Simulation of Irreversible Cyclization of Bifunctional Chains. A Computer-aided Approach to the Synthesis of Many-membered Rings and to the Evaluation of Effective Molarities by Preparative Experiments

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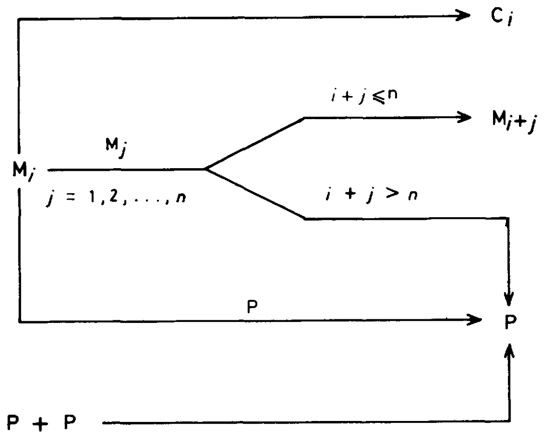
Two complementary kinetic models for the reaction of a bifunctional reactant A–B to give macrocycles under either batch-wise or influxion (Ziegler high dilution) conditions, are described. The degree of accuracy of both models is variable at will, depending on the value of the maximum polymerization degree accounted for by the models themselves. On the basis of these models, a computer program (CYCLES) has been developed, serving both as an useful tool for the optimization of reaction conditions in the synthesis of many-membered rings, and as the essential means of obtaining effective molarities by preparative experiments. The program CYCLES performs fourth-order Runge–Kutta numerical integration of the set of differential rate equations pertinent to each kinetic model for an arbitrary value of the degree of polymerization.

The preparation of macrocycles from long-chain bifunctional molecules of the type A–B requires a careful choice of the reaction conditions in order to control the two competitive processes of polymerization and cyclization. Although approximate kinetic treatments[1–3] have substantiated the principle that high dilution favours the formation of the monomeric ring at the expense of polymerization, they are useless whenever oligomeric rings, such as the cyclic dimer, trimer, and so on, are required. In fact, optimum reaction conditions are generally found empirically. Hence there is a great need for a general kinetic treatment which, taking into account all the necessary parameters, is able to predict the complete distribution of cyclic products (the direct problem). The 'necessary parameters' refer in part to experimental conditions and in part to the ring-closing tendencies of the various acyclic i-mers. The latter are measured by the corresponding effective molarities, which are the fundamental physicochemical parameters characterizing intramolecular processes.[4,5] Needless to say, the converse problem, *i.e.* the recovery of the EM values from the experimental yields of cyclo-oligomers, is also of great interest. Both of these problems should be based on complex kinetic models not amenable to analytical solution. However, this difficulty may be circumvented by numerical methods, which, owing to the wide availability of personal computers, are nowadays more accessible than previously. Therefore, we report here the description of two complementary kinetic models the degree of accuracy of which can be varied at will, by varying the value of the maximum degree of polymerization accounted for by the models themselves. This approach toward solving both the direct and the converse problems has been implemented using the computer program CYCLES, which performs numerical integration of the rate equations pertinent to both the kinetic models, for an arbitrary value of the polymerization degree.



Scheme 1. $i = 1,2,\ldots,n$

Principles and Discussion

The Underestimating Model.—Consider a bifunctional chain molecule A–B, where A and B are two different functional groups each capable of reacting irreversibly with the other only. It is assumed that the inherent reactivity (k_{inter}) of the functional groups is independent of the size of the molecule to which they are attached.[6] Consider, moreover, the reaction system outlined in Scheme 1, where M_i and C_i represent the acyclic and cyclic i-meric oligomers, respectively, and n is the maximum degree of polymerization accounted for by the scheme itself, the value of which can be prefixed at will. In this scheme the possible formation of polymeric ring products C_i with $i > n$ is neglected, in that any reaction between M_i and M_j, with $i + j > n$, leads to an open-chain polymeric material P which is assumed to undergo only intermolecular reactions. On the other hand, when $i + j \leqslant n$ the product M_{i+j} is capable of intramolecular as well as intermolecular reactions, analogously to its precursors M_i and M_j. Accordingly, the complete set of differential rate equations can be formulated as follows:

