Synthesis of alkyl glycerolipids with various cationic groups linked directly to the glycerol backbone

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A number of positively charged lipids containing pyridinium, *N*-methylmorpholinium, *N*-methylimidazolinium, 4-*N*,*N*-dimethylaminopyridinium, and 4-*N*,*N*-dimethylcyclohexylammonium groups linked directly to the C(3) atom of 1,2-di-*O*-alkylglycerols with Br^-, MsO^-, and TsO^- anions as counterions were synthesized.

Key words: cationic lipids, alkyl glycerolipids, transfection.

Phosphorus-free modified lipids (cationic lipids) are the object of intense investigations due to the wide range of their biological activities.[1] The design of cationic liposomes that facilitate delivery of genetic material (DNA, mRNA) and oligonucleotides into cells of plant and animal origin for correcting genetic defects of cells and treating the genetic diseases is one of the areas of application of cationic lipids.[2—6] Cationic liposomes as delivering systems have a number of advantages over viral vectors: liposomes protect DNA, mRNA, and oligonucleotide molecules from inactivation and degradation by cellular enzymes; they are not infectious and immunogenic, can easily be prepared, and can be stored for a long time.

Design of cationic lipids for gene therapy is essentially aimed at changing the geometry of the cationic head (which can be branched or linear), at modifying the spacer group, and at varying the length and saturation of the chains in the hydrophobic area of the lipid domain.[1,3,5,7] The aim of such studies is the creation of the most stable and the least cytotoxic liposomal compositions capable of effectively transfecting various cell lines. Synthesis and studies of the structure—activity relations of new cationic lipids is a promising direction in bioorganic chemistry. We have already synthesized various representatives of cationic lipids as a part of systematic investigations.[8—10]

This work deals with the further development of these investigations and is connected with obtaining glycerolipids with various alkyl substituents and cationic groups (predominantly heterocyclic ones) linked directly to the glycerol backbone (Schemes 1 and 2). These compounds are the analogs of the commercially available cationic lipid, *rac*-*N*-[2,3-di(oleyloxy)propyl]-*N*,*N*,*N*-trimethylammonium chloride (DOTMA, GIBCO BRL), and can be considered as potential mediators of gene transfer into eucaryotic cells.

3-*O*-Tosyl (**4**, **5**), 1-bromo-1-deoxy (**6**), and 1-*O*-mesyl (**7**, **8**) derivatives of 1,2-di-*O*-alkylglycerols obtained by the method previously developed[11] were used as the starting compounds in the synthesis of cationic lipids (**10—16**, **18**). Tosyl derivatives **4** and **5** were prepared by treating the corresponding 1,2-di-*O*-alkylglycerols (**1**, **2**) with an excess of TsCl in anhydrous pyridine. Heating tosylate **4** with LiBr in ethyl methyl ketone resulted in the formation of *rac*-1-bromo-1-deoxy-2,3-di-*O*-octadecylglycerol (**6**). The mesyl group was introduced by treating 1,2-di-*O*-alkylglycerols **1** and **3** with methanesulfonyl chloride in triethylamine.[12]

Lipids **9** and **10** with pyridinium group were obtained by heating either tosylate **5** or bromide **6** with an excess of pyridine in 86 or 95% yield, respectively. Quaternization of *N*,*N*-dimethylcyclohexylamine with bromide **6** by boiling in an excess of the base gave cationic lipid **11** in 31% yield. Heating bromide **6** or mesylate **7** with *N*-methylmorpholine in MeCN for a long time resulted in the formation of cationic lipids **12** and **13** containing the *N*-methylmorpholinium group. The yields were low (from 5 to 19%).

