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Temperature regiocontrol of intramolecular cyclization of di-hydroxysecoacids†

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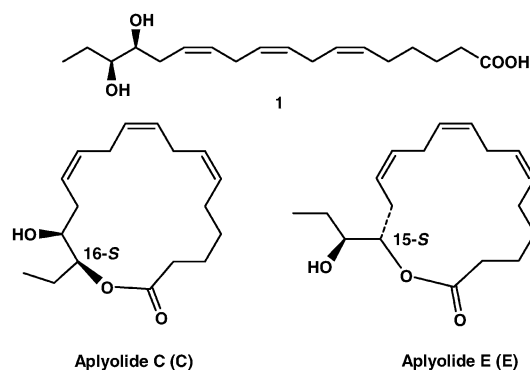
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The synthesis of macrocycles from acyclic precursors is an important reaction class for both the realization of size-designed cavities to be used as building blocks in supramolecular chemistry and for the synthetic production of natural substances with pharmacological activity, the case of several macrolactones (macrolides), occurring in a wide variety of ring sizes.¹

Although there is a large amount of literature on macrocyclization, most work has been concerned with the effect of acyclic precursor concentration on the yields of the competitive intramolecular and intermolecular reactions,^{1–4} so that little is yet known about the factors which play a role in controlling the ring size of macrocyclization products when competitive intramolecular cyclization pathways are available. Only a few selective macrocyclizations of di- or tri-hydroxyacids without protection have been reported in the literature,⁵ but in these cases selectivity is achieved because of the very different sizes of the rings which can be formed, as discussed in several seminal papers.^{3,4}

In this communication we report results concerning the macrocyclization of (15*S*,16*S*)-15,16-dihydroxy-octadecyl-(6*Z*,9*Z*,12*Z*)-trienoic acid (**1**), leading to Aplyolide **C** (**C**) and Aplyolide **E** (**E**),⁶ showing that the reaction occurs under thermodynamic control and that the relative yields of the two products depend on the reaction temperature to such an extent that an efficient regiocontrol can be obtained by simply changing the reaction temperature, notwithstanding the similar size of the two cycles.



When synthesized according to the standard Yamaguchi procedure ($T = 383\text{ K}$)⁷ from **1**, see Supporting Information,† **C** and **E** are obtained with a total yield of 80%, in the ratio of 1.68 : 1.00, respectively.⁸ That ratio is possibly temperature-dependent, because, from the data reported in the literature for macrocycles with 12–20-membered rings, both ring strain and conformational entropy loss are expected to play a role in regulating the relative abundance of the products.^{3,4} Guided by this, and by quantum mechanical computations which pointed out that the formation of the smaller ring **E** should be preferred

Table 1 Relative yields of **C** and **E** at different reaction temperatures in toluene

$T/\text{K} (\pm 1)$	439 ^a	383	363	343	323	303
$[\text{C}]/[\text{E}]$	1.92	1.68	1.54	1.18	1.04	0.80

^a In mesitylene solution.

at $T = 0\text{ K}$, *vide infra*, we addressed the possible dependence of the yield ratio on the reaction temperature. This expectation was confirmed by experimental results: in Table 1 the relative yields of **C** and **E** obtained at different temperatures in the range 300–440 K are reported. At $T = 323\text{ K}$, **C** and **E** are obtained in nearly the same amount and at lower temperatures **E** becomes the most abundant product.

To our knowledge, this is the first example in the literature of an efficient temperature regiocontrol of a di-hydroxy-secoacid macrolactonization.

In order to better rationalize the above data, we have first addressed the question of whether the yield distribution of **C** and **E** is under kinetic or thermodynamic control. The purified **C** product was therefore put in a dry toluene solution containing trichlorobenzoic acid and 4-(dimethylamino)pyridine in the same concentrations as used in the Yamaguchi cyclization; at $T = 323$ and 363 K . After 20 h, both **C** and **E** were present in solution in nearly the same ratio as that obtained from **1**. Thus the cyclization of **1** is a reversible reaction under thermodynamic control. The plot of $\ln K$ versus $1/T$, for the equilibrium



yields a straight line (Fig. 1) whose least-squares analysis leads to $\Delta H = 2.2 \pm 0.2\text{ kcal mol}^{-1}$ and $\Delta S = 6.7 \pm 0.5\text{ cal mol}^{-1}\text{ K}^{-1}$ (the errors are estimated standard deviations).

