Mass Spectral Determination of Azomethyne Macrocycle Distributions Formed in Polycondensation Reactions

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FAB–MS spectra have been used in order to detect the distribution of cyclic oligomers formed in the polycondensation of isophthaldehyde and ethylenediamine. The relative percentage of the macrocycles formed decreases in proportion to $X^{-2.5}$ according to a thermodynamic equilibrium. The relevant aspect for structural organic chemists is that such FAB–MS techniques can be generally used to determine, in a rapid and convenient way, the distribution of cyclic compounds formed in a polycondensation reaction without resorting to a prior separation of the oligomers formed. This fact can be of use in optimizing the reaction conditions so as to obtain macrocycles of the desired ring size.

Chemical reactions yielding synthetic macrocycles are well known, and the efforts of chemists today are very much oriented in the direction of developing synthetic strategies which can produce the desired macrocycles in high yield. Furthermore, in several cases, the synthetic procedure is aimed towards the formation of complex cyclic compounds which can mimic the action of important biologically active molecules.[1]

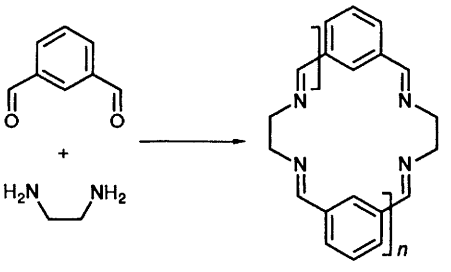
Special techniques such as the high dilution principle[2] and template reactions[3] are widely employed in forcing bifunctional compounds to produce macrocycles. However, due to polymerization the yield of the desired macrocycles can often be quite low so that long and tedious separation techniques are required in order to isolate the macrocycles and to establish the reliability of the chosen cyclization reaction. Furthermore, even if the latter reaction predominates over the random polymerization side-reaction, the synthetic strategy chosen can still be plagued by the formation of cycles of different ring size.

Recently, Montaudo[4] has shown how FAB–MS techniques can be widely used for detecting, among other substrates, the distribution of cyclic oligomers produced during a polymerization reaction, or during thermal degradation of polymeric substrates.

Although mass spectrometry (MS) is a powerful method for identifying species of different molecular weight, even in a mixture, the use of the electron impact (EI) technique prevents the quantitative determination of single oligomers due to the lack of correlation between EI peak intensities and the concentration of oligomers present in the mixture.[5,6] On the other hand, the FAB–MS technique has overcome this difficulty and compelling evidence reported in the literature suggests that, in many cases, the peak intensities of the molecular ions appearing in the FAB spectra correlate well with the relative concentration of the oligomers present in the mixture.[7,8] In fact, several examples[8] indicate that, for a reaction mixture, the FAB–MS method provides quantitative information on all the cyclic oligomers detected by other analytical techniques (GPC, HPLC, *etc.*) allowing their identification within a molecular weight up to the limit of the magnet used.

Furthermore, it has been proved[9] that polymeric materials, accurately purified from low molecular weight components, do not show significant peaks in their FAB mass spectra, in contrast to crude unfractionated materials for which the observed molecular peaks coincide with the percentage found in the mixture of cyclic oligomers.[9,†] This finding is inherent in the positive-ion FAB technique which, in contrast to negative-ion FAB spectrometry, allows the desorption of undecomposed compounds which yield intense positive molecular ions, showing very little or no fragmentation pattern.[7] It follows that FAB–MS can now be usefully used in order to identify the cyclic oligomers formed in a polymerization reaction, and quantitative information on their distribution can be rapidly extracted.

In this paper we report an example of how such rapid and powerful analytical techniques can be employed in order to determine the distribution of cyclic compounds formed in the condensation of isophthalaldehyde with ethylenediamine. This produces macrocyclic Schiff bases of great interest as metal complexing agents[10] (see Scheme 1).



Scheme 1

The reaction in Scheme 1 was chosen for the following reasons. (i) The reagents are easily coupled at room temperature in a variety of solvents. (ii) Planar or nearly planar macrocycles are formed with high symmetry skeletons (D_{2h} for $n = 1$) in which steric constraints are not too demanding. (iii) Macrocycles with 9 ($n = 0$), 18 ($n = 1$), 27 ($n = 2$) and 36 ($n = 4$) *etc.* atoms in the ring can also be generated.

Experimental

Basic materials included commercial products which were purified before use. Poly-Schiff bases were synthesized by condensing equimolar amounts of isophthalaldehyde and ethylenediamine in absolute EtOH at room temperature, using different dilutions (Table 1). A few drops of CH_3CO_2H were added in order to initiate the reaction.

