Lariat Ether Bola-amphiphiles: Formation of Crown Ether Based Bola-amphisomes

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The first crown ether-based bola-amphiphiles are prepared and are shown to aggregate into a previously unknown type of niosome.

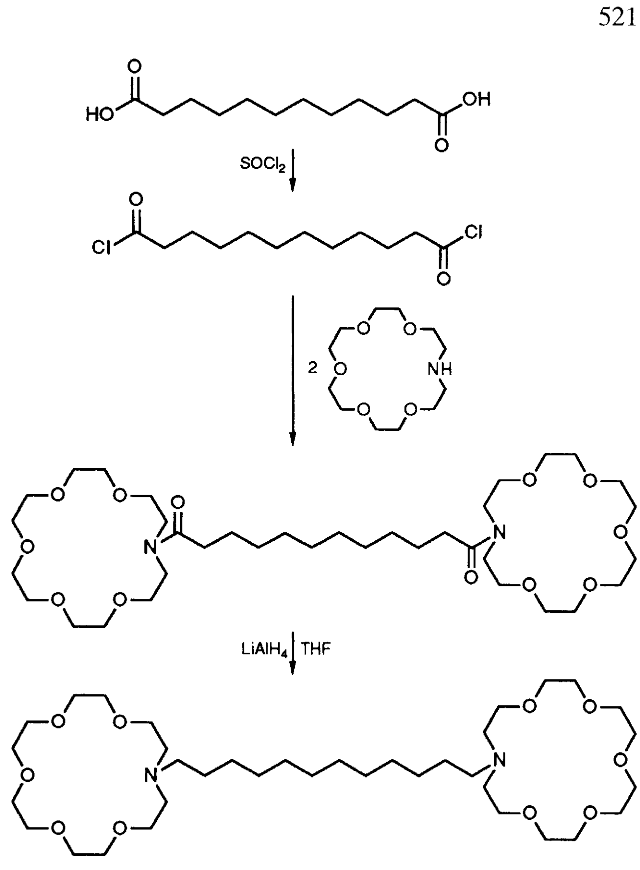
The lariat ethers[1] were designed originally to incorporate the binding dynamics of a crown ether with the three-dimensionality of cryptands[2] and thus be useful as trans-membrane carrier molecules. A branch of this effort sought to use the sidearms not as secondary donor groups but as non-polar sidechains in crown ether-based amphiphiles. Indeed, when aza-15-crown-5 was attached to either cholesterol or cholestanol *via* a glycine unit, these novel monomers formed niosomes (vesicles in which the amphiphiles are uncharged).[3] We now report a family of novel bis(crown) ether molecules that have the potential to form vesicles in which the two non-charged headgroups are linked covalently in the fashion originally

Table 1 Preparation of lariat ether bola-amphiphiles from aza-crowns[a]

Compound no.	Ring size	Spacer chain identity	Syn. proc.	Yield (%)	State or m.p./°C
1	15	$(CH_2)_{12}$	Alk	76	Oil
2	15	$(CH_2)_{16}$	Alk	78	65–66
3	18	$(CH_2)_{10}$	Alk	45	Oil
4	18	$CO-(CH_2)_{10}-CO$	Ac	79	Oil
5	18	$(CH_2)_{12}$	Ar	72	Oil
6	18	$CO(CH_2)_{11}S(CH_2)_{12}$-$S(CH_2)_{11}CO$	Ac	57	Wax

[a] All compounds are new and have IR and NMR spectra in accord with their assigned structures. Combustion analyses for **1**–**6** were within ±0.4% of the calculated value.

developed by Fuhrhop and coworkers[4] and named bola-amphiphiles or bolytes.† Two of the compounds prepared have been studied in detail and found to form the first example of niosomes arising from such monomers, *i.e.* bola-amphisomes. The reaction of an aza-crown ether with a diacid chloride [Cl–CO–$(CH_2)_n$–CO–Cl] affords a bola-amphiphile in which the crown is bound to the spacer chain by an amide link. Reduction of the bis(amide) to the tertiary amine affords a compound of the type crown–chain–crown. Alternatively, the bola-amphiphile can be prepared by direct alkylation of an aza-crown nitrogen atom with an α,Ω-ditosylate, TsO–$(CH_2)_n$–OTs. Both methods have been successfully utilized. The family of monomers can be varied easily by changing the spacer chain length and/or structure as well as by altering the structure of each crown. The compounds prepared for this study are recorded in Table 1.‡



Scheme 1

Compounds **1** and **5** were, in separate experiments, dispersed in water by ultrasonic irradiation at 10 °C. In each case, the resulting suspension was optically transparent. The hydrodynamic diameters of the aggregates were 730 Å [dynamic turbidimetry, 760 Å by transmission electron microscopy (TEM)] and ≈1200 Å (by either method) for **1** and **5**, respectively. A light scattering study of **5** (dispersed in water at 2.00 mmol dm^{-3} by mild ultrasonic irradiation) was undertaken. The turbidity was found to correlate linearly with the reciprocal square power of the wavelength in the range 420–600 nm. Extrapolation of the turbidance to infinite wavelength gave an intercept at ≈0 ± 0.003. The bolyte vesicles are clearly Debye scatterers.