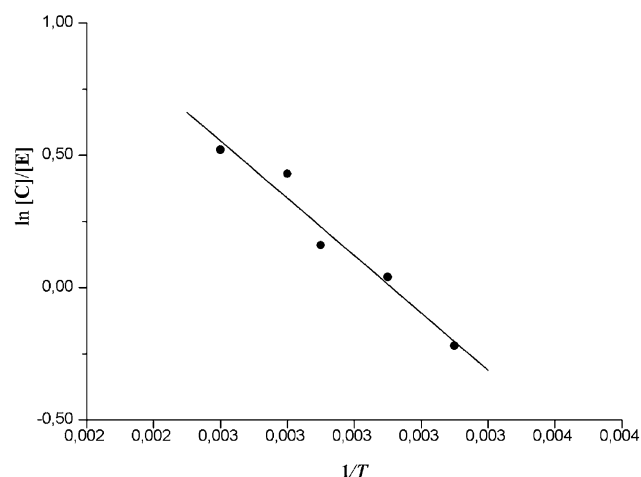


Fig. 1 Plot of $\ln K$ versus $1/T$ for the equilibrium $\text{C} \rightleftharpoons \text{E}$.

The experimental value of ΔH is in line with the computed internal energies, *vide infra*, assigning to cycle **C** a comparatively

† Electronic supplementary information (ESI) available: synthetic and analytical procedures, computational methods, conformational geometries. See <http://www.rsc.org/suppdata/ob/b4/b413564d/>

Table 2 Energies (E), entropies (S_0) and free energies (G_0) of the most stable conformers of **E** and **C**

Conformer	Class	DFT			Molecular mechanics		
		$E/\text{kcal mol}^{-1}$	$G_0/\text{kcal mol}^{-1}$	$S_0/\text{cal mol}^{-1} \text{ K}^{-1}$	$E/\text{kcal mol}^{-1}$	$G_0/\text{kcal mol}^{-1}$	$S_0/\text{cal mol}^{-1} \text{ K}^{-1}$
E1	I	0	0	0	0	0	0
E2	III	4.5	3.1	3.6	2.3	1.6	1.4
C1	I	0.6	0.2	0.6	4.6	3.9	1.9
C2	II	1.8	0.1	4.4	4.6	2.2	6.7
C5	III	4.4	3.4	3.1	7.2	6.2	2.7

larger strain energy. The origin of the entropic contribution favouring **C** at higher temperatures can be assigned both to the number of accessible conformers of **C** and **E** as well as to intramolecular vibrational contributions associated with peculiar structural features of the two rings. As a first step, we have therefore selected the whole set of accessible conformers of **C** and **E** by using the rotational isomeric state (RIS) method (see Supporting Information for more details).⁹ About half a million (4.7×10^5) conformers of **1** were generated and those satisfying the geometric constraints for ring closure were selected and analyzed. As far as the number of accessible conformers is concerned, the RIS method yields a slight preference for ring **C**, the ratio of the partition function of **C** and **E** is 1.81 at 298 K. The energies given by the RIS method are not accurate enough for discussing the equilibrium (eqn. (1)). We have therefore optimized the geometry of the conformers selected by RIS, both by using molecular mechanics (Merck force field) and density functional theory methods (B3LYP/6-31G); only the conformers with the ending ethyl group in the T conformation were considered in these computations. It must be remarked that the known accuracy of both computational methods does not allow for a quantitative treatment of the equilibrium (eqn. (1)), but it is certainly sufficient for understanding the chemical factors which can play a role. Both computational methods yield very similar results, which can be summarized as follows:

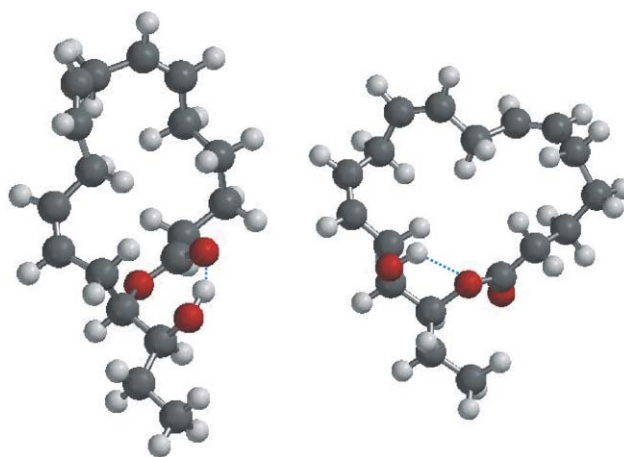
(i) The optimized conformers can be grouped in three classes, in class I there are the conformers characterized by a strong intramolecular H-bond between the hydroxyl proton and the carbonyl oxygen, in class II those exhibiting a weak intramolecular H-bond between the hydroxyl proton and the ester oxygen, and in class III the conformers with no intramolecular H-bonds.

