

Short Communications

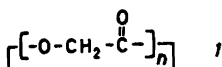
Cyclic Oligo-esters of Glycolic Acid

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Cyclic oligo-peptides of the simple α -amino acids have been studied extensively. Thus, from *N*-methylglycine (sarcosine) cyclic peptides of any ring size can be synthesized.^{1,2} The energies of *cis*- and *trans*-*N*-methyl amide groups are similar, and for each ring a characteristic *cis,trans* sequence has been observed^{1,2} which is in no case all-*trans*, not even for cyclodecasarcosyl. Cyclic tetra- and hexapeptides of glycine had been prepared even earlier,³ but attempts to synthesize cyclo-triglycyl led to doubling. This is most likely due to the well-established *trans* preference of the NH amide group,⁴ which is also demonstrated by the absence of any indication of *cis* amide groups in cyclohexaglycyl. Cyclo-tetraglycyl on the other hand exists in two different crystal forms having different IR spectra,⁵ hence different conformations; the one chosen in solution has the amide sequence *cis,trans,cis,trans*.⁵

It was now of interest to examine the situation in cyclic oligoesters I of the simplest α -hydroxy acid, glycolic acid.



No member of this series higher than the diglycolide ($n=2$, often simply called "glycolide") has been reported.⁶ A synthetic approach meets with difficulties because of the narrow margin between the stability of the ester group and the available protecting and activating groups necessary for a systematic synthesis and final cyclization. Direct isomerization of the diglycolide by catalytic systems providing no permanent end groups, such as gaseous BF_3 , seemed to offer an alternative, since the imposed *cis* ester configuration in the diglycolide might be expected to constitute a sufficient driving force on the basis of the known⁷ *trans* preference of the ester group in open chains and lactones larger than nine ring members. In methyl acetate⁸ the *cis*

configuration is in fact higher in energy by as much as 18 kJ mol^{-1} . However, in no case could we obtain any higher cyclic oligomers, and when new compounds were indeed observed, these were shown to be open chains and polymers formed under conditions that did not exclude the incorporation of end groups. Likewise, only polymer and diglycolide were obtained from the carbonic anhydride of glycolic acid⁹ (1,3-dioxolan-2,4-dione) by initiators, such as BF_3 or pyridine, which are not expected to remain as permanent end groups, but to enforce cyclization. It thus seems that the thermodynamic equilibrium between oligoglycolides is very much on the diglycolide side. This suggests that the *cis* ester group in a six-membered ring, where "interacting" methylene groups are tied together, is much less unstable than in open chains or larger rings.

We have now found that the crude product from the preparation of diglycolide by pyrolysis of sodium chloroacetate⁶ can be fractionally resublimed to yield small amounts of pentaglycolide ($n=5$, yield 0.12 %, m.p. 230°C) and hexaglycolide ($n=6$, yield 0.03 %, m.p. 215°C). Similarly, when the diglycolide is prepared by pyrolysis of polyglycolic acid,⁶ the crude product again contains small amounts of penta- and hexaglycolide. In no case has it been possible to detect even traces of other cyclic products, such as the tri- and tetraglycolide, which should be favoured in the pyrolysis by their higher volatility and by entropy gain, or heptaglycolide and higher. Since general medium-ring strain would be expected to disfavour mainly the 9-membered ring of the triglycolide but hardly the 12-membered ring of the tetraglycolide,* we take this observation to confirm a very strong *trans* preference of the ester group, and we conclude that the 15-membered ring of the pentaglycolide is the smallest that can comfortably accommodate all ester groups in *trans*.