The crude compound was separated on evaporation as a yellowish powder. The remaining portion of the material was recovered by elimination of the solvent under reduced pressure. The melting points of the different materials obtained ranged from 175–195 °C.

† As already reported,[9] this observation indicates that high molecular weight polymers do not yield significant fragmentation on application of the FAB–MS technique.

Table 1 Distribution of cyclic oligomers generated in the polycondensation reaction of Scheme 1

Experiment	Reaction conditions[a]	X	m/z	FAB–MS Obs.[b]	FAB–MS Calc.[b]
1	[C] = 0.37 mol dm^{-3} T = 25 °C	2	316	17.7	17.7
		3	474	8.8	6.4
		4	632	2.3	3.1
		5	790	0.7	1.8
		6	948	0.3	1.1
2	[C] = 0.15 mol dm^{-3} T = 25 °C	2	316	17.7	17.7
		3	474	10.1	6.4
		4	632	2.8	3.1
		5	790	1.2	1.8
		6	948	0.4	1.1
3	[C] = 0.4 mol dm^{-3} T = 25 °C	2	316	17.7	17.7
		3	474	9.0	6.4
		4	632	2.4	3.1
		5	790	1.1	1.8
		6	948	0.4	1.1
4	[C] = 0.05 mol dm^{-3} T = 50 °C	2	316	17.7	17.7
		3	474	9.4	6.4
		4	632	2.9	3.1
		5	790	0.9	1.8
		6	948	0.6	1.1

[a] Equimolar amounts of reagents were used. Concentration is reported in molarity. [b] The relative intensity of the first MS peak reported here has been taken as equal to that calculated theoretically[c] for the corresponding cyclic oligomer. [c] Theoretical values are calculated according to the distribution law: $C_x = X^{-2.5}$.

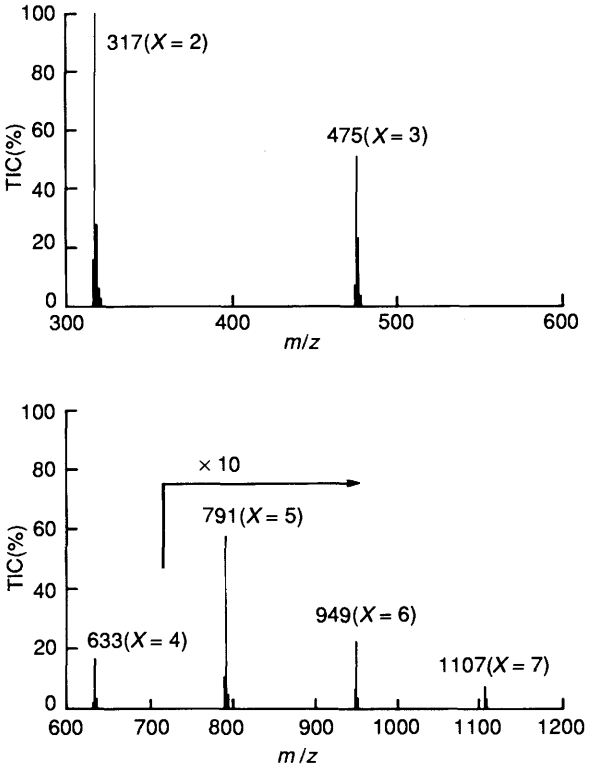


Fig. 1 FAB–MS spectrum of the product obtained in experiment no. 3 (see Table 1) after subtraction of the contribution due to the matrix (3-nitrobenzylalcohol) and normalized with respect to the peak at 317 Da (100%)

The ^{1}H NMR spectra in $CDCl_3$ showed, for all samples, two signals of almost equal intensity at δ 3.96 and 4.00 (4 H, s, NCH_2), multiplets at 7.37 and 7.80 (4 H, m, ArH) and a singlet at δ 8.30 (2 H, s, CH).

Mass spectra were obtained using a double focusing Kratos MS 50S instrument equipped with the standard FAB source and a DS 90 data system.

The FAB gun (ION TECH) was operated with 7–8 kV Xenon beam. The instrument was scanned from m/z 2000–60, with a scan rate of 3 s decade^{-1}. The accelerating voltage was 8 kV. Caesium and rubidium iodide (50/50 w/w) were used for computer calibration. The resolution was 2000. 3-Nitrobenzylalcohol was used as a matrix. The estimated error in repeated experiments does not exceed 5%. This error does not alter significantly the estimated values of the cyclic compounds detected by FAB–MS analyses.

