Conformational Preferences next to the *trans* Ester Group

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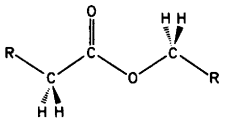
A survey of published crystal structures of simple acyclic esters shows that the favoured conformation next to the *trans*-ester group is *anti* both on the carbonyl side and on the alkoxy side. A survey of our own and reported crystal structures of macrocyclic oligolactones and oligoesters reveals a second conformational minimum which is *gauche* (~ 60°) on the carbonyl side, but *orthogonal* (80–90°) on the alkoxy side. The unusual value of the latter is attributed to steric hindrance involving the carbonyl oxygen. Both torsional minima are, however, shallow and barriers low.

The much higher stability of the planar *trans* configuration of the ester group than of the *cis* configuration is well established.[1,2] To the best of our knowledge, the *cis* configuration has never been encountered in acyclic esters,[3] but only in lactones of small or normal ring size. In 8- and 9-membered lactones, it occurs in competition with the *trans* configuration[1], which is then, presumably, markedly nonplanar. In macrocyclic lactones and oligoesters, the ester group is always planar *trans*, as discussed in the preceding paper.

Much less is known about the more subtle conformational preferences in the single bonds next to the ester group on either side. If the classical mesomeric structure *1* were the dominant one, it would be expected that an *anti* CH_2CH_2 unit of an alkane chain is simply replaced by the *trans* ester group, leading to preferred torsion angles of ±60



and 180° on the carbonyl side ($-CH_2-\overset{\overset{O}{\|}}{C}-$) and on the alkoxy side ($-O-CH_2-$). If, on the other hand, the "olefinic" mesomeric structure *2* with charge separation were dominant, torsional minima at ±120 and 0° would be expected. Intermediate mesomeric situations should tend to cancel any torsional minima and barriers.

Fig. 1. Conformations expected for the *trans* ester group assuming two extreme mesomeric situations.

Acyclic esters

There are not many reported crystal structures of simple acyclic esters with CH_2 next to the ester group on *both* sides. Ethyl stearate[4], propyl stearate[5], ethyl triiodothyropropionate[6] and benzoylleucylglycine ethyl ester[7] all have a stretched chain with *anti* conformation on both sides of the *trans* ester group, thus confirming the dominance of formulation *1*. On the other hand, there are a large number of reported crystal structures for ethyl esters of carboxylic acids of more complicated chemical structure, the majority of which show the same *anti* conformation of the $-O-CH_2-$ bond. In ~25% of the cases, however, an alternative conformation was found which is clearly not *gauche*, but rather *orthogonal*, and only these will be quoted here. For the ethyl ester of a leucine derivative[8], the torsion angle is given numerically as 80°. For ethyl esters of derivatives of phenylglycine,[9] phenylalanine,[10]

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triphenyl-1,2-diazetidine-3-one-carboxylic acid[11], and acrylic acid[12] the angle can be estimated visually from published drawings to be in the range 80–90°. This torsion angle is remarkably close to 85° as found by microwave spectroscopy[13] for the second torsional minimum of ethyl formate in the gas phase. It is only very slightly higher in energy than the *anti* minimum and separated from it by a barrier of only 1.2 kcal/mol. The large torsion angle of 85° was attributed to steric repulsion between the carbonyl oxygen and the methyl group, with an estimated *syn* barrier as high as ~5 kcal/mol.[13] Actually, the energy varies by only about 1 kcal/mol in the continuous range of torsion angle values from 60 to 180°, and this is in good agreement with an earlier complete analysis of X-ray structural data for esters of primary alcohols.[3] Interestingly, the same analysis of crystal structures for esters of secondary alcohols[3] reveals torsion angles from 60 to 120° (180 to −120° for the other carbon atom) with a preference for ~85° (~−155°). No microwave data seem to be available for esters having an ethyl group on the carbonyl side (= propionates). There is however no reason why a second minimum should here be different from 60°, since a corresponding repulsion is not present.

