabo apparatus. IR spectra (ν, cm^{-1}) were recorded on a Perkin-Elmer 683 spectrophotometer. ^1H and ^{13}C NMR spectra (δ, ppm, TMS as internal reference) were obtained on Bruker AC 80 or Bruker AC 200 instruments.

Typical Procedure for the Synthesis of Compounds 5

A solution of dimethylamine (33% of ethanol) (3 10^{-2} mol) and dibromoalkane (10^{-2} mol) was added to sodium carbonate (2 10^{-2} mol) in 60 ml of ethanol and 15 ml of water. The reaction mixture was stirred at reflux for 24 h. Then the resulting compound was isolated by filtration and evaporating of the solvent under reduced pressure. The crude product, washed with 10 ml of water, was extracted with EtO_2. The organic phase was dried on anhydrous Na_2SO_4 and evaporated in vacuo. The crude oil was purified by distillation.

1,8-bis(N,N-dimethylamino)octane, **5a**

Yield: 98%. Colourless oil, bp = 40°C/0.02 Torr. ^1H NMR (200 MHz, $CDCl_3$): δ 1.1 (m, 12H, $(CH_2)_6$), 1.9 (m, 16H, NCH_2, NCH_3); ^{13}C NMR (200 MHz, $CDCl_3$): δ 27.23–28.3 ($(CH_2)_6$), 45.20 (NCH_3), 59.66 (NCH_2). Anal calcd. (%) for $C_{12}H_{28}N_2$ (200.37), C: 71.93; H: 14.09; N: 13.97; found, C: 71.66; H: 14.15; N: 14.13.

1,12-bis(N,N-dimethylamino)dodecane, **5b**

Yield: 98%. Colourless oil, bp = 80–82°C/0.05 Torr. ^1H NMR (200 MHz, $CDCl_3$): δ 1.1 (m, 20H, $(CH_2)_{10}$), 2.05 (m, 16H, NCH_2, NCH_3); ^{13}C NMR

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

(200 MHz, $CDCl_3$): δ 27.43–28.53 ($(CH_2)_{10}$), 45.42 (NCH_3), 59.87 (NCH_2). Anal calcd. (%) for $C_{16}H_{36}N_2$ (256.47), C: 74.86; H: 14.03; N: 10.92; found, C: 74.73; H: 13.90; N: 10.62.

Typical Procedure for the Synthesis of Compounds 3

Bromoacetic acid (2.2 10^{-2} mol) was added to a mixture of α,ω-bis(N,N-dimethylamino)-alkane **5** (10^{-2} mol) in MeOH (50 ml) and Na_2CO_3 (2 10^{-2} mol). The reaction mixture was stirred at reflux for 24 h. The mineral compounds were separated by filtration. The solvent was evaporated in vacuo. The white product was collected, washed successively with acetone and ether, and dried in vacuo.

1,8-bis(N,N-dimethyl, N-sodium acetate ammonium bromide)octane, **3a**

Yield: 94%. White powder, mp = 220°C. IR (KBr): ν 1480 ($C{-}N^+$), 1750 (C=O), 1610 (CO_2^-). ^{1}H NMR (80 MHz, D_2O): δ 1.2 (m, 12H, $(CH_2)_6$), 3.1 (m, 12H, NCH_3), 3.4 (t, 4H, NCH_2), 3.7 (s, 4H, CH_2CO_2); ^{13}C NMR (200 MHz, D_2O): δ 24.53–30.34 (6C, $(CH_2)_6$), 53.81 (NCH_3), 66.14 (NCH_2), 67.21 (CH_2CO_2), 171.95 (CO_2). Anal calcd. (%) for $C_{16}H_{32}N_2O_4Na_2Br_2$ (522.23), C: 36.78; H: 6.13; N: 5.36; found, C: 36.20; H: 6.61; N: 4.99.

1,12-bis(N,N-dimethyl, N-sodium acetate ammonium bromide)dodecane, **3b**

Yield: 88%. White powder, mp = 170°C. IR (KBr): ν 1480 ($C{-}N^+$), 1750 (C=O), 1610 (CO_2^-). ^{1}H NMR (200 MHz, D_2O): δ 1.2 (m, 16H, $(CH_2)_8$), 1.6 (m, 4H, $N{-}C{-}CH_2$), 3.14 (m, 12H, NCH_3), 3.4 (t, 4H, NCH_2), 3.7 (s, 4H, CH_2CO_2); ^{13}C NMR (200 MHz, D_2O): δ 24.5–31 ($(CH_2)_{10}$), 53.6 (NCH_3), 66 (NCH_2), 67.2 (CH_2CO_2), 171.8 (CO_2). Anal calcd. (%) for $C_{20}H_{40}N_2O_4Na_2Br_2$ (578.34), C: 41.52; H: 6.92; N: 4.84; found, C: 41.13; H: 7.09; N: 4.81.