Quaternization of 4-*N*,*N*-dimethylaminopyridine with *rac*-1-*O*-mesyl-2,3-di-*O*-octadecylglycerol **7** upon heating in MeCN resulted in the formation of cationic lipid **14** in 56% yield. Alkylation of aminopyridines under the usual conditions is known to occur at the aromatic nitrogen atom.[13] However, the signal at 6.89 ppm in the ^{1}H NMR spectrum of compound **14** attracts particular attention, since such an upfield signal cannot be assigned to the protons of the pyridinium ring (the signals of β-protons of the pyridinium ring in compounds **9** and **10** are situated at 8.04 and 8.08 ppm, respectively). At the same time the presence of the signal of the methyl groups at 3.25 ppm in the ^{1}H NMR spectrum of compound **14** points to the fact that the corresponding methyl groups are situated at the charged nitrogen atom

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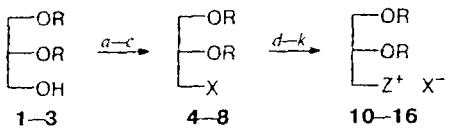
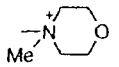
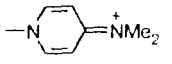
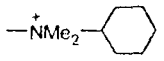
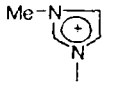
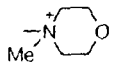
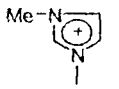
Scheme 1



1–3 **4–8** **10–16**

Compound	R	Compound	X
1, **4**, **6**, **7**, **9–15**	n-$C_{18}H_{37}$	**4**, **5**, **9**	TsO
2, **5**	n-$C_{16}H_{31}$	**6**, **10–12**	Br
3, **8**, **16**	$(CH_2)_8CH{=}CH(CH_2)_7Me$	**7**, **8**, **13–16**	MsO

Compound	Z	Compound	Z
9		**13**	
10		**14**	
11		**15**	
12		**16**	

Reagents and conditions:

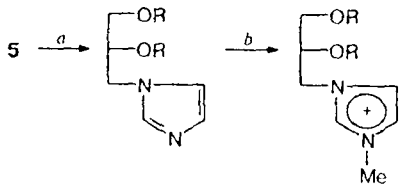
Variant	Compound	Reagents	T /°C	Time /h
a	**4**, **5**	TsCl/Py	60	6
b	**6**	LiBr/MeCOEt	80	5
c	**7**, **8**	MsCl–Et_3N/anhydr. $CHCl_3$	20	48
d	**9**	Py	90	9
e	**10**	Py	90	15
f	**11**	*N*,*N*-Dimethylcyclohexylamine	95	96
g	**12**	*N*-Methylmorpholine	95	103
h	**13**	*N*-Methylmorpholine/MeCN	120	20
i	**14**	DMAP/MeCN	110	19
j	**15**	*N*-Methylimidazole/MeCN	100	15
k	**16**	*N*-Methylimidazole/MeCN	100	12

(*cf.* 3.13 ppm for **11** and 3.36 ppm. for **12**). Thus, the presence of such unusual signals confirms the structure of compound **14** reported herein.

We tried different approaches to introduce the *N*-methylimidazolium group into 1,2-di-*O*-alkylglycerols. One of them included treating mesylates **7** and **8** with *N*-methylimidazole in MeCN (see Scheme 1). The yields of lipids **15** and **16** were 44 and 15%, respectively.

The other variant (see Scheme 2) was based on first obtaining *rac*-*N*-[2,3-di(hexadecyloxy)propyl]imidazole

Scheme 2



17 **18**

Reagents and conditions: *a*. Imidazole/MeCOEt, 80 °C, 45 h. *b*. MeI, Me_2CO, 50 °C, 9 h.

(**17**) by treating tosylate **5** with imidazole in ethyl methyl ketone (65% yield) and subsequently treating the tertiary amine **17** with MeI. The yield of compound **18** was 84%.

The second approach appears to be preferable, as the isolation and purification of compounds are facilitated and thus allows one to increase the yield slightly.

Thus, we have synthesized novel cationic glycerolipids with various cationic heads linked to the C(3) atom of 1,2-di-*O*-alkylglycerols. We plan to use the obtained compounds in gene therapy as mediators of transfection.

Experimental

Distilled solvents and reagents of domestic manufacture — TsCl, LiBr, Py, Et_3N, MeCN — and also ethyl methyl ketone (Reanal, Hungary), octadecanol MsCl, imidazole, *N*-methylimidazole, *N*-methylmorpholine, 4-*N*,*N*-dimethylaminopyridine, and *N*,*N*-dimethylcyclohexylamine (Fluka) were used in this work.