$$\mathrm{d}[\mathrm{C}_i]/\mathrm{d}t = (k_{\text{intra}})_i[\mathrm{M}_i] \qquad i = 1,2,\ldots,n \qquad (1)$$

$$-\mathrm{d}[\mathrm{M}_i]/\mathrm{d}t = (k_{\text{intra}})_i[\mathrm{M}_i] - k_{\text{inter}}\sum_{j=1}^{i-1}[\mathrm{M}_j][\mathrm{M}_{i-j}] + 2k_{\text{inter}}[\mathrm{M}_i]\sum_{j=1}^{n}[\mathrm{M}_j] + 2k_{\text{inter}}[\mathrm{M}_i][\mathrm{P}] \qquad i = 1,2,\ldots,n \qquad (2)$$

$$-\mathrm{d}[\mathrm{P}]/\mathrm{d}t = -k_{\mathrm{inter}}\sum_{j=n+1}^{2n}\sum_{k=j-n}^{n}[\mathrm{M}_k][\mathrm{M}_{j-k}] + k_{\mathrm{inter}}[\mathrm{P}]^2 \quad (3)$$

where $(k_{\mathrm{intra}})_i$ is the specific rate for cyclization of the acyclic i-mer. In formulating the above rate equations allowance has been made for the following facts: (*i*) Two molecules of M_i disappear upon $\mathrm{M}_i + \mathrm{M}_i$ dimerizations; (*ii*) the reactions $\mathrm{M}_i + \mathrm{M}_j$ with $i \neq j$ and the reactions $\mathrm{M}_i + \mathrm{P}$ are, statistically, twice as likely than the reactions $\mathrm{M}_i + \mathrm{M}_j$ with $i = j$ and the reaction P + P.[7] It should be noted that Scheme 1 with $n = 1$ coincides with a previously proposed kinetic scheme[2] the treatment of which has been successively re-examined.[7]

Since the critical parameter characterizing intramolecular reactions is the effective molarity (EM), defined as the ratio $k_{\mathrm{intra}}/k_{\mathrm{inter}}$, it is convenient to divide the equations (1)—(3) by a dimensionless constant f of the same numerical value of k_{inter}. This operation changes the time scale ($t' = ft$) and makes the terms $(k_{\mathrm{intra}})_i$ and k_{inter} numerically equal to EM_i and 1, respectively. Therefore the set of equations (1)—(3) simplifies to equations (4)—(6).

$$\mathrm{d}[\mathrm{C}_i]/\mathrm{d}t' = \mathrm{EM}_i[\mathrm{M}_i] \qquad i = 1,2,\ldots,n \qquad (4)$$

$$-d[\mathrm{M}_i]/\mathrm{d}t' = \mathrm{EM}_i[\mathrm{M}_i] - \sum_{j=1}^{i-1}[\mathrm{M}_j][\mathrm{M}_{i-j}] + 2[\mathrm{M}_i]\sum_{j=1}^{n}[\mathrm{M}_j] + 2[\mathrm{M}_i][\mathrm{P}] \qquad i = 1,2,\ldots,n \quad (5)$$

$$-\mathrm{d}[\mathrm{P}]/\mathrm{d}t' = -\sum_{j=n+1}^{2n}\sum_{k=j-n}^{n}[\mathrm{M}_k][\mathrm{M}_{j-k}] + [\mathrm{P}]^2 \quad (6)$$

There are two main techniques according to which cyclization reactions are usually carried out for preparative purposes. One is the *batch-wise* procedure, where m moles of a bifunctional reactant M_1 are added all at once to a volume V of solvent, where the proper conditions are set. The other is the *influxion* procedure, which corresponds to the well known Ziegler high-dilution technique,[8] where the monomer M_1 is slowly introduced into the reaction medium, in order to prevent its accumulation.

A batch-wise experiment is characterized by the initial monomer concentration $[\mathrm{M}_1]_0 = m/V$, whereas an influxion experiment is characterized by the feed rate v_f (in mol l^{-1} s^{-1}) which represents the moles of bifunctional reactant M_1 added per second per litre of reaction solution. It is assumed that this addition does not change the volume of the reaction medium to a significant extent.

