Pergamon

Tetrahedron Letters 41 (2000) 9119–9123

TETRAHEDRON LETTERS

Synthesis and monolayer behavior of amphiphilic per(2,3-di-*O*-alkyl)-α- and β-cyclodextrins and hexakis(6-deoxy-6-thio-2,3-di-*O*-pentyl)-α-cyclodextrin at an air–water interface

Monika Wazynska,[a] Andrzej Temeriusz,[a,*] Kazimierz Chmurski,[b] Renata Bilewicz[a] and Janusz Jurczak[a,b]

[a]*Department of Chemistry, Warsaw University, Pasteura 1, 02-093 Warsaw, Poland*
[b]*Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland*

Received 26 July 2000; revised 15 September 2000; accepted 20 September 2000

Abstract

A synthesis of amphiphilic per(2,3-di-*O*-alkyl)-α- and β-cyclodextrins and hexakis(6-deoxy-6-thio-2,3-di-*O*-pentyl)-α-cyclodextrin and their monolayer behavior on a water surface is presented. Long alkyl chains were introduced by a treatment of the per(6-*O*-*tert*-butyldimethylsilyl) derivatives with an appropriate alkyl iodide in dimethylformamide in the presence of sodium hydride. A standard desilylation procedure followed by an iodination reaction afforded per(6-deoxy-6-iodo) analogues. In the latter reaction step, sulphur containing groups were introduced by nucleophilic substitution of the iodine with benzothiolate ion in dimethylformamide. The hexakis(6-deoxy-6-*S*-benzyl-2,3-di-*O*-pentyl)-α-cyclodextrin was transformed into extremely interesting hexakis(6-deoxy-6-thio-2,3-di-*O*-pentyl)-α-cyclodextrin. The surface pressure–mean molecular area (π–A) isotherms indicated that the synthesised amphiphilic cyclodextrin derivatives were capable of forming stable monolayers at the air–water interface. The shapes of the isotherms were typical for solid-like monolayers except for hexakis(6-deoxy-6-thio-2,3-di-*O*-pentyl)cyclomaltohexaoses which formed a more liquid monolayer.

Keywords: cyclodextrins; synthesis; thio; amphiphilic.

In continuation of our interest in the synthesis and application of amphiphilic cyclodextrins,[1,2] we have designed supramolecular systems which would be capable of acting in a double fashion, as an amphiphile and as a receptor to anchor on the surface of the electrode. Amphiphilic cyclodextrins, in general, may be formed in two ways using chemical modifications: hydrophobic