TLC was performed on Silufol UV-245 plates (Chemapol, Czech Republic) for compounds **4–6**, and **10–18** and on Kieselgel 60 plates (Merck) for compounds **7–9**. The spots on Silufol plates were visualized by treating with iodine vapor or $KMnO_4$, or by heating. The spots on Kieselgel 60 were visualized by spraying with 50% H_2SO_4 and subsequent heating. The Dragendorff reagent[14] was used to identify the derivatives of tertiary amines and cationic lipids. TLC was performed using the following developing systems: petroleum ether–Et_2O (A) 3 : 1, (B) 9 : 1, (C) 1 : 1; $CHCl_3$–MeOH (D) 4 : 1, (E) 8 : 1, (F) 5 : 1, (G) 6 : 1, (H) 50 : 1. Column chromatography was performed on Silica gel L 100/250 μm (Chemapol, Czech Republic). Melting points were determined on a Boetius instrument (Germany). ^1H NMR spectra were registered on a Bruker MSL-200 spectrometer (200 MHz) in $CDCl_3$ or $CDCl_3$–CD_3OD (3 : 1). Mass spectra were taken on an MSBKh (Sumy, Ukraine) plasma desorption mass spectrometer with ionization by the products of ^{252}Cf fission and at an accelerating voltage of ±5 or ±20 kV.

***rac*-1,2-Di-*O*-octadecyl-3-*O*-(4-toluenesulfonyl)glycerol (4).** Tosyl chloride (0.3529 g, 1.8511 mmol) in 10 mL of anhydrous Py was added to a solution of 1.0038 g (1.6812 mmol) of *rac*-1,2-di-*O*-octadecylglycerol[11] (**1**) in 45 mL of anhydrous Py with stirring, and the reaction mixture was heated for 6 h at 60 °C. Then molecular sieves 4 Å were added, and the reaction mixture was refluxed for 6 h. The cooled reaction mixture was diluted with 25 mL of $CHCl_3$,

washed with 10% HCl and water, and dried over Na_2SO_4. The solvent was removed, and the residue was chromatographed (eluent: benzene—Et_2O, 95 : 5) to give 0.4737 g (37.5%) of compound **4**, R_f 0.58 (A), m.p. 50—51 °C (lit.[15]: m.p. 50—50.5 °C).

***rac*-1,2-Di-*O*-hexadecyl-3-*O*-(4-toluenesulfonyl)glycerol (5)** (1.25 g, 92 %) was obtained analogously from 1 g of *rac*-1,2-di-*O*-hexadecylglycerol[11] (**2**). R_f 0.65 (F). IR, ν/cm^{-1}: 3030, 2900, 1610, 1475, 1380, 1150, 1100, 1040, 720 (lit.[15]: IR, ν/cm^{-1}: 3030, 2940, 1610, 1475, 1380, 1150—1050, 720).

***rac*-1-Bromo-1-deoxy-2,3-di-*O*-octadecylglycerol (6).** Lithium bromide (1.7 g, 19.6 mmol) was added to a solution of 3.6 g (4.8 mmol) of tosylate **4** in 40 mL of MeCOEt. The mixture was refluxed for 5 h and cooled to ~20 °C, and 30 mL of Et_2O was added. The precipitate was filtered off and washed with Et_2O (3×10 mL). The ethereal solution was passed through Al_2O_3 and evaporated. The residue was chromatographed (eluent: heptane—Et_2O, 95 : 5) to yield 2.3 g (72.8%) of compound **6**, R_f 0.68 (B), m.p. 38—39 °C (lit.[15]: m.p. 38—38.5 °C).

***rac*-1-*O*-Methanesulfonyl-2,3-di-*O*-octadecylglycerol (7).** Triethylamine (0.37 mL, 2.664 mmol) and MsCl (0.14 mL, 1.776 mmol) were added to a solution of 0.663 g (1.11 mmol) of *rac*-1,2-di-*O*-octadecylglycerol[11] (**1**) in 3 mL of anhydrous $CHCl_3$ at stirring. The reaction mixture was stirred for 48 h at 18—20 °C. Then the reaction mixture was diluted with $CHCl_3$ (20 mL), washed with water (3×10 mL), 5% HCl (3×10 mL), saturated $NaHCO_3$ solution (1×10 mL), and saturated NaCl solution (1×10 mL). After the removal of the solvent, the residue was crystallized from 20 mL of EtOH to yield 0.642 g (85.6%) of compound **7**, R_f 0.71 (C), m.p. 58—60 °C. MS, *m/z* (I_{rel} (%)): 674.9 $[M]^+$ (100%).