In order to adapt the set of differential equations (4)—(6) to the influxion case, equation (5) with $i = 1$ is modified as shown in equation (7), where $v_{f'}$ ($= v_f/f$) can be considered as a normalized feed rate.

$$-\mathrm{d}[\mathrm{M}_1]/\mathrm{d}t' = -v_{f'} + \mathrm{EM}_1[\mathrm{M}_1] + 2[\mathrm{M}_1]\sum_{j=1}^{n}[\mathrm{M}_j] + 2[\mathrm{M}_1][\mathrm{P}] \quad (7)$$

Therefore the complete set of differential equations for the influxion case includes equation (4) with $i = 1,2,\ldots,n$, equation (7), equation (5) with $i = 2,3,\ldots,n$, and equation (6).

In order to integrate numerically the systems of differential rate equations for either the batch-wise or the influxion case, the EM_i values ($i = 1,2,\ldots,n$) must be known. These are largely dependent upon the structure of the rings being formed. In particular for ring sizes ranging from 8* to *ca.* 25 an estimate of the effect of the structure on the EM can be obtained by the rather large body of EM data currently available.[5] For larger ring sizes the EM is determined solely by the conformational entropy change upon cyclization. Accordingly the EM values for such rings can be calculated from equation (8), where N_{A} is

$$\mathrm{EM} = \frac{1\,000}{N_{\mathrm{A}}}\left(\frac{3}{2\pi\langle r^2\rangle}\right)^{3/2} \quad (8)$$

Avogadro's constant, and EM is expressed in mol l^{-1} when r is given in cm.[5,9,10] The mean-square chain-end displacement $\langle r^2\rangle$ is related to the number x and length b of skeletal bonds through equation (9), where C_x is the characteristic ratio.[10]

$$\langle r^2\rangle = C_x x b^2 \quad (9)$$

The characteristic ratio for polymeric chains of infinite length (C_∞) is usually in the range 4—11.[10] An intermediate value of $C_x \approx C_\infty = 8$ was found to account well for the cyclization behaviour of long polymethylene and polyoxyethylene chains in Me$_2$SO.[5]†

In the batch-wise case the differential rate equations (4)—(6) are integrated from 0 to t' when condition (10) is verified, *i.e.* until the total concentration of the residual acyclic molecules M_i, expressed as weight %, is <0.5%.

$$100\sum_{i=1}^{n} i[\mathrm{M}_i]_{t'}/[\mathrm{M}_1]_0 < 0.5 \quad (10)$$

When this condition is verified, the concentration of reduced functional groups is so low that the major fraction of the residual M_i molecules, if allowed to react, would yield the corresponding cyclo-oligomers C_i. Therefore it can be safely assumed that $[\mathrm{C}_i]_\infty = [\mathrm{C}_i]_{t'} + [\mathrm{M}_i]_{t'}$.

Yields of the various cyclo-oligomers are calculated from their final concentrations $[\mathrm{C}_i]_\infty$ by equation (11), whereas the amount of polymer, P, expressed in terms of weight %, is calculated by equation (12).

$$\%\mathrm{C}_i = 100i[\mathrm{C}_i]_\infty/[\mathrm{M}_1]_0 \qquad i = 1,2,\ldots,n \quad (11)$$

$$\%\,\mathrm{P} = 100 - \sum_{i=1}^{n}\%\,\mathrm{C}_i \quad (12)$$

In the influxion case, numerical integration of the differential equations (7), (5) with $i = 2,3,\ldots,n$, and (6) shows that after a certain amount of time a steady state for all the oligomers M_i and the residual polymer P is reached.‡ The assumption is made that the steady state is maintained long enough to render negligible the amount of reaction products formed in the initial part (*i.e.* before the steady state is reached) and in the final part

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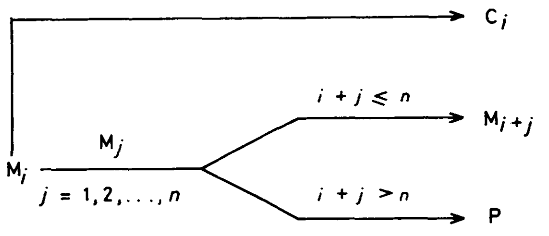
* For ring sizes lower than 8, the EMs are generally so high that polymerization does not effectively compete with the formation of the monomeric ring.[5]

† Equations (8) and (9) (with $C_x = 8$) have been implemented in the program CYCLES to facilitate the evaluation of the EMs from a certain i value up to n. Making use of this facility, one is only required to input the EMs of those cyclo-oligomers which are not sufficiently large to allow the application of equation (8), otherwise all the EMs from $i = 1$ to n must be supplied.