(ii) The conformers belonging to class I exhibit a lower internal energy with respect to those of the other classes, but because of the strong H-bond, their vibrational entropy is significantly lower.

The geometries of the lowest free energy conformers **E1** and **C2** optimized at the DFT level of computation are shown in Fig. 2.

The existence of intramolecular H-bonds was experimentally confirmed by narrow bands observed in the IR spectra of **C** and **E**, centered at 3617 and 3588 cm^{-1} , respectively.

The computed internal energies, Gibbs' free energies (G_0) and entropies (S_0) at $T = 298 \text{ K}$ are reported in Table 2 for the lowest energy conformers. At $T = 298 \text{ K}$, the lowest free energy conformer is one of **E** belonging to class I (**E1**), but because of the higher entropic term, the conformer **C2** falls nearly at the same Gibbs' free energy, even though its internal energy is higher than that of **E1** by 1.8 kcal mol^{-1} . Thus **C2** is the most stable conformer at $T = 550 \text{ K}$, in line with the experimental results. When both the conformational and the vibrational entropy are considered, the inversion of the relative stability of **C** and **E** is predicted to occur at $T = 220 \text{ K}$, suggesting that both contributions play a role. The results of molecular mechanics computations exhibit the same trend as DFT computations, even though the internal energies of the **C** conformers are predicted to be significantly higher than those of **E**, so that the inversion of the relative stability is predicted at higher temperatures.

**Fig. 2** Optimized DFT geometries of conformer **E1** (left) and **C2** (right). Hydrogen bonds are displayed as blue dashed lines.

In summary, for **1**, a simple and efficient regiocontrol of the macrolactonization reaction can be obtained by controlling the reaction temperature. In fact, while energetic factors favour the formation of the smaller ring, entropic factors drive the cyclization toward the formation of the larger ring. There are two different physico-chemical factors which contribute to the entropic term: the higher number of conformers of the larger ring and vibrational contributions arising from low frequency modes. Work aimed to better elucidate the relative weight of these two factors is in progress.

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References

- S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders and J. F. Stoddart, *Angew. Chem. Int. Ed.*, 2002, **41**, 898–952.
- H. J. Jacobson and W. H. Stockmayer, *J. Chem. Phys.*, 1950, **18**, 1600–1606; H. J. Jacobson, W. H. Stockmayer and C. O. Beckmann, *J. Chem. Phys.*, 1950, **18**, 1607–1612.
- C. Galli, G. Illuminati, L. Mandolini and P. Tamborra, *J. Am. Chem. Soc.*, 1977, **99**, 2591–2597; G. Illuminati and L. Mandolini, *Acc. Chem. Res.*, 1981, **14**, 95–102; L. Mandolini, *Adv. Phys. Org. Chem.*, 1986, **22**, 1–111.
- A. Dalla Cort, G. Ercolani, A. L. Iamiceli, L. Mandolini and P. Mencarelli, *J. Am. Chem. Soc.*, 1994, **116**, 7081–7087.
- I. Paterson, *Angew. Chem. Int. Ed.*, 2002, **41**, 4632–4653; A. F. Petri, S. M. Kuhnert, F. Scheufler and M. E. Maier, *Synthesis*, 2003, **6**, 940–955 and references therein.
- A. Spinella, E. Zubia, E. Martinez, J. Ortea and G. Cimino, *J. Org. Chem.*, 1997, **62**, 5471.
- M. Yamaguchi, J. Inanaga, K. Hirata, H. Saeki and T. Katsuki, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989–1993.
- T. Caruso and A. Spinella, *Tetrahedron: Asymmetry*, 2002, **13**, 2071–2073.
- P. J. Flory, *Statistical Mechanics of Chain Molecules*; Wiley-Interscience, New York, 1969.