***rac*-1-*O*-Methanesulfonyl-2,3-di-*O*-(octadec-9-en-1-yl)glycerol (8)** was synthesized as described for mesylate 7 from 0.0902 g (0.152 mmol) of *rac*-1,2-di-*O*-(octadec-9-en-1-yl)glycerol[11] (**3**). The target compound was purified by column chromatography on Silica gel L 40/100 μm, eluent: heptane—Et_2O (98 : 2). Yield: 0.0816 g (80%) of compound **8**, R_f 0.71 (C). MS, *m/z* (I_{rel} (%)): 571.0 $[M]^+$ (100%).

***rac*-*N*-[2,3-Di(octadecyloxy)prop-1-yl]pyridinium toluenesulfonate (9).** A mixture of 0.2100 g (0.2795 mmol) of tosylate **4** and 7 mL of anhydrous Py was heated for 9 h at 90 °C. Pyridine was then removed, and the residue was crystallized from Et_2O to yield 0.1971 g (84.9%) of compound **9**, R_f 0.60 (D), m.p. 70—71 °C. MS, *m/z* (I_{rel} (%)): 658.7 $[M - TsO]^+$ (100%). ^1H NMR, δ: 0.86 (t, 6 H, 2 $(CH_2)_{15}C\underline{H}_3$, J = 7 Hz); 1.24 (br.s, 60 H, 2 $(C\underline{H}_2)_{15}CH_3$); 1.55 (m, 4 H, 2 $OCH_2C\underline{H}_2$); 2.33 (s, 3 H, $C_6H_4C\underline{H}_3$); 3.25 (t, 4 H, 2 $OC\underline{H}_2CH_2$, J = 7 Hz); 3.31—3.50 (m, 2 H, $CH_2OC_{18}H_{37}$); 3.85 (m, 1 H, $CHOC_{18}H_{37}$); 4.61 (dd, 1 H, CH_2N^+, J = 8.5 Hz, J = 13 Hz); 4.92 (dd, 1 H, CH_2N^+, J = 3 Hz, J = 13.5 Hz); 7.16 (m, 2 H) and 7.71 (m, 2 H, $C_6\underline{H}_4CH_3$); 8.04 (m, 2 H); 8.52 (m, 1 H) and 8.89 (m, 2 H, $C_5H_5N^+$).

***rac*-*N*-[2,3-Di(octadecyloxy)prop-1-yl]pyridinium bromide (10).** A mixture of 0.4094 g (0.6203 mmol) of bromide **6** and 9 mL of anhydrous Py was heated for 15 h at 90 °C. Isolation and purification of the target compound were performed as described above to yield 0.4306 g (95.1%) of compound **10**, R_f 0.67 (D), m.p. 106—107 °C. MS, *m/z* (I_{rel} (%)): 658.5 $[M - Br]^+$ (100%). ^1H NMR, δ: 0.86 (t, 6 H, 2 $(CH_2)_{15}C\underline{H}_3$, J = 7 Hz); 1.23 (br.s, 60 H, 2 $(C\underline{H}_2)_{15}CH_3$); 1.56 (m, 4 H, 2 $OCH_2C\underline{H}_2$); 3.20—3.70 (m, 6 H, 2 $OC\underline{H}_2CH_2$, $CH_2OC_{18}H_{37}$); 3.96 (m, 1 H, $CHOC_{18}H_{37}$); 4.65 (dd, 1 H, CH_2N^+, J = 8 Hz, J = 13 Hz); 4.97 (dd, 1 H, CH_2N^+, J = 3 Hz, J = 13 Hz), 8.08 (m, 2 H), 8.57 (m, 1 H) and 8.96 (m, 2 H, $C_5H_5N^+$).