‡ In the influxion case there is no need to integrate numerically equation (4) (*vide infra*).



Scheme 2. $i = 1,2,\ldots,n$

(*i.e.* after the addition of reactant is stopped) of the experiment.* Therefore, in order to calculate the yields of cyclic oligomers, we only need the steady state concentrations for all of the M_i species ($[M_i]_{st}$ with $i = 1,2,\ldots,n$) which are obtained by the numerical integration procedure.

Since the residual polymer, P, is the last species to reach the steady state, the integration is carried out until the derivative $d[P]/dt'$ becomes negligibly small. According to equation (6) the derivative of [P] is given by the difference of two terms. This difference can be considered to be negligibly small when it is less thatn 0.1% of the sum of the above two terms, *i.e.* when condition (13) is verified.

$$100\,\frac{[\mathrm{P}]^2 - \sum_{j=n+1}^{2n}\sum_{k=j-n}^{n}[\mathrm{M}_k][\mathrm{M}_{j-k}]}{[\mathrm{P}]^2 + \sum_{j=n+1}^{2n}\sum_{k=j-n}^{n}[\mathrm{M}_k][\mathrm{M}_{j-k}]} < 0.1 \qquad (13)$$

Yields of cyclic products are given by equation (14), where the numerator of the fraction represents the weight amount of C_i produced per unit of time and volume under the steady-state conditon, whereas the amount of polymer, P, is calculated according to equation (12).

$$\%\mathrm{C}_i = \frac{i\,\mathrm{EM}_i\,[\mathrm{M}_i]_{\mathrm{st}}}{v_{\mathrm{f}'}}\,100 \qquad (14)$$
$$i = 1,2,\ldots,n$$

Independently of the technique being considered (batch-wise or influxion), accurate yield data for the cyclo-oligomers are obtained when the value of n is high enough to render low the %P value. Whenever the %P value is significant, yields of cyclo-oligomers are underestimated, as Scheme 1, neglecting the intramolecular reactivity of P, exaggerates the probability of intermolecular reactions between the M_i species and P. For this very reason we indicate the kinetic model outlined in Scheme 1 as the *underestimating model* (UM).

The Overestimating Model.—It is worth remarking that in some cases,† to obtain low %P values, n should be very large, and this would make calculations impractically wasteful of computer time. In these cases, instead of increasing n, it may be more advantageous to repeat the calculations according to the *overestimating model* (OM) outlined in Scheme 2. In this scheme the residual polymer P has no influence on the reaction course, thus implying that P may be viewed as being either unreactive or capable of undergoing only intramolecular reactions.

We have shown in previous work that, for a batch-wise experiment, the set of differential rate equations pertinent to Scheme 2 can be formulated as follows:[7]

$$d[\mathrm{C}_i]/dt' = \mathrm{EM}_i[\mathrm{M}_i] \qquad i = 1,2,\ldots,n \qquad (15)$$

$$-d[\mathrm{M}_i]/dt' = \mathrm{EM}_i[\mathrm{M}_i] - \sum_{j=1}^{i-1}[\mathrm{M}_j][\mathrm{M}_{i-j}] + 2[\mathrm{M}_i]\sum_{j=1}^{n}[\mathrm{M}_j] \qquad i = 1,2,\ldots,n \qquad (16)$$

whereas for an influxion experiment equation (16) with $i = 1$ must be modified as shown in equation (17), the other equations remaining unchanged.[11]

$$-d[\mathrm{M}_1]/dt' = -v_{\mathrm{f}'} + \mathrm{EM}_1[\mathrm{M}_1] + 2[\mathrm{M}_1]\sum_{j=1}^{n}[\mathrm{M}_j] \qquad (17)$$

