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Synthesis of amphiphilic diacyl derivatives of 3,7-diazabicyclo[3.3.1]nonan-9-one

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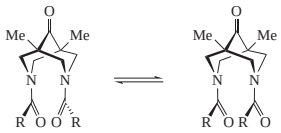
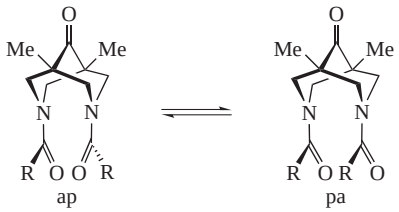
Novel amphiphilic candidates for incorporation into lipid bilayer, 3,7-diacyl-3,7-diazabicyclo[3.3.1]nonan-9-ones, have been synthesized.



Nowadays the development of new drug delivery systems providing the decrease of drug dosage and elimination of some side effects is a worldwide trend.[1,2] The technologies that use liposomes to deliver active molecules are considered to be the most advanced ones for this purpose.[3,4] Medicines, peptides, proteins, nucleic acids can be included into internal water volume of liposomes, which promotes the use of the latter for delivery of various substances to certain organs and tissues. The outer part of liposomes, a lipid bilayer, can be modified by inclusion of amphiphilic compounds, which can cause either stabilization or destabilization (under the influence of external factors) of liposomes depending on the included components. In this way, release of the substances encapsulated in the internal volume of liposomes can be accomplished.[5–7]

Previously,[8–10] we have demonstrated that lipid-like amphiphilic alkyl derivatives of 3,7-diazabicyclo[3.3.1]nonan-9-one with long substituents included into the bilayer are capable to undergo conformational reorganization both upon protonation and the formation of complexes with divalent metal cations, thereby to stimulate a release of water-soluble compounds from the liposomal nanocontainers.

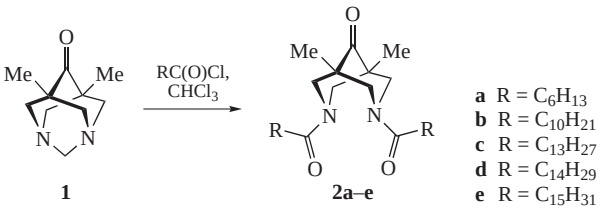
Here we describe the synthesis of acyl derivatives of 3,7-diazabicyclo[3.3.1]nonan-9-one with long lipophilic substituents, which can be incorporated into the lipid bilayer. Earlier it was shown that 3,7-diacyl-3,7-diazabicyclo[3.3.1]nonanes[11,12] adopting a chair-chair conformation[13,14] could switch from antiparallel (ap) to parallel (pa) orientation of acyl groups (Scheme 1) upon addition of $LaCl_3$ or solvent polarity increase.[15] This effect can be used to affect the lipid bilayer permeability due to the movements of long lipophilic substituents during the conformational transition. Compounds **2a–e** were synthesized from 5,7-dimethyl-1,3-diazaadamantan-6-one[16] **1** according to Scheme 2.† It should be noted that with the increase of the length of substituents the purification becomes more difficult due to the emulsion formation.



ap pa

Scheme 1

Keeping in mind that lipophilic bulky substituents could have more substantial impact on the liposomal membrane than the



1 **2a–e**

a R = C_6H_{13}
b R = $C_{10}H_{21}$
c R = $C_{13}H_{27}$
d R = $C_{14}H_{29}$
e R = $C_{15}H_{31}$

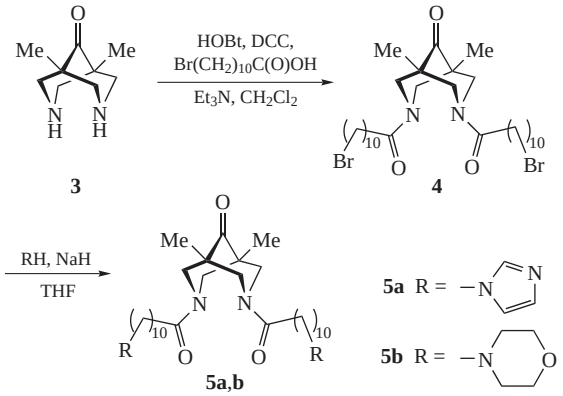
Scheme 2

† NMR spectra were recorded on a Bruker Avance 400 spectrometer using $CDCl_3$ for calibration. High-resolution mass spectra were measured with an Orbitrap Elite Thermo Scientific instrument. The IR spectra were recorded on a UR-20 spectrophotometer.

Compounds **2a–e** *(general procedure)*. A mixture of compound **1** (1 g, 5.6 mmol) and the corresponding acyl chloride (11.2 mol) was refluxed in anhydrous chloroform for 4–5 h (TLC control). After cooling, the mixture was treated with a saturated solution of $KHCO_3$ (pH 8) and this mixture was stirred for 1 h. Note that with the growth of hydrocarbon chains in acyl chlorides the stirring time should be prolonged up to 24 h. The organic layer was separated and the aqueous one was extracted with $CHCl_3$ (2 × 30 ml), the combined extracts were dried over Na_2SO_4. After evaporation of the solvent, the product was recrystallised from hexane to give yellow crystals (**2a**), or purified by column chromatography on silica gel using chloroform as the eluent (**2b–e**).