***rac*-*N*-[2,3-Di(octadecyloxy)prop-1-yl]-*N*,*N*-dimethyl-*N*-cyclohexylammonium bromide (11).** A mixture of 0.2430 g (0.3680 mmol) of bromide **6** and 2.1 mL of *N*,*N*-dimethylcyclohexylamine was heated for 96 h at 95 °C. The reaction mixture was evaporated *in vacuo* (water aspirator pump) and dried for 2 h (1 Torr, 40 °C). The residue was crystallized from heptane to give 0.0884 g (31%) of compound **11**, R_f 0.61 (E). MS, *m/z* (I_{rel} (%)): 708.1 $[M - Br]^+$ (100%). ^1H NMR, δ: 0.85 (t, 6 H, 2 $(CH_2)_{15}C\underline{H}_3$, J = 7 Hz); 1.23 (br.s, 60 H, 2 $(C\underline{H}_2)_{15}CH_3$); 1.50 (m, 4 H, 2 $OCH_2C\underline{H}_2$); 1.91—2.30 (m, 11 H, NC_6H_{11}); 3.13 (s, 6 H, $N^+(CH_3)_2$); 3.31—4.07 (m, 9 H, 2 $OC\underline{H}_2CH_2$, $C\underline{H}_2OC_{18}H_{37}$, $C\underline{H}OC_{18}H_{37}$, CH_2N^+).

***rac*-*N*-[2,3-Di(octadecyloxy)prop-1-yl]-*N*-methylmorpholinium bromide (12).** A mixture of 0.4002 g (0.6064 mmol) of bromide **6** and 6 mL of *N*-methylmorpholine was heated for 103 h at 95 °C. The reaction mixture was evaporated *in vacuo* (water aspirator pump) and dried for 2 h (1 Torr, 40 °C). The residue was crystallized from heptane to give 0.0231 g (5%) of compound **12**, R_f 0.43 (E). MS, *m/z* (I_{rel} (%)): 680.1 $[M - Br]^+$ (100%). ^1H NMR, δ, : 0.83 (t, 6 H, 2 $(CH_2)_{15}C\underline{H}_3$), J = 7 Hz); 1.23 (br.s, 60 H, 2 $(C\underline{H}_2)_{15}CH_3$); 1.54 (m, 4 H, 2 $OCH_2C\underline{H}_2$); 3.36 (s, 3 H, N^+CH_3); 3.41—4.10 (m, 15 H, 2 $OC\underline{H}_2CH_2$, $CH_2OC_{18}H_{37}$, $CHOC_{18}H_{37}$, 2 NCH_2CH_2O); 4.32 (dd, 1 H, CH_2N^+, J = 6 Hz, J = 12 Hz); 4.39 (dd, 1 H, CH_2N^+, J = 2 Hz, J = 12 Hz).

***rac*-*N*-[2,3-Di(octadecyloxy)prop-1-yl]-*N*-methylmorpholinium methanesulfonate (13).** A mixture of 0.1025 g (0.1518 mmol) of mesylate 7 and 1.17 mL of *N*-methylmorpholine in 2 mL of anhydrous MeCN was heated for 32 h at 100 °C. The reaction mixture was evaporated *in vacuo* (water aspirator pump) and dried for 2 h (1 Torr, 40 °C). The residue was chromatographed (eluent: $CHCl_3$—MeOH, 85 : 15) to yield 0.0227 g (19.3%) of compound **13**, R_f 0.72 (F). MS, *m/z* (I_{rel} (%)): 679.8 $[M - MsO]^+$ (100%). ^1H NMR, δ: 0.88 (t, 6 H, 2 $(CH_2)_{15}C\underline{H}_3$, J = 7); 1.26 (br.s, 60 H, 2 $(C\underline{H}_2)_{15}CH_3$); 1.54 (m, 4 H, 2 $OCH_2C\underline{H}_2$); 2.75 (s, 3 H, CH_3SO_2); 3.40—4.30 (m, 20 H, 2 $OC\underline{H}_2CH_2$, N^+CH_3, $C\underline{H}_2OC_{18}H_{37}$, $C\underline{H}OC_{18}H_{37}$, 2 NCH_2CH_2O, CH_2N^+).