Macrocyclic esters and lactones

Macrocyclic esters and lactones* are particularly well suited for a study of this problem since such rings must have $g\pm g\pm$ corners or $g\pm$ bends.[15] The bonds next to the ester function may therefore be compelled to populate alternative torsional minima. Fortunately, macrocyclic oligolactones and oligoesters are most often crystalline substances, whereas the simple acyclic esters are most often liquids. Recently, several macrocyclic oligolactones were prepared (preceding paper), and their crystal structures have been determined. They revealed a general pattern and will now be discussed together with published crystal structures of related macrocyclic compounds.

The central compounds are the trimer[16] and the tetramer[17] of 3-propanolide (β-propiolactone), the dimer[18] and trimer[18] of 5-pentanolide (δ-valerolactone), and the dimer[19] of 6-hexanolide (ε-caprolactone). All torsion angles are given in Fig. 2 directly on bird's-eye-view projections of their crystal conformations. Torsion angles connected with the *trans*-ester groups are arranged in Table 1 according to type and together with additional data for relevant compounds not shown in Fig. 2.

The most significant structure is that of the *14-ring dilactone* (Fig. 2a). For the corresponding cycloalkane, a single, perfect, strain-free, diamond lattice conformation [3434] is uniquely defined. It has four "corners", each with two adjacent *gauche* bonds of the same sign.[15] The fact that the 14-ring dilactone adopts exactly this conformation[19] suggests that it is description *1* of the ester group which is basically correct and not *2*. A most interesting aspect is the choice of location for the *trans* ester groups. The original proposal[14] was that they should be in the short "sides" with oppositely oriented ester dipoles (Fig. 3a). However, there are altogether three possible locations as shown in Fig. 3, and all give antiparallel dipole orientation. It is very significant that a single location is chosen instead of a statistical distribution. To rationalize this, the following three factors are of importance:

1. Only the choice of *anti* conformation for the $-O-CH_2-$ bond is compatible with a diamond lattice; an *orthogonal* one is sufficiently different from *gauche* to destroy this perfect cyclic skeleton.
2. The carbonyl oxygen enters into a serious steric conflict with a CH_2 hydrogen only when it is β to a corner (Fig. 3*a* and *b*), not when it is α (*c*).
3. Favourable interactions can occur between the alkoxy oxygen and *gauche*-related CH_2 hydrogens across corners. Such interactions are clearly stabilizing in analogous macrocyclic ethers[20,21] and formals.[22,23] In *a* and *c* there are four of these; in *b* only two.

Also of prime significance is the structure of the *12-ring dilactone* (Fig. 2b). The unique quadrangular non-diamond lattice conformation [3333] for the corresponding cycloalkane[15,24] has four equivalent "sides", so that there is only one location for the *trans*-ester groups. This should lead to parallel orientation of the ester dipoles, which is exactly what is found.[18] Furthermore, the carbonyl groups must now be β to corners, and the expected *orthogonal* torsion angles are observed in the two alkoxy bonds. All four *anti*

* Only compounds derived from hydroxy acids (like lactic acid) can properly be called lactones. Compounds prepared from dicarboxylic acids and diols should be called cyclic esters.[14]

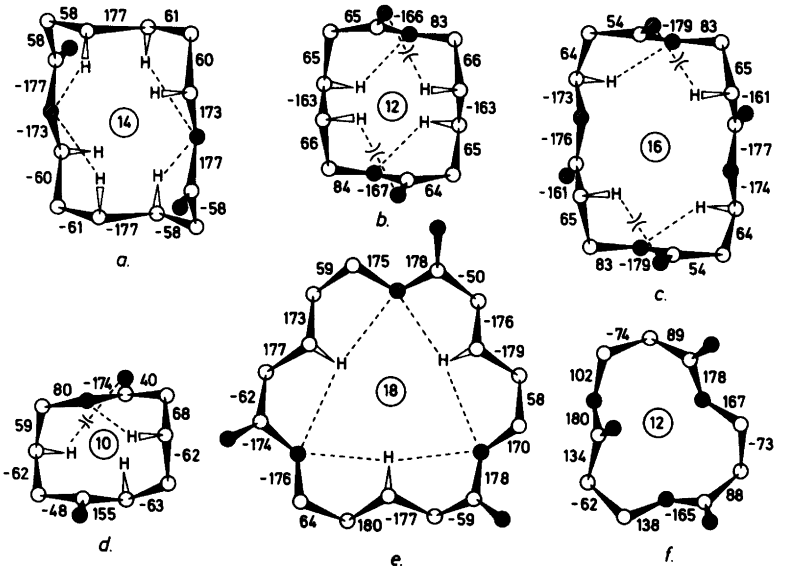

Fig. 2. Crystal conformations of macrocyclic lactones. External CH_2 hydrogens are omitted. Oxygen atoms are shaded. Symbol ----) (---- stands for repulsive and ------- for attractive interactions. Ring size (in circle) and skeletal torsion angles are indicated.