The analytical solutions for both the batch-wise and the influxion techniques relative to Scheme 2 with $n = 1$,[3] and a number of calculations‡ relative to Scheme 2 with $n = 12$,[7,11] have been reported. The differential rate equations relative to Scheme 2 in the batch-wise case, likewise those relative to Scheme 1, are integrated until condition (10) is verified. The corresponding yields of cyclic products and of the residual polymer are given by equations (11) and (12), respectively. By contrast, the rate equations relative to Scheme 2 in the influxion case are integrated until condition (**18**) is verified, *i.e.* until a steady state is reached, in which the monomer added during the small time interval s (the step size of the numerical integration) does not change the population of open-chain molecules to a significant extent, *i.e.* more than 0.1%.

$$\frac{\sum_{i=1}^{n} i\,|[\mathrm{M}_i]_{t'} - [\mathrm{M}_i]_{t'-s}|}{v_{\mathrm{f}'}s}\,100 < 0.1 \qquad (18)$$

$\%C_i$ and %P are calculated using equation (14) and (12), respectively. Clearly, whenever %P is significant, Scheme 2 overestimates the yields of cyclic products, in that it does not take into account the intermolecular reactions between P and the M_i species, that would occur in competition with the ring-closure processes.[7]§ Therefore, the two models provide a lower and an upper limit for the yields of each of the n-cyclo-oligomers. Obviously on increasing n the two limits converge to the true value of the yield, which is given by both models when %P is low. This is shown in Tables 1 and 2, in which are reported results obtained using the program CYCLES. The results in Table 1 refer to a hypothetical cyclization carried out under batch-wise conditions ($[M_1]_0 = 0.1$ M) of a bifunctional chain leading to a 10-membered ring, so that C_2 is 20-membered, C_3 30-membered, and so on. The typical values of 1×10^{-2} mol l^{-1}, and 3×10^{-2} mol l^{-1} were assumed for EM_1 and EM_2 respectively,[7] whereas the values from EM_3 onwards were calculated by the program according to equations (8) and (9) with $C_x = 8$ and $b = 1.54 \times 10^{-8}$ cm. The calculations were

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* This condition need not be strictly followed in practice since the amount of cyclic products formed in the final part of the reaction tends to compensate the smaller amount of cyclic products formed before the steady state is reached.

† These cases are characterized by high $[M_1]_0$ or $v_{f'}$ values and/or low EM values.

‡ These calculations which refer to the cyclization of typical A–B chains under batch-wise and influxion conditions were carried out using an early version of the program, based on the time-consuming Euler method as the integration algorithm, and which was only capable of OM calculations with $n = 12$.

§ It could be shown that $\%P_{UM}$ must tend to zero monotonically on increasing n, and that for the same n value, $\%P_{UM}$ is always higher than $\%P_{OM}$. Therefore $\%P_{OM}$ must also tend to zero for sufficiently high n-values. However, $\%P_{OM}$ may not vary monotonically.

Table 1. Percent yields of C(1)—C(10) and P for a batch-wise cyclization as given by the two models (UM, OM) for selected *n* values[a]

	n				
	1	3	5	10	50[b]
C_1	8.7—15.3	9.6—11.6	9.9—10.9	10.1—10.4	10.1—10.1
C_2		17.9—22.0	18.6—20.1	18.8—19.1	18.9—18.9
C_3		16.2—20.8	16.9—18.4	17.1—17.3	17.1—17.1
C_4			10.0—11.5	10.2—10.5	10.3—10.3
C_5			6.8—8.4	7.0—7.3	7.1—7.1
C_6				5.2—5.6	5.3—5.3
C_7				4.1—4.5	4.1—4.1
C_8				3.2—3.7	3.3—3.3
C_9				2.6—3.1	2.7—2.7
C_{10}				2.1—2.6	2.2—2.3
P	91.3—84.8	56.3—45.6	37.9—30.6	19.4—15.9	1.6—1.4

[a] All the numerical integrations were carried out with step size = 1. [b] The yields of C(11)—C(50) are not reported.