***rac*-*N*,*N*-Dimethyl-*N*-{1-[2,3-di(octadecyloxy)prop-1-yl]-1,4-dihydropyridin-4-ylidene}ammonium methanesulfonate (14).** *N*,*N*-Dimethylaminopyridine (0.064 g, 0.523 mmol) was added to 0.0674 g (0.010 mmol) of mesylate 7 in 1 mL of anhydrous DMSO, and the mixture was heated for 19 h at 110 °C. The solvent was removed, and the residue was dried for 4 h (1 Torr, 40 °C) and dissolved in MeOH. The target compound was precipitated with Et_2O to give 0.0456 g (59.4%) of compound **14**, R_f 0.60 (G), m.p. 70—71 °C. MS, *m/z* (I_{rel} (%)): 700.8 $[M - MsO]^+$ (100%). ^1H NMR, δ: 0.85 (t, 6 H, 2 $(CH_2)_{15}C\underline{H}_3$, J = 7 Hz); 1.23 (br.s, 60 H, 2 $(CH_2)_{15}C\underline{H}_3$); 1.50 (m, 4 H, 2 $OCH_2C\underline{H}_2$); 2.19 (s, 3 H, CH_3SO_2); 3.25 (s, 6 H, $N^+(CH_3)_2$); 3.38—3.65 (m, 6 H, 2 $OC\underline{H}_2CH_2$, $C\underline{H}_2OC_{18}H_{37}$); 3.90 (m, 1 H, $C\underline{H}OC_{18}H_{37}$); 4.15 (dd, 1 H, CH_2N, J = 7 Hz, J = 14 Hz); 4.46 (dd, 1 H, CH_2N, J = 3.5 Hz, J = 14 Hz); 6.89 (m, 2 H) and 8.12 (m, 2 H, C_5H_4N).

***rac*-*N*-[2,3-Di(octadecyloxy)prop-1-yl]-*N*′-methylimidazolium methanesulfonate (15).** *N*-Methylimidazole (1 mL) was added to 0.0862 g (0.128 mmol) of *rac*-1-*O*-methanesulfonyl-2,3-di-*O*-octadecylglycerol (**7**) in 2 mL of anhydrous MeCN, and the mixture was heated for 15 h at 100 °C. The excess of *N*-methylimidazole was removed *in vacuo* as the azeotropic mixture with toluene. The residue was dried *in vacuo* (2 h, 1 Torr, 40 °C) and then chromatographed (eluent: $CHCl_3$—MeOH, 96 : 4) to yield 0.043 g (44%) of compound **15**, R_f 0.77 (D). MS, *m/z* (I_{rel} (%)): 661.3 $[M - MsO]^+$ (100%). ^1H NMR, δ: 0.89 (t, 6 H, 2 $(CH_2)_{15}C\underline{H}_3$, J = 7 Hz); 1.25

(br.s, 60 H, 2 $(CH_2)_{15}CH_3$); 1.55 (m, 4 H, 2 OCH_2CH_2); 2.10 (s, 3 H, CH_3SO_2); 3.36—3.60 (m, 6 H, 2 OCH_2CH_2, $CH_2OC_{18}H_{37}$); 3.85 (m, 1 H, $CHOC_{18}H_{37}$); 4.01 (s, 3 H, N^+CH_3); 4.26 (dd, 1 H, CH_2N^+, J = 7 Hz, J = 14 Hz); 4.54 (dd, 1 H, CH_2N^+, J = 3.5 Hz, J = 14 Hz); 7.24 (d, 2 H, —CH=CH, J = 2 Hz); 10.10 (s, 1 H, —CH=N).