It has not been possible to obtain more detailed information about the conformation of these two new glycolides. Their solid state infrared spectra are compared with those of the diglycolide and polyglycolic acid in Fig. 1. The spectral simplicity for the hexaglycolide suggests that its conformation is of relatively

* The structurally similar cyclotetrasarcosyl is formed easily without using high-dilution techniques and is very stable.¹

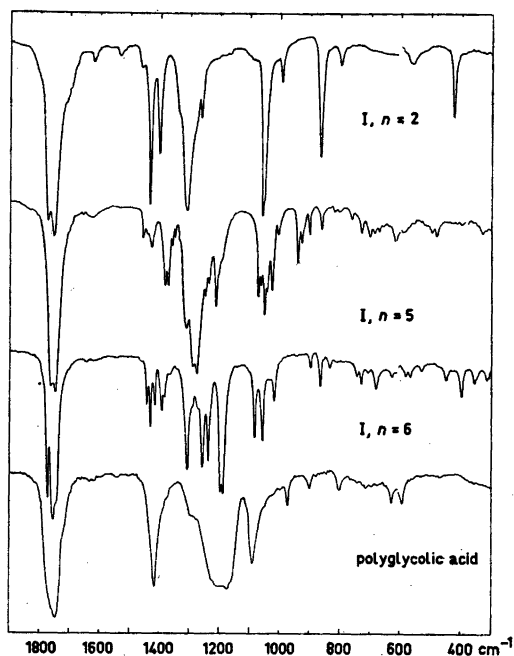


Fig. 1. Infrared spectra in KBr of diglycolide, pentaglycolide, hexaglycolide and polyglycolic acid.

higher symmetry. Insolubility in CCl_4 and CS_2 precludes comparison with solution spectra to allow conclusions about conformational homogeneity, and also the determination of dipole moments. The ^1H NMR spectra in CDCl_3 show single lines for each ring at higher field than the diglycolide. Cooling of a CHFCl_2 solution of pentaglycolide to -70°C produced no splitting either into several single lines or into one or more quartets. This supports the conclusion that all ester groups are *trans*, since at such a temperature *cis,trans* configuration exchange should be frozen, assuming a rotational barrier at least as high as in methyl acetate⁸ (42 kJ mol^{-1}). The lack of quartet structure might in itself be explicable on the basis that *cis,trans* isomerization is still rapid on the NMR time scale at -70°C , but other site exchange processes, such as rotation of the *trans* ester group "through" the ring,^{10,11} should be more rapid in rings of this size.

Experimental. Sodium chloroacetate (Fluka, pract.) was purified by suspending the powder in acetone; the acetone was then removed by filtration and the solid dried in a rotary evaporator. The purified sodium chloroacetate (30 g) was placed in a cold-finger sublimation apparatus and covered with glass wool. After evacuation (0.01 mmHg) the mixture was heated in an oil bath at $220\text{--}240^\circ\text{C}$ for half

an hour. The sublimed product was suspended in ether to remove oily by-products,* the ether decanted, and the residue dried for 10 min at 60°C . Resublimation at 100°C (0.01 mmHg) for 1–2 h permitted the removal of about all the diglycolide, m.p. 83°C (9 g, 45%). The remaining powder was transferred to a glass tube¹² and sublimed at gradually rising temperature; traces of diglycolide sublimed (0.01 mmHg) at $80\text{--}100^\circ\text{C}$, a mixture of penta- and hexaglycolide at $140\text{--}180^\circ\text{C}$ (30 mg), with only a small residue of non-volatile "polymer" remaining ($\sim 50\text{ mg}$). The mixture of penta- and hexaglycolide was fractionally crystallized from acetonitrile, the pentaglycolide crystallizing first as plates, m.p. 230°C (25 mg, 0.12%) and the hexaglycolide crystallizing after concentration of the mother liquor as prisms, m.p. 215°C (5 mg, 0.03%). Mass spectrometry showed the correct molecular ions 290 and 348; in addition the pentaglycolide gave by osmometry in acetonitrile a mol.wt. of 292 ± 2 (calc. 290) and anal. $\text{C}_{10}\text{H}_{10}\text{O}_{10}$: C, H. ^1H NMR chemical shifts in CDCl_3 , were for di-, penta- and hexaglycolide δ 4.94, 4.82 and 4.81.

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* The formation of oily substances could be suppressed by mixing the chloroacetate with 10% of celite before pyrolysis. The yield of oligoglycolides was not thereby increased.