Typical Procedure for the Synthesis of Compounds 7 and 6

A mixture of diamine **5** (10^{-2} mol) and ethyl bromoacetate (2.3 10^{-2} mol) in ether (40 ml) was stirred for 1 h at room temperature (route a), or in alcohol heated at reflux under agitation for 6 h (route b). The solvent was evaporated in

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

vacuo. The residual oil was triturated from ether. The crude solid was purified by crystallisation from methanol-ether: (1–9).

1,8-bis(N,N-dimethyl, N-ethyl acetate ammonium bromide)octane, **7a**

Yield: 98%. White powder, mp = 196–198°C. IR (KBr): ν 1500–1400 ($C–N^+$), 1750 (C=O), 1250 (CO_2Et). ^{1}HNMR (80 MHz, D_2O): δ 1.2 (m, 18H, $(CH_2)_6$, CH_3-C), 3.2 (m, 16H NCH_2, NCH_3), 4.3 (m, 8H, $\underline{CH_2}$-CH_3, $CH_2CO_2^-$); ^{13}C NMR (200 MHz, D_2O): δ 15.7 (CH_3-C), 24–30 ($(CH_2)_6$), 54 (NCH_3), 63.8 (NCH_2), 66 (OCH_2), 68.3 (CH_2CO_2), 167.8 (CO_2). Anal calcd. (%) for $C_{20}H_{42}N_2O_4Br_2$ (534.37), C: 44.95; H: 7.92; N: 5.24; found, C: 44.36; H: 7.94; N: 5.09.

1,12-bis(N,N-dimethyl, N-ethyl acetate ammonium bromide)dodecane, **7b**

Yield: 98%. White powder, mp = 145°C. IR (KBr): ν 1500–1400 ($C–N^+$), 1750 (C=O), 1235 (CO_2Et). ^{1}H NMR (80 MHz, D_2O): δ 1.2 (m, 26H, $(CH_2)_{10}$, CH_3-C), 3.2 (m, 16H, NCH_2, NCH_3), 4.3 (m, 8H, $\underline{CH_2}$-CH_3, $CH_2CO_2^-$); ^{13}C NMR (200 MHz, D_2O): δ 15.9 (CH_3-C), 24.7–31.37 ($(CH_2)_{10}$), 54.60 (NCH_3), 63.8 (NCH_2), 66 (OCH_2), 68.2 (CH_2CO_2), 167.8 (CO_2). Anal calcd. (%) for $C_{24}H_{50}N_2O_4Br_2$ (590.48), C: 48.77; H: 8.46; N: 4.75; found, C: 48.98; H: 8.12; N: 4.53.

1,8-bis(N,N-dimethyl, N-methyl acetate ammonium bromide)octane, **6a**

Yield: 98%. White powder, mp = 180°C. IR (KBr): ν 1500–1400 ($C–N^+$), 1750 (C=O), 1240 (CO_2CH_3). ^{1}H NMR (200 MHz, D_2O): δ 1.3 (m, 8H, $(CH_2)_4$), 1.7 (qt, 4H, N–C–CH_2), 3.2 (m, 12H, NCH_3), 3.5 (t, 4H, NCH_2), 3.6 (s, 6H, OCH_3), 4.2 (s, 4H, CH_2CO_2); ^{13}C NMR (200 MHz, D_2O): δ 24.5–30.3 ($(CH_2)_6$), 54.2 (NCH_3), 55.9 (OCH_3), 63.7 (NCH_2), 66.4 (CH_2CO_2), 68.2 (CH_2CO_2), 168.3 (CO_2). Anal calcd. (%) for $C_{18}H_{38}N_2O_4Br_2$ (506.32), C: 42.7; H: 7.56; N: 5.53; found, C: 42.59; H: 7.86; N: 4.98.