Table 2. Percent yields of C(1)—C(10) and P for an influxion cyclization as given by the two models (UM, OM) for selected *n* values[a]

	n				
	1	3	5	10	50[b]
C_1	14.6—20.0	15.8—17.7	16.1—17.3	16.4—16.9	16.4—16.6
C_2		18.0—24.5	19.1—23.0	19.7—21.7	20.1—20.5
C_3		12.6—20.4	13.9—18.7	14.6—17.0	15.0—15.5
C_4			6.2—9.5	6.7—8.3	7.0—7.3
C_5			3.4—5.7	3.8—5.0	4.0—4.2
C_6				2.4—3.5	2.6—2.8
C_7				1.7—2.6	1.8—2.0
C_8				1.2—2.0	1.3—1.5
C_9				0.9—1.6	1.0—1.2
C_{10}				0.7—1.3	0.8—0.9
P	85.4—80.0	53.6—37.5	41.3—25.9	31.7—20.0	24.0—19.3
t'_{st}	73	78	83	116	263

[a] All the numerical integrations were carried out with step size = 0.5. [b] The yields of C(11)—C(50) are not reported.

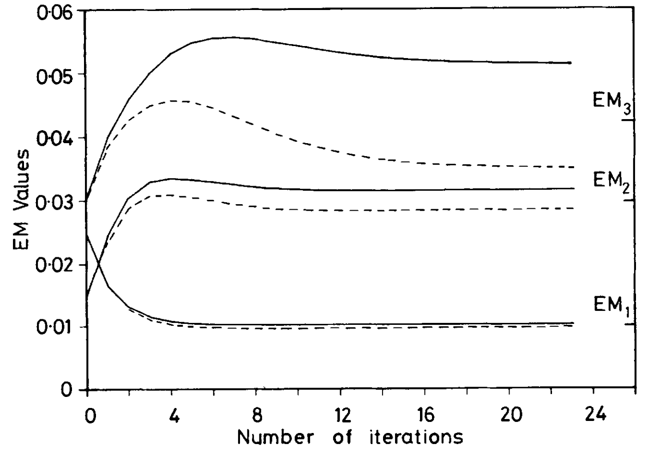

Figure. Solution of the converse problem for $n = 3$, $[M_1]_0 = 0.02$ mol l^{-1}, and $\%C_1^{exp} = 36.2$, $\%C_2^{exp} = 34.9$, $\%C_3^{exp} = 16.8$. The solid lines refer to the UM whereas the dashed lines refer to the OM. The 'experimental yields' were actually calculated with the EM values indicated on the right side of the figure using an extended model which rendered %P negligible

made according to both the UM and the OM for increasing values of the polymerization degree. It can be seen that the yields given by the two models coincide when %P is sufficiently low. Analogously, in Table 2 are reported the results obtained when the same cyclization is carried out under influxion conditions ($v_{f'} = 0.001$ mol l^{-1} s^{-1}).

Also reported in Table 2 is the time $t_{st'}$ required to reach the 99.5% of the steady-state concentration of M_1 as given by the OM. Of course if %P is not negligible the $t_{st'}$ value is approximate. Knowledge of the value of t_{st} ($t_{st} = t_{st'}/f$) is useful to carry out properly an influxion experiment aimed at the preparation of the lower cyclo-oligomers in that the corresponding acyclic *i*-mers reach the steady-state shortly after M_1.

The Converse Problem.—The previous sections illustrated the direct problem, *i.e.* the problem of finding the yields of all the cyclo-oligomers under certain experimental conditions, provided that the values of all the EM's are known. Now let us consider the converse problem, *i.e.* the recovery of the EM values from the experimental yields of cyclic products.

For the sake of accuracy and experimental convenience, the batch-wise technique is the elective procedure to obtain experimental yields aimed to the evaluation of EMs. Accordingly the program CYCLES, when dealing with the converse problem, only takes into account this technique. A method for solving the converse problem with reference to the overestimating model, has been outlined previously.[7] The same method can be applied to the underestimating model.