The observation of Debye light-scattering profiles[5] defines several properties of the bolyte vesicles: (*i*) their linear dimension is large (comparable to the wavelength of incident radiation); (*ii*) they are spherical rather than rod-like or prolate spheroids; and (*iii*) their refractive index is small, nearly the same as that of the aqueous medium. Dynamic light scattering confirmed the large hydrodynamic radius (200 ± 60 nm) and TEM confirmed the spherical shape. The refractive index is similar to that of the solvent (*i.e.* relative refractive index ≈1); this is probably due to the low hydrocarbon density inside the ultrathin hydrophobic matrix.

In addition, dynamic turbidimetry as a function of isotonic dilution, and increasing temperature in acidic media, on a suspension of 1,12-bis(*N*-aza-15-crown-5)dodecane bola-amphisomes, suggests that the contribution of micelle–vesicle equilibria to the aggregation state of the bolyte surfactant is negligible. Thus, in neutral or slightly alkaline pH at 35 °C, it is observed that the vesicles grow irreversibly, to yield large (possibly multilamellar) aggregates.

Conversely, in acidic media at pH 2, the bola-amphisomes do not coalesce, even at 65 °C. The stability of aza-crown ether bola-amphiphilic vesicles in acidic media is attributed primarily to the cooperative formation of intermonomeric hydrogen-bonded domains along the *endo*- and *exo*-vesicular surfaces. The presence of hydrogen-bonded networks minimizes fusion events by inhibiting both vertical diffusion, thus intervesicular exchange of surfactant monomers, and transient lateral dissociation of the membrane, by which vesicles may rupture and subsequently reform to yield larger, heterogeneous, multilamellar organizates.[6]

Judging from Corey–Pauling–Koltun (CPK) atomic models, the conformation of **1** that appears most stable is fully extended. It is an interesting question whether the crown rings fold perpendicular to the spacer chain or partly extend into the aqueous layer that must be at the vesicular surface. In any event, the two-headed lariat ether compounds reported here are novel and versatile structures that form, in the two cases studied in detail, the first example of this class of amphisomes. Additional structures are in preparation and details of those structures and their aggregation behaviour will be reported in due course.

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† After the South American slingshot having two leather balls attached to a string.

‡ Preparation of **5**. A solution of $HOCO(CH_2)_{10}CO_2H$ (4.4 mmol) in $SOCl_2$ (2 ml) was stirred at reflux for 12 h. The excess of $SOCl_2$ was removed azeotropically (PhMe, 3 × 20 ml). Aza-18-crown-6 (2.28 g, 8.68 mmol) and Et_3N (8 mmol) in benzene (100 ml) was added (0–5 °C) to a vigorously stirred solution of diacyl chloride in benzene (100 ml) and then stirred at room temperature for 48 h. The salts were filtered, washed with CH_2Cl_2 (3 × 30 ml), evaporated, redissolved in CH_2Cl_2 (100 ml), washed with HCl (3 × 20 ml, 3 mol dm^{-3}), Na_2CO_3 (2 × 20 ml), H_2O (2 × 30 ml), dried, evaporated, and chromatographed over alumina to yield **4** (79%). ^1H NMR ($CDCl_3$): δ 1.2–1.8 (br s, 16H), 2.3 (m, 4H), 3.6–3.8 (m, 48H). Dioxobolyte **4** (1.72 g, 2.39 mmol) and $LiAlH_4$ (1.82 g, 47.9 mmol) in THF (500 ml) were vigorously stirred at reflux for 24 h. Workup followed by chromatography (alumina, 0–5% Pr^{i}OH–hexanes, then 0–2% MeOH–CH_2Cl_2) gave **5** (1.19 g, 72%) as a thick yellow oil. ^1H NMR ($CDCl_3$): δ 1.14–1.68 (br s, 20H), 2.3–2.52 (m, 4H), 2.76 (t, 8H), 3.48–3.76 (m, 40H).

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