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Autocatalytic ring opening of \(N\)-acylaziridines. Complete control over regioselectivity by orientation at interfaces

Peter J. J. A. Buijsters,ab Martinus C. Feiters,a Roeland J. M. Nolte,a Nico A. J. M. Sommerdijkac and Binne Zwanenburg

a Department of Organic Chemistry, NSR Centre, University of Nijmegen, Toernooiveld NL-6525 ED Nijmegen, The Netherlands. E-mail: N.Sommerdijk@tue.nl
b Department of Medicinal Chemistry, Janssen Research Foundation, Beerse, Belgium
c Laboratory of Macromolecular and Organic Chemistry, Eindhoven University of Technology, Eindhoven, The Netherlands

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Ring opening of 1-alkanoyl-2-phenoxymethylaziridines by phosphate ions yielding self-assembling phospholipid analogues proceeds in an autocatalytic fashion and with complete regioselectivity at an organic–aqueous interface.

Biological transformations are known to take place with high rates and high degrees of regio- and stereospecificities. This is achieved—amongst others—by positioning the reactants in a well defined manner with respect to each other, e.g. in the active site of an enzyme or at the surface of a biomembrane. Many model systems have been developed in order to mimic the supreme action of biomolecules. This has led to important improvements in conversion rates of molecules and in increased regio- and stereospecificities of their reactions. Of special interest in this respect are the autocatalytic and self-replicating biomimetic systems that have been reported in the literature. In the present communication we describe a reaction, i.e. the synthesis of chiral amide containing surfactants, which proceeds in an autocatalytic manner and with complete regioselectivity by orienting the reactants at an organic–aqueous interface.

The self-assembly of amide-containing phospholipid analogues (e.g. 2 and 3), has yielded a variety of interesting, and in many cases chiral, aggregate morphologies. Thus far these compounds have been prepared from enantiopure \(N\)-acylaziridines (1) via a nucleophilic ring opening with dibenzyl phosphoric acid in organic solvent (Scheme 1). However, in all cases this procedure led to the formation of the two regioisomeric products, i.e. compounds 2 and 3, in molar ratios ranging from 1:1 to 6:1. We hypothesised that in order to achieve a selective ring opening the \(N\)-acylaziridine molecules must be preorganised in such a way that only one of the ring carbon atoms is accessible to the nucleophilic species. It was anticipated that compound 1 would orient itself at an aqueous interface such that the C(1) carbon atom of the aziridine ring points towards the aqueous layer while the hydrophobic part of the molecule minimises its contact with water (Fig. 1a).

The ring opening of compound 1 was performed at 40 °C in a two phase system comprising an aqueous phosphate buffer (2.0 mM, pH = 7.0, 4.0 ml) and a top layer in which the starting material (9.0 \(\mu\)mol) is present as an oil. The progress of the reaction was conveniently monitored by determining the concentration of the aziridine in the aqueous phase using reversed phase HPLC. The generated products were analysed by capillary electrophoresis using a borate buffer containing \(\beta\)-cyclodextrin.

As an example the conversion of 1a \((R = C_{12}H_{25})\) to 2a is given. In the first 9 h of the reaction neither compound 1a nor any reaction products were detected in the aqueous phase, suggesting that at this stage the ring opening was slow since it could only take place at the oil–aqueous buffer interface. After this period vesicles with diameters of 75–350 nm were formed as was demonstrated by electron microscopy (Fig. 1b). Concomitant with the formation of the vesicles the concentration of 1a in the aqueous phase increased, suggesting that these vesicles facilitated the transfer of the \(N\)-acylaziridine to the water layer. The concentration of 1a in the buffer reached a maximum after 24 h (~25% of 1a in the aqueous phase). Thereafter, it decreased, and the reaction was completed after approximately 80 h. Increasing the buffer concentration to 10.0 mM led to an enhancement of the reaction rate (complete

Scheme 1: \(\text{cis-C}_{5}H_{10}\text{ClO}_{2}\text{P(O)OH}, \text{CH}_{2}Cl_{2}, \text{ii, H}_{2}, \text{Pd/C}, \text{iii: Dowex, Na}^+\) form.

Fig. 1 (a) Proposed mechanism for the regioselective ring opening of 1; (b) transmission electron micrograph of vesicles produced by ring opening of 1a (negative staining, bar represents 350 nm); (c) the conversion of 1a in the absence of preformed vesicles of 2a. Inset: idem, in the presence of preformed vesicles of 2a.
conversion after 24 h) indicating that the phosphate anions are the kinetically significant species. Capillary electrophoresis in combination with 1H NMR on authentic samples revealed that in both cases the reaction proceeded with complete regioselectivity (>99%), leading to the formation of the primary phosphate 2a exclusively. As outlined above this selectivity can be explained by attack of a phosphate ion on the C(1) ring carbon atom which is exposed to the aqueous phase due to orientation of the N-acylaziridine molecules at the interface. Activation of the aziridine ring most probably occurs through reversible protonation of the carbonyl group of 1a by protonated phosphate groups, either from the buffer or from previously generated molecules of 2a.