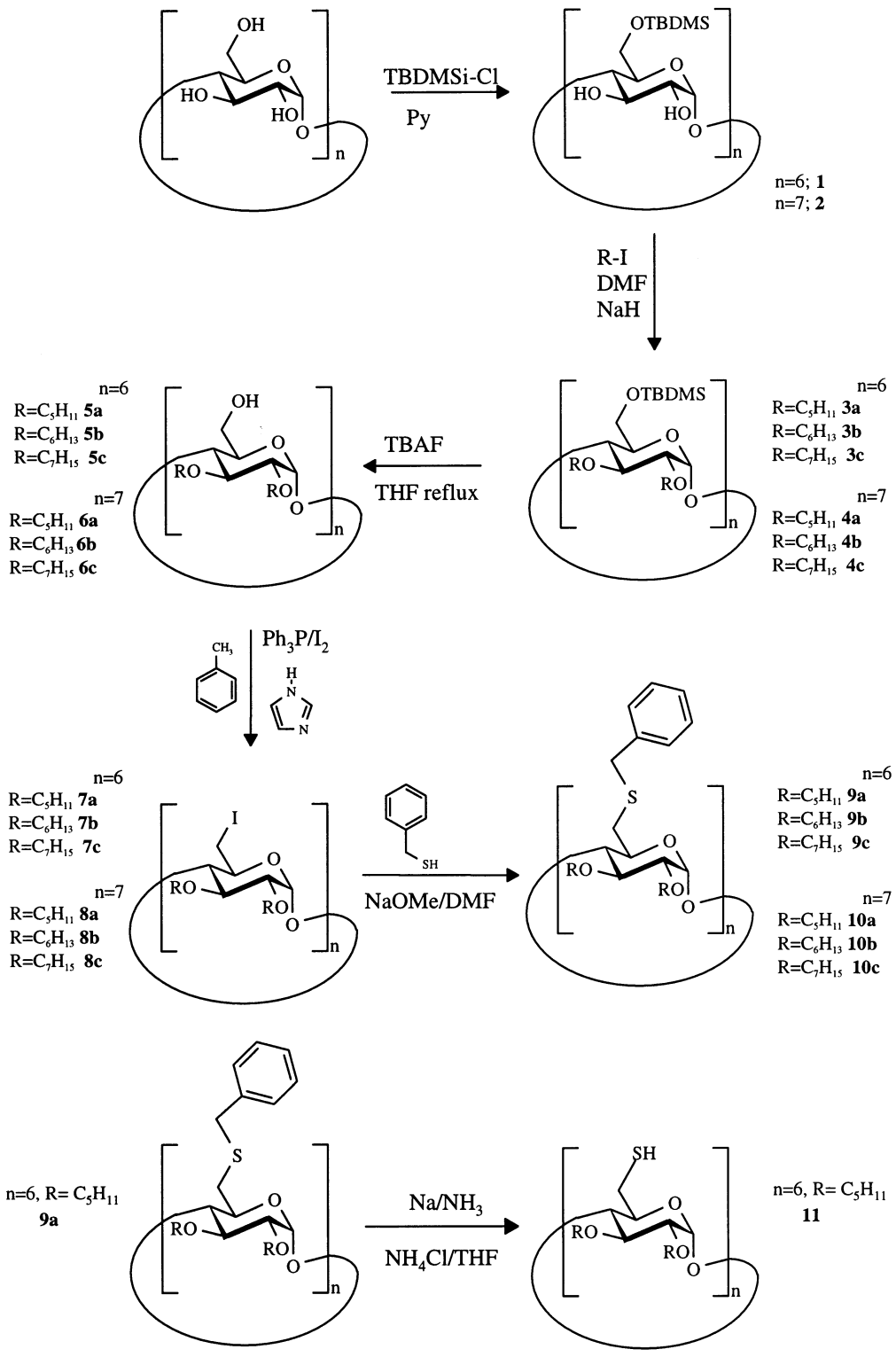
* Corresponding author. Tel: (0-22)8222325; fax: (0-22)8225996; e-mail: atemer@chem.uw.edu.pl

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01628-2

substituents can be introduced at the primary or secondary rim of the cyclodextrin torus. Amphiphilic cyclodextrins which have been described so far, include per-derivatives with alkyl-amino,[3] alkyl-thio,[4] and alkyl-sulfoxo[5] substituents at the primary positions of each glucose unit of the cyclodextrin. The second type of amphiphilic cyclodextrin possesses the hydrophobic functionality attached to the secondary hydroxyl position by an ester[6] or ether[7] linkage. Long alkyl chains (five–seven carbon atoms) attached via an ether linkage were chosen to introduce lipophilic character to the secondary face of the cyclodextrin molecule. In our synthetic approach (Scheme 1), we have regioselectively 6-*O*-protected the starting α- and β-cyclodextrins using *tert*-butyldimethylsilyl chloride in pyridine.[8] Treatment of **1** with a 10-fold excess of alkyl (*n*-pentyl, *n*-hexyl, *n*-heptyl) iodide in DMF in the presence of a 12-fold excess of sodium hydride for 3 days,[9] gave per(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-alkyl)-cyclomaltooligosaccharides (**3a**–**c**) and (**4a**–**c**). Derivatives **3a**–**c** and **4a**–**c** were desilylated using a standard procedure (tetrabutylammonium fluoride in boiling tetrahydrofuran)[10] to give amphiphilic per(2,3-di-*O*-alkyl)-α, β-cyclodextrins (**5a**–**c**) and (**6a**–**c**). All the free hydroxy groups at position C-6 were exchanged to iodo functions by treatment with a toluene solution of triphenylphosphine/I_2 and stoichiometric amounts of imidazole,[11] to give per(6-deoxy-6-iodo-2,3-di-*O*-alkyl) derivatives (**7a**–**c**) and (**8a**–**c**). The *S*-alkylation reactions between an excess of benzyl mercaptan and per(6-deoxy-6-iodo) cyclodextrin derivatives **7a**–**c** or **8a**–**c**, were carried using 3 M sodium methoxide at 60°C in DMF for 24 h to give hexakis(6-thiobenzyl-6-deoxy-2,3-di-*O*-alkyl)cyclomaltohexaoses (**9a**–**c**) in 94, 95, and 85% yield, respectively† and heptakis(6-deoxy-6-*S*-benzyl-2,3-di-*O*-alkyl)cyclomaltoheptaoses (**10a**–**c**).‡ *S*-Benzyl functionalities were introduced at the primary rim of the amphiphilic cyclodextrins in order to recover the anchoring SH groups by the reductive cleavage of benzyl groups using sodium in liquid ammonia to give