3,7-Diheptanoyl-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one **2a**. Yield 75%, yellow solid, R_f 0.25 ($CHCl_3$), mp 90.5–91.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, 6H, *J* 10 Hz), 1.05 (s, 6H), 1.30 (m, 12H), 1.56 (m, 4H), 2.29 and 2.46 (dt, 4H, ^2J 15 Hz, ^3J 7.5 Hz), 2.75, 3.22, 4.13 and 5.04 (dd, bispidine, 8H, ^2J 13.5 Hz, ^4J 2 Hz). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ: 14.05, 16.65, 22.54, 24.90, 29.03, 31.67, 33.15, 46.08, 53.49, 56.91, 172.44, 212.16. IR (ν/cm^{-1}): 1720 (C=O), 1650 (=N–C=O). Found (%): C, 70.39; H, 10.37; N, 7.22. Calc. for $C_{23}H_{40}N_2O_3$ (%): C, 70.37; H, 10.27; N, 7.14.

1,5-Dimethyl-3,7-diundecanoyl-3,7-diazabicyclo[3.3.1]nonan-9-one **2b**. Yield 60%, yellow solid, R_f 0.27 ($CHCl_3$), mp 55–57 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 6H, *J* 10 Hz), 1.06 (s, 6H), 1.26 (m, 28H), 1.56 (m, 4H), 2.30 and 2.44 (dt, 4H, ^2J 15 Hz, ^3J 7 Hz), 2.76, 3.23, 4.13 and 5.05 (dd, bispidine, 8H, ^2J 13.5 Hz, ^4J 2 Hz). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ: 14.12, 16.66, 22.69, 24.96, 29.38, 31.89, 33.15, 46.08, 53.50, 56.91, 172.45, 212.17. IR (ν/cm^{-1}): 1720 (C=O), 1650 (=N–C=O). Found (%): C, 73.87; H, 11.12; N, 5.45. Calc. for $C_{31}H_{56}N_2O_3$ (%): C, 73.76; H, 11.18; N, 5.55.



Scheme 3

normal aliphatic ones, we have also synthesized compounds **5a**,**b** (Scheme 3).

The starting compound **3** was synthesized according to the published procedure.[17] A modified acylation procedure[18] was used for the synthesis of bis(11-bromoundecanamide) **4**‡ which was then converted into the final products **5a**,**b**.§ It is of note that the presence of long hydrocarbon chains in the molecules complicated their purification which result in their moderate yields.

Thus, a series of new amphiphilic compounds have been synthesized, which are supposed to be incorporated into liposomal membranes and to change the stability of thus modified liposomes under the influence of external factors.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.01.006.

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1,5-Dimethyl-3,7-ditetradecanoyl-3,7-diazabicyclo[3.3.1]nonan-9-one **2c**. Yield 52%, white solid, R_f 0.30 ($CHCl_3$), mp 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, 6H, *J* 10 Hz), 1.06 (s, 6H), 1.26 (m, 40H), 1.60 (m, 4H), 2.33 and 2.45 (dt, 4H, ^2J 15 Hz, ^3J 7 Hz), 2.76, 3.22, 4.14 and 5.05 (dd, bispidine, 8H, ^2J 13.5 Hz, ^4J 2 Hz). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ: 14.12, 16.66, 22.71, 24.93, 29.72, 31.89, 33.15, 46.08, 53.50, 56.91, 172.44, 212.17. IR (ν/cm^{-1}): 1720 (C=O), 1650 (=N–C=O). Found (%): C, 75.79; H, 11.61; N, 4.73. Calc. for $C_{37}H_{68}N_2O_3$ (%): C, 75.46; H, 11.64; N, 4.76.

1,5-Dimethyl-3,7-dipentadecanoyl-3,7-diazabicyclo[3.3.1]nonan-9-one **2d**. Yield 60%, light yellow solid, R_f 0.28 ($CHCl_3$), mp 69–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, 6H, *J* 10 Hz), 1.06 (s, 6H), 1.27 (m, 44H), 1.58 (m, 4H), 2.30 and 2.46 (dt, 4H, ^2J 15 Hz, ^3J 7 Hz), 2.74, 3.22, 4.14 and 5.05 (dd, bispidine, 8H, ^2J 13.5 Hz, ^4J 2 Hz). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ: 14.07, 16.61, 22.65, 24.92, 29.66, 31.89, 33.11, 46.04, 53.49, 56.89, 172.38, 212.09. IR (ν/cm^{-1}): 1720 (C=O), 1650 (=N–C=O). Found (%): C, 75.75; H, 12.00; N, 4.53. Calc. for $C_{39}H_{72}N_2O_3$ (%): C, 75.92; H, 11.76; N, 4.54.