1,12-bis(N,N-dimethyl, N-methyl acetate ammonium bromide)dodecane, **6b**

Yield: 98%. White powder, mp = 140°C. IR (KBr): ν 1500–1400 ($C–N^+$), 1750 (C=O), 1255 (CO_2CH_3). ^{1}H NMR (200 MHz, D_2O): δ 1.2 (m, 16H, $(CH_2)_8$),

1.7 (qt, 4H, N–C–CH_2), 3.1 (m, 12H, NCH_3), 3.4 (t, 4H, NCH_2), 3.7 (s, 6H, OCH_3), 4.2 (s, 4H, CH_2CO_2); ^{13}C NMR (200 MHz, D_2O): δ 24.4–31.1 ($(CH_2)_{10}$), 54.2 (NCH_3), 55.8 (OCH_3), 63.6 (NCH_2), 68.4 (CH_2CO_2), 168.3 (CO_2). Anal calcd. (%) for $C_{22}H_{46}N_2O_4Br_2$ (562.43), C: 46.98; H: 8.42; N: 4.98; found, C: 46.34; H: 8.09; N: 4.72.

Typical Procedure for the Synthesis of Compounds 1

A mixture of compound **6** or **7** (10^{-2} mol) and 25 g of anion-exchange resin (OH^-) (IRA 400) was stirred for 3 h at room temperature. Then the mixture was filtered and evaporated in vacuo. The residual oil was triturated from ether and crystallised from ether-methanol: (9–1).

1,8-bis(N,N-dimethyl, carboxybetaine)octane, **1a**

Yield: 95%. White powder, mp = 260°C. IR (KBr): ν 1480 (C-N^+), 1750 (C=O), 1610 (CO_2). ^{1}H NMR (80 MHz, D_2O): δ 1.26 (m, 12H, $(CH_2)_6$), 3.09 (m, 12H, NCH_3), 3.4 (t, 4H, NCH_2), 3.7 (s, 4H, CH_2CO_2); ^{13}C NMR (200 MHz, D_2O): δ 24.51–30.33 ($(CH_2)_6$), 53.8 (NCH_3), 66.14 (NCH_2), 67.14 (CH_2CO_2), 171.82 (CO_2). Anal calcd. (%) for $C_{16}H_{32}N_2O_4$ (316.44), C: 60.73; H: 10.19; N: 8.85; found, C: 60.90; H: 10.22; N: 8.63.

1,12-bis(N,N-dimethyl, carboxybetaine)dodecane, **1b**

Yield: 92%. White powder, mp = 180°C. IR (KBr): ν 1480 (C–N^+), 1750 (C=O), 1610 (CO_2). ^{1}H NMR (80 MHz, D_2O): δ 1.19 (m, 20H, $(CH_2)_{10}$), 3.06 (m, 12H, NCH_3), 3.4 (t, 4H, NCH_2), 3.7 (s, 4H, CH_2CO_2); ^{13}C NMR (200 MHz, D_2O): δ 24.57–31 ($(CH_2)_{10}$), 53.7 (NCH_3), 66.12 (NCH_2), 67.25 (CH_2CO_2), 171.8 (CO_2). Anal calcd. (%) for $C_{20}H_{40}N_2O_4$ (372.55), C: 64.48; H: 10.82; N: 7.52; found, C: 63.97; H: 10.94; N: 6.97.

Typical Procedure for the Synthesis of Compounds 2

Compounds **2** were prepared by the addition of diamine **5** (10^{-2} mol) to 1.3 propane sultone (2.2 10^{-2} mol) in 100 ml of anhydrous acetonitrile. The solution was stirred at reflux for 4 h, then cooled and filtered. After crystallisation from methanol-acetone (1–9), pure compounds **2** were obtained as solid which decomposed during melting point determination.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

1,8-bis(N,N-dimethyl, 1–3 propanesulfobetaine)octane, **2a**

Yield: 95%. White powder, mp = 210°C. IR (KBr): ν 1480 (C-N^+), 1040 (S=O). ^{1}H NMR (200 MHz, D_2O): δ 1.2 (m, 12H, $(CH_2)_6$), 1.9 (qt, 4H, CH_2-C-SO_3), 2.9 (t, 4H, CH_2SO_3), 3.02 (s, 12H, NCH_3), 3.24 (t, 4H, CH_2N), 3.38 (t, 4H, CH_2N); ^{13}C NMR (200 MHz, D_2O): δ 20.69–31.06 ($(CH_2)_6$), 49.82 (CH_2-C-SO_3), 53.12 (NCH_3), 64.4 (NCH_2), 66.7 (CH_2SO_3). Anal calcd. (%) for $C_{18}H_{40}N_2S_2O_6$ (444.64), C: 48.62; H: 9.07; N: 6.30, S: 14.42; found, C: 48.96; H: 9.30; N: 5.94; S: 13.97.