† Hexakis(6-deoxy-6-*S*-Bzl-2,3-di-*O*-alkyl) α-CD selected data: **9a** oil, $[\alpha]_D^{22}$ +139.0° (*c* 1, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 97.80 (C-1), 81.13 (C-4), 80.08, 71.74 (C-2,3,5), 33.59 (C-6), 37.69 (CH_2–Ph), 138.93, 129.07, 128.24, 126.65 (Aromatic), 73.92, 71.58 (2×$C_\alpha H_2$), 30.21, 29.97 (2×$C_\beta H_2$), 28.26, 28.19 (2×$C_\gamma H_2$), 22.81, 22.65 (2×$C_\delta H_2$), 14.07, 14.04 (2×$C_\Omega H_3$); LSIMS(+) NBA *m*/*z* 2450.2 $[M+H]^+$, calc. for $C_{138}H_{216}O_{24}S_6$ 2450.4 $[M+H]^+$. Compound **9b** oil, $[\alpha]_D^{22}$ +107.4° (*c* 1, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 97.96 (C-1), 81.28 (C-4), 80.16, 80.05, 71.79 (C-2,3,5), 33.62 (C-6), 37.72 (CH_2–Ph), 138.97, 129.12, 128.29, 126.69 (Aromatic), 74.02, 71.70 (2×$C_\alpha H_2$), 32.10, 31.90 (2×$C_\beta H_2$), 30.56, 30.28 (2×$C_\gamma H_2$), 25.85, 25.74 (2×$C_\delta H_2$), 22.77, 22.70 (2×$C_\varepsilon H_2$), 14.08, 14.05 (2×$C_\Omega H_3$); LSIMS (+) NBA *m*/*z* 2618.0 $[M+H]^+$, calc. for $C_{150}H_{240}O_{24}S_6$ 2620.6 $[M+H]^+$. Compound **9c** oil, $[\alpha]_D^{22}$ +212.2° (*c* 1, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 98.00 (C-1), 81.36 (C-4), 80.18, 80.00, 71.81 (C-2,3,5), 33.60 (C-6), 37.72 (CH_2–Ph), 138.98, 129.12, 128.28, 126.69 (Aromatic), 74.03, 71.70 (2×$C_\alpha H_2$), 32.08, 31.95 (2×$C_\beta H_2$), 30.66, 30.34 (2×$C_\gamma H_2$), 29.66, 29.40 (2×$C_\delta H_2$), 26.21, 26.04 (2×$C_\varepsilon H_2$), 22.70, 22.69 (2×$C_\xi H_2$), 14.10(d) (2×$C_\Omega H_3$); LSIMS (+) NBA *m*/*z* 2788.8 $[M+H]^+$, calc. for $C_{162}H_{264}O_{24}S_6$ 2789.2 $[M+H]^+$.