It should be noted that in the converse problem whenever %P is significant, the EMs are underestimated by the OM and overestimated by the UM. Of course the two models coincide when %P is low, yielding the same EM values. The method consists of an iterative procedure refining a trial set of EM values on the basis of the experimental yields of cyclo-oligomers. After each iteration a new EM set (EM_i^{new}, $i = 1,2,\ldots,n$) is calculated from the old one (EM_i^{old}, $i = 1,2,\ldots,n$) by equation (19) where $\%C_i^{exp}$ and $\%C_i^{calc}$ are the experimental and the

$$EM_i^{new} = \frac{\%C_i^{exp}}{\%C_i^{calc}} EM_i^{old} \qquad i = 1,2,\ldots,n \tag{19}$$

calculated percentage yields of the *i*-meric ring, respectively. The latter is calculated using either Scheme 1 or Scheme 2 with the old EM set. The iteration is continued until $\%C_i^{calc}$ coincides with $\%C_i^{exp}$ for all the cyclo-oligomers.

It seems likely that in most cases of practical interest, precise yield data can be obtained only for the lower cyclo-oligomers, despite the fact that the yields of the higher ones would be not negligible. In this case if *n* coincides with the number of cyclo-oligomers for which the yield is known, the two models will afford a lower and an upper limit for the EM of each of them, as shown for example in the Figure. However, if it is possible to estimate the EMs of the higher cyclo-oligomers, for example on the basis of equation (8), the value of *n* can be higher, and more precise EM values for the lower cyclo-oligomers can be obtained. Of course, since in this case equation (19) is limited to those rings for which the experimental yield is available the EMs of the other rings cannot be optimized.

The Program CYCLES.—CYCLES is a computer program based on the principles described above. It performs fourth-order Runge-Kutta[12] numerical integration of the set of differential rate equations pertinent to either Scheme 1 or Scheme 2, under either batch-wise or influxion conditions. It was written and compiled with a 'Turbo BASIC' compiler

(Borland International Inc.), and runs on IBM PCs and compatibles. However, it can be easily translated into other BASIC dialects or languages (FORTRAN, PASCAL, *etc.*) to run on other computers.

The listing of the program CYCLES is available as Supplementary Publication No. SUP 56729 (7 pp).* The program was conceived to be a useful tool for the optimization of reaction conditions in the synthesis of many-membered rings, and as the essential means of obtaining EM values from preparative experiments. For both applications a number of requisites must be fulfilled by the reaction system. In particular, besides the assumptions already indicated that should be verified in practice, it is necessary that the reaction medium is homogeneous and that no side-reactions occur. Moreover batch-wise reactions must be carried out to completion, whereas influxion experiments should be conducted under steady-state conditions for a period of time sufficiently longer than the time t_{st}.

The synthetic chemist aiming to synthesize a certain cyclo-oligomer from a chain molecule of the type A–B, should first estimate the pertinent set of EMs. In some cases an *a priori* estimate based on known EM data or on equation (8), which presupposes a regular structure of the A–B chain, may be difficult. In these cases a batch-wise experiment should be carried out with a medium $[M_1]_0$ value of, say, *ca.* 1×10^{-2} mol l^{-1}. On the basis of the experimental yields of the cyclo-oligomers so obtained, the program CYCLES will afford the desired set of EM values by solution of the converse problem.† With this set in hand it is possible to predict, using the program CYCLES, the outcome of any possible batch-wise or influxion experiment, selecting those experimental conditions which would give the best results. However in order to perform an influxion experiment, the value, or at least a rough estimate, of k_{inter} is necessary to allow the calculation of the actual feed rate v_f from the $v_{f'}$ value ($v_f = v_{f'}f$).

In previous work[11] we have shown that there is a close correlation between yields and selectivities as obtained using either the batch-wise or the influxion technique. The criteria of choice between the two procedures, established on the basis of practical convenience, have been discussed.[11] The extension of the program CYCLES to include two-component ring closure,[13,14] *i.e.* A–A + B–B, is under current investigation.

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* For details of Supplementary Publications see Instructions for Authors (1989), *J. Chem. Soc., Perkin Trans. 2*, 1988, Issue 1, p. xvii.

† If the aim is evaluation of accurate EM data, it is advisable to carry out a certain number of batch-wise experiments using different $[M_1]_0$ values.