1,12-bis(N,N-dimethyl, 1–3 propanesulfobetaine)dodecane, **2b**

Yield: 95%. White powder, mp = 215°C. IR (KBr): ν 1480 (C-N^+), 1040 (S=O). ^{1}H NMR (200 MHz, D_2O): δ 1.2 (m, 20H, $(CH_2)_{10}$), 2.2 (qt, 4H, CH_2-C-SO_3), 2.6 (t, 4H, CH_2SO_3), 3.03 (s, 12H, NCH_3), 3.18 (t, 4H, CH_2N), 3.3 (t, 4H, CH_2N); ^{13}C NMR (200 MHz, D_2O): δ 20.7–31.09 ($(CH_2)_{10}$), 49.8 (CH_2-C-SO_3), 53.14 (NCH_3), 64.4 (NCH_2), 66.8 (CH_2SO_3). Anal calcd. (%) for $C_{22}H_{48}N_2S_2O_6$ (500.75), C: 52.77; H: 9.66; N: 5.29, S: 12.8; found, C: 52.13; H: 9.42; N: 5.39; S: 12.23.

REFERENCES

1. Fuhrhop, J.H.; Bach, R. *Advances in Supramolecular Chemistry*, Gokel, G.W., Ed.; JAI Press, Inc.: Greenwich, CT, 1992, Vol. 2, 25.
2. Jayasuriya, N.; Bosak, S.; Regen, S.L. J. Am. Chem. Soc. **1990**, *112*, 5851.
3. Amato, I. Science **1993**, *260*, 491.
4. Fylest, T.M.; Zeng, B. Chem. Commun. **1996**, 2295.
5. Bunton, C.A.; Dorwin, E.L.; Savelli, G.; Si, V.C. Recl. Trav. Chim. Pays-Bas **1990**, *109*, 64.
6. Scrimin, P.; Tecilla, P.; Tomellato, U. J. Am. Chem. Soc. **1992**, *134*, 5086.
7. Ikeda, K.; Esumi, K.; Meguro, K. Colloïd and Interf. Science **1989**, *130*, 290.
8. Yasuda, M.; Ikeda, K.; Esumi, K.; Meguro, K. Langmuir **1990**, *6*, 949.
9. Fuhrhop, J.H.; David, H.H.; Mathieu, J.; Liman, U.; Winter, H.J.; Boehema, E. J. Am. Chem. Soc. **1986**, *108*, 1785.
10. Fuhrhop, H.; Spiroski, D.; Bettcher, C. J. Am. Chem. Soc. **1993**, *115*, 1600.
11. Brisset, F.; Garelli-Calvet, R.; Azema, J.; Chebli, C.; Rico-Lattes, I.; Lattes, A. New. J. Chem. **1996**, *20*, 595 and references cited therein.
12. Mansur, C.R.E.; Spinelli, L.S.; Lucas, E.F.; Gonzalez, G. Colloïd Surface A. **1999**, *149* (1–3), 291.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

13. Bluestein, B.R.; Hilton, C.L, Eds. *Amphoteric Surfactant*, Surface Sciences Series n°12, Marcel Dekker, Inc.: New York, 1982.
14. Chevalier, Y.; Kamenka, N.; Chorro, M.; Zana, R. Langmuir **1996**, *12*, 3225.
15. Laughlin, R.G.; U.S. Patent, 4.287.174 **1981**.
16. Beckett, A.H.; Woodward, R.J. J. Pharm. Pharmacol. **1963**, *15*, 422.
17. Molineux, P.; Rhodes, C.T.; Swrbrik, J. Trans. Faraday. Soc. **1965**, *61*, 1043.
18. McGrady J.; Laughlin, R.C. Synthesis **1984**, 426.
19. Chevalier, Y.; Brunel, S.; Le Perchec, P. J. Chim. Phys. **1995**, *92* (5), 1025.
20. Chevalier, Y.; Storet, Y.; Pourchet, S.; Le Perchec, P. Langmuir **1991**, *7*, 848.
21. Laughlin, R.G. Langmuir **1991**, *7*, 842.
22. Fendler, E.J.; Day, C.L.; Fendler, J.H. J. Phys. Chem. **1972**, *76*, 1460.
23. Spencer, T.A.; Onofrey, T.J.; Cann, R.O.; Russel, J.S.; Lee, L.E.; Blanchard, D.E.; Castro, A.; Gu, P.; Jiang, G.; Shechter, I. J. Org. Chem. **1998**, *64*, 807.