‡ Heptakis(6-deoxy-6-*S*-Bzl-2,3-di-*O*-alkyl) β-CD selected data: **10a** oil, $[\alpha]_D^{22}$ +220.9° (*c* 1, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 97.83 (C-1), 80.91 (C-4), 80.23, 80.02, 71.75 (C-2,3,5), 33.66 (C-6), 37.69 (CH_2–Ph), 138.85, 129.06, 128.30, 126.65 (Aromatic), 73.98, 71.54 (2×$C_\alpha H_2$), 30.18, 29.91 (2×$C_\beta H_2$), 28.32, 28.17 (2×$C_\gamma H_2$), 22.82, 22.62 (2×$C_\delta H_2$), 14.07 (2×$C_\Omega H_3$); LSIMS (+) NBA *m*/*z* 2859.5 $[M+H]^+$, calc. for $C_{161}H_{252}O_{28}S_7$ 2861.2 $[M+H]^+$. Compound **10b** oil, $[\alpha]_D^{22}$ +112.5° (*c* 1, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 97.90 (C-1), 80.99 (C-4), 80.29, 80.05, 71.78 (C-2,3,5), 33.67 (C-6), 37.71 (CH_2–Ph), 138.88, 129.11, 128.35, 126.71 (Aromatic), 74.10, 71.68 (2×$C_\alpha H_2$), 32.13, 31.87 (2×$C_\beta H_2$), 30.54, 30.23 (2×$C_\gamma H_2$), 25.93, 25.72 (2×$C_\delta H_2$), 22.77, 22.73 (2×$C_\varepsilon H_2$), 14.09, 14.07 (2×$C_\Omega H_2$); LSIMS (+) NBA *m*/*z* 3054.0 $[M+H]^+$, calc. for $C_{175}H_{280}O_{28}S_7$ 3057.8 $[M+H]^+$. Compound **10c** oil, $[\alpha]_D^{22}$ +94.6° (*c* 0.56, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 97.92 (C-1), 81.03 (C-4), 80.32, 80.05, 71.71 (C-2,3,5), 33.67 (C-6), 37.71 (CH_2–Ph), 138.88, 129.11, 128.35, 126.71 (Aromatic), 74.13, 71.71 (2×$C_\alpha H_2$), 32.07, 31.98 (2×$C_\beta H_2$), 30.65, 30.30 (2×$C_\gamma H_2$), 29.69, 29.39 (2×$C_\delta H_2$), 26.27, 26.03 (2×$C_\varepsilon H_2$), 22.70 (2×$C_\xi H_2$), 14.10 (2×$C_\Omega H_2$); LSIMS(+) NBA *m*/*z* 3254.9 $[M+H]^+$, calc. for $C_{189}H_{308}O_{28}S_7$ 3253.9 $[M+H]^+$.


OH
HO
HO
O
n
TBDMSi-Cl
Py
OTBDMS
n=6; 1
n=7; 2
R-I
DMF
NaH
n=6
R=C5H11 5a
R=C6H13 5b
R=C7H15 5c
n=7
R=C5H11 6a
R=C6H13 6b
R=C7H15 6c
TBAF
THF reflux
RO
n=6
R=C5H11 3a
R=C6H13 3b
R=C7H15 3c
n=7
R=C5H11 4a
R=C6H13 4b
R=C7H15 4c
Ph3P/I2
CH3
H
N
I
n=6
R=C5H11 7a
R=C6H13 7b
R=C7H15 7c
n=7
R=C5H11 8a
R=C6H13 8b
R=C7H15 8c
SH
NaOMe/DMF
S
n=6
R=C5H11 9a
R=C6H13 9b
R=C7H15 9c
n=7
R=C5H11 10a
R=C6H13 10b
R=C7H15 10c
n=6, R= C5H11
9a
Na/NH3
NH4Cl/THF
n=6, R= C5H11
11

Scheme 1.

hexakis(6-deoxy-6-thio-2,3-di-*O*-pentyl)cyclomaltohexaoses (**11**).[§] Compound **11** has two important properties: the ability to act as an amphiphile and the ability for chemisorption on metal substrates. The electrochemical studies of the modified surfaces are in progress now in our laboratory.

