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

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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.1 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 autocatalytic2 and self-replicating3 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.4 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 6:1.5 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 µmol) 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.4 The generated products were analysed by capillary electrophoresis using a borate buffer containing β-cyclodextrin.§

As an example the conversion of 1a (R = C12H25) 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: (C6H6CH2O)2P(O)OH, CH2Cl2, ii, H2, Pd/C, iii: Dowex, Na+ form.

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C17H35) was used. Interestingly in this case, upon standing for aggregates the hydrophobic alkyl chain will minimise the bilayers of the vesicles. When incorporated within these the aqueous phase (Fig. 1a).

The sigmoidal conversion curve of 1a (Fig. 1c) suggests that the ring opening reaction is catalysed by the vesicles that are 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 mM phosphate buffer, pH 7.0), the reaction was complete in 20 min (Fig. 1c). The high concentration of the N-acylaziridine 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 alkyl chain will minimise the contact with water by dissociation 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 = C6H5C=O) 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 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.

The authors thank B. Martens for performing HPLC and Capillary Electrophoresis experiments.

Notes and references

1. For synthetic procedures and for the physical data of 1–3b see reference 5. (a) 25-1-Dodecanoylaminopropan-2-yl phosphate, 3a

2. 2-(Dodecanoylamino)propan-2-yl phosphate, 3a

3. -Disodium (2)-3-phenoxy-2-dodecanoylamino propane-1-yl phosphate, 2a

4. Ribbons in 2.0 mM phosphate buffer pH 7.0; (b) tubes in aqueous 9 mM CaCl2 (pH 7.0); (c) rods mineralised in a solution containing 1 mM FeSO4·KNO3 adjusted to pH 11. Bars represent 250 nm.

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.

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Similar results are obtained when N-acylaziridine 1b (R = C6H5C=O) 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 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).

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Similar results are obtained when N-acylaziridine 1b (R = C6H5C=O) 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 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).