bonds have torsion angles considerably smaller than 180°, which is quite general for 12-membered rings, for example the parent hydrocarbon cyclododecane.[24] The resulting deviation from planarity of the ester groups may explain the higher enthalpy of this dimer, when compared with the trimeric homologue (Fig. 2e), as was deduced from the equilibrium composition (preceding paper).

The *16-ring tetralactone* (Fig. 2c) has a closely related non-diamond lattice conformation [3535].[17] Two diametric ester groups, located in the short sides with dipoles in parallel orientation, have a large *gauche* angle on the alkoxy side and a normal *gauche* angle on the carbonyl side. The other two diametric ester groups are on the long sides, also parallel to each other, but pointing in the opposite direction and have *anti* conformation on either side. One might ask why the alternative diamond lattice ring conformation [4444], as found in the corresponding tetraether,[21] is not chosen. The two *orthogonal* torsion angles would then be *anti* (and two *anti* bonds on the carbonyl side regular *gauche*). The answer is probably that the [3535] conformation is more compact and suitable for crystal packing. Nevertheless, a very recent crystal structure determination of the terpene alkaloid chaksine[25] reveals a tetrasubstituted 16-ring dilactone with a perfect [4444] conformation analogous to the 14-ring dilactone (Fig. 2a), but with an extra CH_2 in each short side. Here of course the four substituents gain more space by occupying corner positions, and the actual substitution pattern fits exactly the [4444] but not the [3535] conformation.

The *18-ring trilactone* (Fig. 2e) adopts a diamond lattice conformation[18] of another type, without "corners", found in cation complexes of 18-crown-6.[15] The three ester groups are virtually identical, with a perfect *anti* torsion angle on the alkoxy side and a perfect *gauche* torsion angle on the carbonyl side. Although no "corners" can be defined, the same stabilization is achieved here as in the 14-ring by six oxa-hydrogen interactions (Fig. 2e). This is not possible with any other location of the ester groups on this skeleton. The perfect planarity of the ester groups supports the explanation given earlier for the lower enthalpy of this trimer when compared with the related dimer (Fig. 2b).

The structure of the *12-ring trilactone* (Fig. 2f) is an unusual case because the three ester groups are very different, having deviating torsion angles on one or both sides.[16] Of course, the constraints of this ring size make it impossible to fit the chemical topology on a reasonable low-energy cyclododecane conformation.[15] What this variety of observed torsion angles actually implies, then, is that the energy minima are shallow and barriers between them low. Furthermore, since *all-trans*-cyclododeca-1,5,9-triene has a

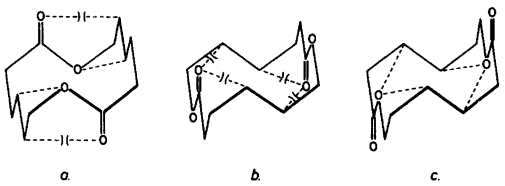

Fig. 3. The three possible ways of accommodating the *trans*-ester groups of 6-hexanolide dimer on a cyclotetradecane skeleton.

strain-free conformation with torsion angles near 120° next to all double bonds,[26] the observation that the present trilactone shows no inclination to follow such a pattern can be taken as an argument against the importance of the mesomeric description *2* for the *trans* ester group.

A *10-ring lactone,* 6-oxo-9-nonanolide, has also been included in Fig. 2 (*d*). Although it is a 10-membered ring with its inherent severe constraints, the crystal structure[27] reveals that it adopts basically the same diamond lattice conformation as cyclodecane, with the *trans* ester group striving towards planarity, but in an unsymmetrical fashion. This produces a wider torsion angle on the alkoxy side, and a rather narrow angle on the carbonyl side. Of course, the carbonyl oxy-

Table 1. Torsion angles in *trans* ester groups $-CH_2-\overset{\overset{O}{\|}}{C}-O-CH_2-$ from crystal structures of macrocyclic lactones and esters.