The surface pressure–mean molecular area (π–A) isotherms[¶] indicate that the amphiphilic cyclodextrin derivatives **5a**, **5c**, **6c**, and **11** are capable of forming monolayers at the air–water interface. The isotherms recorded for these cyclodextrin derivatives are shown in Fig. 1. The compounds formed stable monolayers with high collapse pressure. The collapse pressure values for **5a**, **5c**, **6c** were close to 42 mN/m, whilst the monolayer formed by **11** collapsed at a lower pressure of 21 mN/m. The extrapolated areas per molecule at zero pressure of **5a**, **5c**, **6c**, **11**, were 2.66, 2.77, 3.74, 3.44 nm^2, respectively. Substitution of all primary –OH groups of α-cyclodextrin derivatives by –SH groups lead to increase of molecular area (2.66 nm^2 for **5a** and 3.44 nm^2 for **11**). The isotherms were typical of a solid-like monolayer, except for compound **11**, which formed a more liquid monolayer. This difference was connected with the lower stability

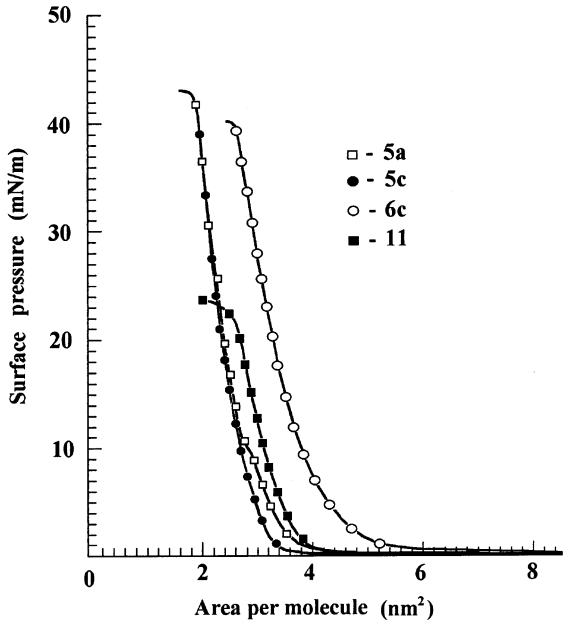


Figure 1. Surface pressure–area isotherms for compounds **5a**, **5c**, **6c** and **11** on pure water

[§] Hexakis(6-deoxy-6-thio-2,3-di-*O*-pentyl) α-CD selected data: **11a** $[\alpha]_D^{22}$ +94.7° (*c* 0.9, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 98.19 (C-1), 81.27 (C-4), 80.07, 80.01 (C-2,3), 74.02, 71.80 ($2\times C_\alpha H_2$), 71.14 (C-5), 30.26, 29.97 ($2\times C_\beta H_2$), 28.31, 28.19 ($2\times C_\gamma H_2$), 27.51 (C-6), 22.84, 22.66 ($2\times C_\delta H_2$), 14.11, 14.06 ($2\times C_\Omega H_3$); LSIMS(+) NBA *m*/*z* 1908.2 $[M+H]^+$, calc. for $C_{96}H_{181}O_{24}S_6$ 1910.1 $[M+H]^+$.

[¶] All solutions were prepared by dissolving the cyclodextrin derivatives (**5a**, **5c**, **6c**, **11**) in pure chloroform ($c = 1.2$ mg/ml). Distilled water used as the subphase was passed through a Milli-Q water purification system. The π–A isotherms were recorded using the KSV Langmuir–Blodgett Trough 5000 equipped with two barriers, and Wilhelmy balance as a surface-pressure sensor. To protect the experimental setup from dust it was placed in the laminar flow hood in which temperature was kept constant 20±1°C. The accuracy of measurements was ±0.1 nm^2 for area per molecule, ±1 mN/m for surface pressure. The procedures of cleaning the trough and monolayer spreading have been described earlier.[12]

of the thiol monolayers on the air–water interface due to less polar properties of the –SH terminal group compared to the more polar hydroxyl headgroups of the other amphiphiles.[13]

Acknowledgements

Financial support from the Warsaw University (BST-623/14/99) and from the Institute of Organic Chemistry, Polish Academy of Sciences, is gratefully acknowledged.