The sigmoidal conversion curve of 1a (Fig. 1c) suggests that the ring opening reaction is catalysed by the vesicles that are formed. Indeed, when the reaction was carried out in the presence of preformed vesicles prepared from phospholipid 2a (80 μmol in 4.0 ml 2.0 M phosphate buffer, pH 7.0), the reaction was complete in 20 min (Fig. 1c). The high concentration of the N-azacylaziridine detected in the aqueous phase (~95% after 2 min) supports the proposed dissolution of 1a in the bilayers of the vesicles. When incorporated within these aggregates the hydrophobic alkyld chain will minimise the contact with water by dissolution in the hydrophobic interior of the membrane, leaving the amide carbonyl group of 1a and consequently also the C(1) ring carbon atom oriented towards the aqueous phase (Fig. 1a).

Similar results are obtained when N-acylaziridine 1b (R = C₈H₁₇) was used. Interestingly in this case, upon standing for approximately a week, the vesicles formed from compound 2b slowly converted into flat multilayer ribbons (Fig. 2a). It was found that these ribbons rolled up to form tubuli under conditions that lead to compensation of the head group charge of the lipid, e.g. at low pH or in the presence of alkali and transition metal ions (e.g. Ca²⁺ and Fe²⁺ ions). Remarkably, the aggregate dimensions did not depend on the conditions used: tubuli of micrometer length and diameters between 20 and 40 nm were generated after lowering the pH to 2.5, after adding calcium ions at pH 5.6 (Fig. 2b) or after exposing the solution to ferric ions at pH 11 (Fig. 2c).

In conclusion, we have shown that the ring opening of the long tail aziridines 1 by phosphate ions at an organic–aqueous interface exclusively leads to the formation of the primary phosphates 2. The self-assembling properties of these compounds facilitate further conversion of the starting material without compromising the selectivity of the reaction and, ultimately, under the appropriate conditions lead to the formation of well-defined self-assembled objects. A detailed investigation of the autocatalytic nature of the system and possible applications are in progress.

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Notes and references

1 For synthetic procedures and for the physical data of 1–3b see reference 5. (–)-25-(1-Dodecanoyl-2-phenoxycyclohexylidene)-2-phenoxycyclohexylidene, 1a: mp 34.6 °C; [α]D₂₀ ⁰ −45.5 (c 1.0, CHCl₃); Calc. for 1a (C₃₂H₃₈NO₄) 76.09, H 10.03, N 4.23. Found: C 75.95, H 9.96, N 4.25%; m/z (FAB MS): 495 [M + Na]⁺, 332 [C₁₀H₈NO₄]⁻, δ₁₁(CDC₁₂), 0.88 (t, J = 6.8 Hz, 3H, CH₃), 1.25 [m, 16H, CH₂(C₂H₅)], 1.65 [m, 2H, CH₂CH₂C(O)], 2.22 (d, J = 3.3 Hz, 1H, NCHO), 2.52–2.42 [m, 3H, NCH₂ and CH₂(C₉H₇)], 2.86 (m, 1H, NCH), 3.99 (dd, J = 6.1, 10.4 Hz, 1H, CH₃COCH₃), 4.13 (dd, J = 10.4, 4.3 Hz, 1H, CH₂COCH₃), 6.89–7.32 (m, 5H, C₆H₅) (→)-Dsidium (2R)-3-phenoxycyclohexylidene-1-y1 phosphate, 2a: mp 125–128 °C; [α]D₂₀ ⁰ −33.4 (c 1.1, CHCl₃); Calc. for 2a (C₃₁H₃₅NO₃P₂H₂O) 49.51, H 7.12, N 2.75. Found C 49.47, H 7.15, N 2.80%. (+)-2(2-Dodecanoylamino)-1-y1 phosphate, 3a: mp 129–131 °C; [α]D₂₀ ⁰ +15.4 (c 1.0, CHCl₃); FAB MS [m/z]: 495 [M + Na]⁺, 474 M + 1⁺. Calc. for 3a (C₃₂H₃₈NO₄P₂) 368.85, H 7.58, N 2.70. Found C 46.67, H 7.60, N 2.73%. The enantioemic purities of the starting aziridines used were >95% as determined from NMR analysis of (→)-camphoramide derivatives of both the enantiopture aziridine and the racemate. No loss of enantioemic integrity during ring opening (either in organic solvents or at organic aqueous interfaces) was observed when comparing enantiomerically pure and racemic compounds.

2 The concentration of 1 in the aqueous phase was determined using a RP18 reversed phase column, UV detection at 280 nm and a mobile phase of acetonitrile–phosphate buffer [2 mM, pH = 7.0, 9:1 (v/v)]. Samples (25 μl) of the aqueous phase were diluted with acetonitrile (225 μl) before analysis.

3 The regioselectivity of the reaction was determined by capillary electrophoresis (30 kV, 10 °C; UV detection at 280 nm) using a buffer (Na₂HPO₄–NaH₂PO₄ 50 mM, pH = 9.3) containing 26.7 mM 5-s-cyclodextrin to avoid aggregate formation. Samples (25 μl) of the aqueous phase were diluted with sodium borate buffer (150 μl). From authentic samples the retention times of 2 and 3 were determined.