Results and Discussion

In a general polyreaction the distribution of cyclic oligomers might originate from: (i) a thermodynamically-controlled regime; (ii) a kinetically-controlled regime.

According to the theory of macrocyclization equilibria formulated by Jacobson and Stockmayer[11] the thermodynamic regime is controlled by the probability that the two reactive sites, in each step of the reaction, collide making the reaction possible; thus, the interaction between an active end and a reactive group within the same chain will generate the cyclic compound through an intramolecular reaction (back-biting). Therefore, (i) if the chains in solution obey the Gaussian statistics, (ii) if all rings are equally probable on steric grounds and (iii) if the reactivity of all functionalities along the growing chain remains the same, the Jacobson–Stockmayer theory[11] will predict that the equilibrium concentration of each cyclic unit should decrease according to the law:

$$C_x = AX^{-2.5} \quad (1)$$

where C_x is the concentration of the given cycle with X repeating units and A is a constant.

Deviations from the thermodynamically-controlled regime can arise if kinetic enhancement (or depression) of cyclic molecules takes place at an early stage of the reaction. This is because firstly, the assumption that terminal reactive groups have equal reactivity is violated, or secondly, some preferred conformations arise in the growing chain which can then lead to intermolecular reactions between reactive groups of different growing chains ('end-biting' process). Such a preferred conformation can also arise by virtue of the solvents and catalysts chosen.

In this latter (end-biting) case the concentration of the cyclic oligomers formed should decrease proportionally to $X^{-1.5}$, where X is still the number of repeating units in the cycle.[12–14] It follows that by plotting the experimental distribution of cyclic oligomers *versus* the number of repeating units (X) present in the molecule a clear distinction between the thermodynamically- and kinetically-controlled macrocyclization processes can be easily achieved.

In other words, to synthetic and structural chemists this information can be of great importance in selecting the optimum conditions which will lead to the formation of the desired macrocycle. Thus, a rapid scan on the MS spectrometer, which avoids tedious and time-consuming sample separations, will immediately give useful information by using a negligible amount of substance.

According to the above discussion, analyses by FAB–MS techniques of the crude reaction mixtures obtained in different polycondensation trials of isophthaldehyde with ethylenediamine in EtOH as solvent, yielded a distribution of cyclic Schiff bases formed in the reaction investigated (Table 1). For example, the FAB–MS spectrum of the powder obtained in a typical reaction is reported in Fig. 1. In the majority of the experiments performed, only peaks due to the cyclic compounds

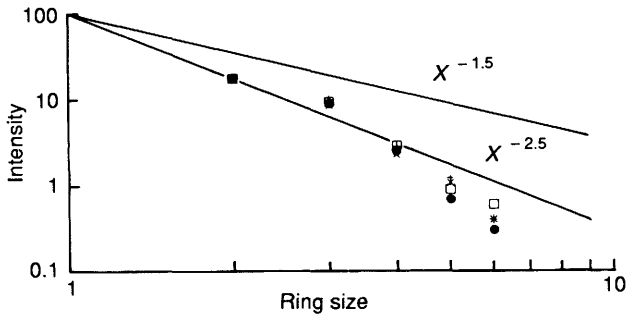


Fig. 2 Experimental macrocycle distributions for the reaction reported in Scheme 1 and Table 1, compared with theoretical distribution laws. Expt. 1, •; expt. 2, +; expt. 3, *; expt. 4, □.

are in evidence indicating that the reaction proceeds essentially without the concomitant formation of linear low-molecular weight polymeric materials.*

In Table 1 and Fig. 2 we report the relative MS abundance of the macrocycles formed in the various reactions chosen. Disregarding small deviations, the relative percentage of the macrocycles formed in all reactions is almost the same, indicating that the experimental conditions play a minor role in such macrocyclization reactions. More importantly, Fig. 2 indicates that the relative concentration of the cyclic molecules decreases according to a factor which is closer to $X^{-2.5}$ than $X^{-1.5}$, indicating that the cyclization reaction follows a thermodynamically-controlled regime.

Such information can therefore be of use to synthetic and structural organic chemists in order to optimize reaction conditions for obtaining macrocycles of the desired ring size.

* Only in some experiments did we observe the presence in the FAB–MS spectra of a small amount (5–8%) of non-cyclic dimeric compounds with H_2N- and –CHO terminal groups ($M^+ + 1 = 335$ Da), and a peak $M^+ + Na$ at 399 Da, with an intensity which could not be reproduced in the series of the experiments performed on linear oligomers ending with $-NH_2$ groups on both sides ($C_{22}H_{28}N_6Na^+$).

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