References

1. Chmurski, K.; Bilewicz, R.; Jurczak, J. *Langmuir* **1996**, *12*, 6114–6118.
2. Chmurski, K.; Coleman, A. W.; Jurczak, J. *J. Carbohydr. Chem.* **1996**, *15*, 787–796.
3. (a) Takahashi, H.; Irinatsu, Y.; Kozuka, S.; Tagaki, W. *Mem. Fac. Osaka City Univ.* **1985**, *26*, 93–99; (b) Tanaka, M.; Ishizuka, Y.; Matsumoto, M.; Nakamura, T.; Yabe, A.; Nakanishi, H.; Kawabata, Y.; Takahashi, H.; Tamura, S.; Tagaki, W.; Nakahara, H.; Fukuda, K. *Chem. Lett.* **1987**, 1307–1310; (c) Taneva, S.; Ariga, K.; Tagaki, W.; Okahata, Y. *J. Colloid Interface Sci.* **1989**, *131*, 561–566.
4. (a) Ling, C.-C.; Darcy, R.; Risse, W. *J. Chem. Soc., Chem. Commun.* **1993**, 438–440; (b) Kawabata, Y.; Matsumoto, M.; Nakamura, T.; Tanaka, M.; Manda, E.; Takahashi, H.; Tamura, S.; Tagaki, W.; Nakahara, H.; Fukuda, K. *Thin Solid Films* **1988**, *159*, 353–358; (c) Kobayashi, K.; Kajikawa, K.; Sasabe, H.; Knoll, W. *Thin Solid Films* **1999**, *349*, 244–249.
5. Nino, H.; Yabe, A.; Ouchi, A.; Tanaka, M.; Kawabata, Y.; Tamura, S.; Miyasaka, M.; Tagaki, W.; Nakahara, H.; Fukuda, K. *Chem. Lett.* **1988**, 1227–1228.
6. (a) Tchoreloff, P. C.; Boissonnade, M. M.; Coleman, A. W.; Baszkin, A. *Langmuir* **1995**, *11*, 191–196; (b) Zhang, P.; Parrot-Lopez, H.; Tchoreloff, P.; Baszkin, A.; Ling, C.-C.; deRango, C.; Coleman A. W. *J. Phys. Org. Chem.* **1992**, *5*, 518–528.
7. Parrot-Lopez, H.; Ling, C.-C.; Zhang, P.; Baszkin, A.; Albrecht, G.; deRango, C.; Coleman, A. W. *J. Am. Chem. Soc.* **1992**, *114*, 5479–5480.
8. Fugedi, P. *Carbohydr. Res.* **1989**, *192*, 366–369.
9. König, W. A.; Icheln, D.; Runge, T.; Pforr, I.; Krebs, A. *J. High Resolut. Chromatogr.* **1990**, *13*, 702–707.
10. Yi, G.; Bradshaw, J. S.; Rossiter, B. E.; Reese, S. L.; Petersson, P.; Markides, K. E.; Lee, M. L. *J. Org. Chem.* **1993**, *58*, 2561–2565.
11. Icheln, D.; Runge, T.; Gehrcke, B.; König, W. A. In *Proceedings of 6th International Symposium on Cyclodextrins*; Chicago, 1992; pp. 616–621.
12. Bilewicz, R.; Majda, M. *Langmuir* **1991**, *7*, 2794–2802.
13. Slowinski, K.; Bilewicz, R.; Kublik, Z. *Langmuir* **1991**, *1*, 437–440.