	Ring size	Number of ester groups	Torsion angles						Ref
			$-CH_2-\overset{\overset{O}{\|}}{C}-$			$-\overset{\overset{O}{\|}}{C}-O-$	$-O-CH_2-$		
6-Hexanolide dimer	14	2	58			−177	−173		19
5-Pentanolide dimer	12	2	65			−166		83	18
			64			−167		84	
5-Pentanolide trimer	18	3	59			−178	−170		18
			50			−178	−175		
			62			174	176		
3-Propanolide trimer	12	3	89			178	167		16
			88			−165	138		
				134		180		99	
3-Propanolide tetramer	16	4		161		177	174		17
			54			−179		83	
2,6-Disubstituted 7-heptanolide dimer (chaksine iodide)	16	2	57			−174	178		25
6-Oxo-9-nonanolide	10	1	40			−174		80	27
Ethylene pentanedioate dimer	18	4		173		−174	−171		30
				141		−175		106	
Ethylene hexanedioate dimer	20	4		169		174	154		30
			31			177	162		
Ethylene nonanedioate dimer	26	4		179		179	179		30
				142		−174		110	
Propylene heptanedioate dimer	22	4		171		176	−179		32
				120		−177	135[a]		
Nonactin (free ligand)	32	4	66[a]			−178	161[a]		28
			78[a]			−177		78[a]	
Nonactin (K^+complex)	32	4		151[a]		178		117[a]	28
				146[a]		177		115	
6,8-Dioxabicyclo [3.2.1]octan-7-one dimer	10	2	37[b]			−165		75[b]	29
6,8-Dioxabicyclo [3.2.1]octan-7-one tetramer	20	4		172[b]		−172		88[b]	29

[a] $-CH(CH_3)-$ instead of $-CH_2-$.
[b] $-CH(CH_2-)$ instead of $-CH_2-$.

gen interacts not only with the 8-hydrogen, but also with the transannular 5-hydrogen. Nevertheless, the structure strongly suggests that this will also be the conformation of the unknown 10-ring dilactone (4-butanolide dimer).

The same basic features, a normal *anti-gauche* situation on the carbonyl side and an *anti-orthogonal* situation on the alkoxy side, can also be recognized in published crystal structures of more complex macrocyclic oligolactones having annelated small rings (Table 1). Because of the particular restrictions of the annelated structure and the presence of several chiral centers, these examples do not warrant a detailed discussion. Suffice it to note that in free nonactin[28], relatively normal torsion angle values are observed, while more unusual angles are adopted in the complexed state.[28] Of significance also is the fact that the main macrocycle of both the dimer and the tetramer of 6,8-dioxabicyclo[3.2.1]octan-7-one have diamond lattice conformations[29], even though this requires that the resulting cavity of the latter be filled with a molecule of acetonitrile.

Finally, the crystal structures (Table 1) of a series of macrocyclic tetraesters prepared from ethylene glycol and dicarboxylic acids[30] reveal two essentially parallel chains connected with shorter bridges similar to the tetralactone shown in Fig. 2c. The ester groups on the long sides have a normal environment *(anti, trans, anti)*, but those on the short sides have unusual torsion angles whose numerical values depend on whether the number of CH_2 in the dicarboxylic acid component is odd or even. The special structural unit here, $-O-CH_2CH_2-O-$, is invariably *gauche,* as in polyethers of ethylene glycol where the strong preference of the 1,4-dioxa unit for *anti, gauche, anti* has long been recognized.[31] This seems to be a dominating feature that forces the bridge ester groups to relax their requirements. An analogous tetraester from propylene glycol has a similar conformation.[32] A 12-ring diester structure has been found for jacobine bromohydrine,[33] but the ring is too heavily strained by fusion with two 5-membered rings to justify a discussion.

Conclusion

Although Table 1 reveals a clear preference for normal *anti* and *gauche* conformation in the single bond next to the carbonyl group of *trans* esters, and a preference for *anti* and *orthogonal* in the alkoxy bond, the potential minima are shallow, and departures from ideal torsion angle values do not require much energy.

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