3,7-Dihexadecanoyl-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one **2e**. Yield 70%, light yellow solid, R_f 0.28 ($CHCl_3$), mp 69–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, 6H, *J* 10 Hz), 1.06 (s, 6H), 1.26 (m, 48H), 1.59 (m, 4H), 2.30 and 2.45 (dt, 4H, ^2J 15 Hz, ^3J 7.5 Hz), 2.74, 3.22, 4.14 and 5.05 (dd, bispidine, 8H, ^2J 13.5 Hz, ^4J 2 Hz). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ: 14.13, 16.66, 22.70, 24.96, 29.72, 31.89, 33.15, 46.08, 53.49, 56.91, 172.45, 212.17. IR (ν/cm^{-1}): 1720 (C=O), 1650 (=N–C=O). Found (%): C, 76.61; H, 11.74; N, 4.61. Calc. for $C_{41}H_{76}N_2O_3$ (%): C, 76.34; H, 11.88; N, 4.34.

‡ A mixture of 11-bromoundecanoic acid (0.3 g, 1 mmol), 1-hydroxybenzotriazole (HOBt, 0.15 g, 1 mmol), DCC (0.23 g, 1 mmol), 1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one **3** (0.1 g, 0.5 mmol) and Et_3N (0.1 ml) in anhydrous CH_2Cl_2 was stirred for 2 days (TLC control). The mixture was washed with water, the water layer was separated and extracted several times with CH_2Cl_2, the combined extracts were dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel using chloroform as the eluent.

3,7-Bis(11-bromoundecanoyl)-1,5-dimethyl-3,7-diazabicyclo[3.3.1]-nonan-9-one **4**. Yield 64%, light yellow solid, R_f 0.81 ($CHCl_3$–EtOH, 50:1), mp 46–48 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.98 (s, 6H), 1.23 (m, 20H), 1.35 (m, 4H), 1.49 (m, 4H), 1.78 (m, 4H), 2.22 and 2.39 (dt, 4H, ^2J 15 Hz, ^3J 7.5 Hz), 3.35 (t, 4H, *J* 7 Hz), 2.76, 3.23, 4.13 and 5.05 (dd, bispidine, 8H, ^2J 13.5 Hz, ^4J 2 Hz). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ: 16.59, 24.85, 28.10, 28.69, 29.60, 32.77, 33.95, 45.98, 53.42, 56.84, 172.45, 212.12. Found (%): C, 56.34; H, 8.13; N, 4.28. Calc. for $C_{31}H_{54}N_2O_3Br_2$ (%): C, 56.19; H, 8.21; N, 4.23.

§ *Compounds* **5a**,**b** *(general procedure*). Sodium hydride (freed from mineral oil by washing with light petroleum, 0.025 g, 1 mmol) was added at 0 °C to a solution of compound **4** (0.2 g, 0.3 mmol) and imidazole (in the case of compound **5a**, 0.04 g, 0.6 mmol) or morpholine (in the case of compound **5b**, 0.05 g, 0.6 mmol) in THF under argon. The mixture was stirred for 1 day, then water was added and the mixture was extracted with diethyl ether several times. The combined extracts were dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel using chloroform and $CHCl_3$–EtOH (50:1) as the eluents.

3,7-Bis-[11-(imidazol-1-yl)undecanoyl]-1,5-dimethyl-3,7-diazabicyclo-[3.3.1]nonan-9-one **5a**. Yield 30%, light brown oil, R_f 0.45 ($CHCl_3$–EtOH, 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (s, 6H), 1.19 (m, 24H), 1.44 (m, 4H), 1.67 (m, 4H), 2.20 and 2.36 (dt, 4H, ^2J 15 Hz, ^3J 7.5 Hz), 3.83 (t, 4H, *J* 7 Hz), 2.65, 3.13, 4.03 and 4.94 (dd, bispidine, 8H, ^2J 13.5 Hz, ^4J 2 Hz), 6.82, 6.97 and 7.43 (s, 6H, imidazole). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ: 16.62, 24.89, 26.48, 29.31, 30.99, 33.09, 46.02, 53.42, 56.85, 128.28, 172.32, 212.12. HRMS (ESI), *m*/*z*: 637.4796 $[M+H]^+$ (calc. for $C_{37}H_{60}N_6O_3$, *m*/*z*: 637.4800).

3,7-Bis(11-morpholinoundecanoyl)-1,5-dimethyl-3,7-diazabicyclo-[3.3.1]nonan-9-one **5b**. Yield 40%, light brown oil, R_f 0.43 ($CHCl_3$–EtOH, 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02 (s, 6H), 1.25 (m, 24H), 1.45 (m, 4H), 1.52 (m, 4H), 2.30 and 2.42 [m, 16H, $CH_2C(O)$, $CH_2N(CH_2)CH_2$], 3.70 (t, 8H, CH_2OCH_2), 2.72, 3.19, 4.10 and 5.01 (dd, bispidine, 8H, ^2J 13.5 Hz, ^4J 2 Hz). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ: 16.62, 24.92, 26.21, 27.42, 29.48, 33.11, 46.03, 53.57, 56.86, 59.11, 66.65, 172.36, 212.10. HRMS (ESI), *m*/*z*: 675.5417 $[M+2H]^+$ (calc. for $C_{39}H_{70}N_4O_5$, *m*/*z*: 675.5405).