***rac*-*N*-[2,3-Di(octadec-9-en-1-yloxy)prop-1-yl]-*N'*-methylimidazolium methanesulfonate (16).** A mixture of 0.0816 g (0.122 mmol) of *rac*-1-*O*-methanesulfonyl-2,3-di-*O*-(octadec-9-en-1-yl)glycerol (**8**) and 0.5 mL of *N*-methylimidazole in 2 mL of anhydrous MeCN was heated for 20 h at 100 °C. Then the reaction mixture was evaporated *in vacuo* (water aspirator pump) and dried for 2 h (1 Torr, 40 °C). The residue was chromatographed (eluent: $CHCl_3$—MeOH, 98 : 2) to yield 0.0141 g (15%) of compound **16**, R_f 0.62 (D). MS, m/z (I_{rel} (%)): 662.1 $[M - MsO]^+$ (100%). ^1H NMR, δ: 0.88 (t, 6 H, 2 $(CH_2)_{13}CH_3$, J = 7 Hz); 1.26 (m, 44 H, 2 $(CH_2)_5CH_2CH{=}CHCH_2(CH_2)_6CH_3$); 1.54 (m, 4 H, 2 OCH_2CH_2); 2.11 (m, 8 H, 2 $CH_2CH{=}CHCH_2$); 2.86 (s, 3 H, CH_3S); 3.41—4.20 (m, 12 H, N^+CH_3, 2 OCH_2CH_2, $CH_2OC_{18}H_{37}$, $CHOC_{18}H_{35}$, CH_2N^+); 5.12 (m, 4 H, 2 CH=CH); 7.90 (d, 2 H, —CH=CH, J = 2 Hz), 10.15 (s, 1 H, —CH=N).

***rac*-*N*-[2,3-Di(hexadecyloxy)prop-1-yl]imidazole (17).** Imidazole (0.0415 g, 0.542 mmol) was added to a solution of 0.234 g (0.337 mmol) of tosylate **5** in 5 mL of MeCOEt, and the mixture was heated for 45 h at 80 °C. The solvent was removed *in vacuo*, and the residue was triturated with Et_2O. The resulting precipitate was filtered off and washed with Et_2O. The combined filtrate was evaporated *in vacuo*, and the residue was chromatographed. The target compound was eluted with $CHCl_3$. Yield: 0.123 g (62%) of compound **17**, R_f 0.17 (H), m.p. 42—43.5 °C. MS, m/z (I_{rel} (%)): 591 $[M]^+$ (100%). ^1H NMR, δ: 0.86 (t, 6 H, 2 $(CH_2)_{13}CH_3$, J = 7 Hz), 1.26 (br.s, 52 H, 2 $(CH_2)_{13}CH_3$); 1.54 (m, 4 H, 2 OCH_2CH_2); 3.26—4.35 (m, 9 H, 2 OCH_2CH_2, $CH_2OC_{16}H_{33}$, $CHOC_{16}H_{37}$, CH_2N^+); 6.98 (d, 2 H, —CH=CH, J = 14 Hz); 7.49 (s, 1 H, —CH=N).

***rac*-*N*-[2,3-Di(hexadecyloxy)prop-1-yl]-*N'*-methylimidazolium iodide (18).** A mixture of 0.0527 g (0.0892 mmol) of *N*-[2,3-di(hexadecyloxy)prop-1-yl]imidazole (**17**) and 0.0083 mL of MeI in 1 mL of acetone was heated for 9 h at 50 °C. The solvent was removed *in vacuo*, and the residue was crystallized from anhydrous Et_2O to yield 0.0549 g (84%) of compound **18**, R_f 0.42 (H), m.p. 66—68 °C. MS, m/z (I_{rel} (%)) 605.5 $[M - I]^+$ (100%). ^1H NMR, δ: 0.87 (t, 6 H, 2 $(CH_2)_{13}CH_3$, J = 7 Hz); 1.26 (br.s, 52 H, 2 $(CH_2)_{13}CH_3$); 1.54 (m, 4 H, 2 OCH_2CH_2); 3.36—3.61 (m, 6 H, 2 OCH_2CH_2, $CH_2OC_{16}H_{33}$); 3.85 (m, 1 H, $CHOC_{16}H_{37}$); 4.01 (s, 3 H, N^+CH_3); 4.26 (dd 1 H, CH_2N^+, J = 7 Hz, J = 14.5 Hz); 4.54 (dd, 1 H, CH_2N^+, J = 3.5 Hz, J = 14.5 Hz); 7.21 (d, 2 H, —CH=CH, J = 2 Hz); 10.13 (s, 1 H, —CH=N).

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