Comments on Some Recent Reports on the Synthesis of Macrolides

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Conclusions from recent literature reports on macrolide synthesis are critically discussed in the light of quantitative evidence currently available in the field of macrocyclisation reactions.

Current literature shows a renewal of interest in the synthesis of macrocyclic compounds. However, in spite of the fact that much of the qualitative and imprecise knowledge of macrocyclisation reactions can nowadays be expressed in terms of quantitative and systematic relationships thanks to extensive physico-organic studies,[1] it appears to us that rather vague

statements, uncertain interpretations, and questionable conclusions are often found in many reports, indicating that there are still obscure areas in this field.

In this communication we first stress briefly the basic principles underlying cyclisation of bifunctional chain molecules to many-membered rings, which have been presented in detail elsewhere[2] and applied to the synthesis of macrocycles.[3,4]

The fundamental quantity in cyclisation reactions is the effective molarity, E.M. This is defined as $k_{\text{intra.}}/k_{\text{inter.}}$ and represents the (sometimes ideal) reactant concentration at which cyclisation ($k_{\text{intra.}}$) and polymerization ($k_{\text{inter.}}$) occur at the same rate. The outcome of a *batch-wise* cyclisation procedure, *i.e.*, a procedure where the reactant is charged all at once (zero time) into the reactor, depends on whether the initial concentration is smaller or greater than the E.M. In the former case cyclisation predominates over polymerization, and the reverse holds in the latter case. The E.M. profile for the lactonisation of ω-bromoalkanoate ions[1] illustrates well how critical is the choice of the initial concentration (Figure 1). Because 10^{-2} M or more dilute solutions are of little or no value in synthetic work, an *influxion* procedure must be adopted in many cases. Here the reactant is introduced very slowly into the reaction medium in order to prevent its accumulation.† The rate of feed v_f is now the critical parameter which has to be adjusted to make cyclisation predominate over polymerization. This is achieved when[2] $v_f <$ E.M. $\times$ $k_{\text{intra.}}$. The rate of feed v_f substantially controls the duration of the process, and is a measure of its efficiency.

We have selected three examples from many in recent work on the synthesis of macrolides to illustrate our point.

Lactonization in microemulsions. The base-promoted cyclisation of 11-bromoundecanoic acid and 15-bromopentadecanoic acid has been carried out in a microemulsion consisting of water, propan-2-ol, and toluene.[5] In spite of the low concentration used (3×10^{-3} M) the expected lactones were formed in low yields, 25 and 22%, respectively, and were accompanied by comparable amounts of polymeric materials. Nevertheless the authors claimed the 'amount of polymer formation is exceedingly low considering the concentrations used.' That this conclusion is not appropriate is readily seen, however, when it is noted that the given cyclisations were carried out at concentration much lower than the corresponding E.M. values (Figure 1). Indeed we found[6] that at a concentration of 0.9×10^{-3} M, potassium 11-bromoundecanoate lactonizes in 100% yield. Therefore we conclude that no advantage results from carrying out cyclisations in microemulsions but, rather, that the substrate is apparently concentrated somewhere in the dispersed system, with an adverse effect on cyclisation.

Cyclisation of caesium ω-halogenoalkanoates. A series of ω-halogeno fatty acids has been cyclised in a batch-wise procedure.[7] Treatment of 1×10^{-2} M solutions of the acids in dimethylformamide (DMF) with Cs_2CO_3 afforded the 13-membered and larger rings in >50% yield. Yields were <50% with the 12- and 11-membered rings, and dropped to zero with the 10-membered ring. This is exactly what one could anticipate from E.M. considerations assuming, as seems justified,[8] that the E.M.s do not change significantly from Me_2SO (Figure 1) to DMF. Thus, the behaviour of this system appears to display no special feature. The superiority of Cs_2CO_3 with respect to other metal ion carbonates might well be due to solubility and/or ion-pairing effects, as the authors themselves point out, but nothing emerges from the results indicating that there is some special influence of the caesium ion specifically exerted on cyclisation. Hence the suggestion that caesium-paired carboxylates 'have a lesser tendency to undergo intermolecular than intramolecular reaction' appears to be unjustified.

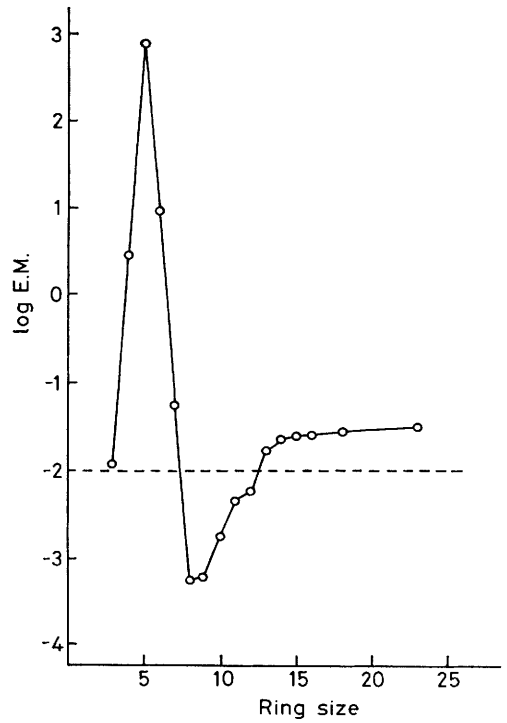

Figure 1. E.M. profile for the lactonisation of ω-bromoalkanoate ions in Me_2SO at 50 °C. At an initial concentration of 10^{-2} M, at which the dashed line is drawn, rings with representative points above the line are formed in preference to polymers and *vice versa*.

Template-driven macrolide closures. A recent report[9] describes the synthesis of 12-, 13-, and 16-membered lactones by the Bu^tOK-promoted cyclisation of crown-functionalized thioesters, crown–$SCO[CH_2]_nOH$. An influxion method was adopted. In the best of these experiments the rate of feed was 3.1×10^{-3} mol h^{-1} (l of solvent)$^{-1}$ and the lactones were obtained in *ca.* 70% yield. It was concluded that 'the cyclisation reaction proceeds *via* a templated conformation in which the ω-alkoxide is held proximate to the thioester through ionic bonding to the crown-bound potassium cation,' and that this enforced interaction served to compensate for the 'entropic disadvantage of macrolide closure.' Although there is no reason to doubt that interaction between the crown-complexed potassium ion and the negative charge of the incoming nucleophile will result in rate enhancement, there is no reason either to believe that this rate enhancement effect should be restricted to cyclisation alone, and should not operate also in the head-to-tail reactions leading to polymers. In our view this is a normal macrocyclisation reaction in which proper activation of the reacting groups increases the efficiency of the influxion procedure. Any factor which increases $k_{\text{intra.}}$ and $k_{\text{inter.}}$ by the same extent leaves the E.M. unchanged, yet increases the E.M. $\times$ $k_{\text{intra.}}$ product, resulting in a favourable effect on yields. The term 'template cyclisation' should be restricted to those cases in which there is definite

† This is the well known Ziegler high-dilution technique. However, since the term high dilution is often used in connection with the batch-wise technique, the term influction is recommended to avoid confusion.

evidence that the E.M. ratio has become larger owing to the operation of a preferential factor on the $k_{\text{Intra.}}$ value.

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