Electronic Supporting Information for

Target-Induced Amplification in a Dynamic Library of Macrocycles. A Quantitative Study

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A Synopsis of the Revised Jacobson-Stockmayer Theory.

The first quantitative theory of macrocyclization equilibrium, due to Jacobson and Stockmayer (J&S), dates back to 1950.[1] About twenty years ago J&S theory was implemented and reproposed in a form aimed at being more easily understandable by non-specialists.[2] Here follows a synopsis of the latter treatment.

When a reversible macrocyclization is started by the addition of a linear monomer M_1 that bears at its ends two reactive functional groups, –X and –Y, after a given time, a ring-chain equilibrium is reached in which all the initial mass of the monomer is distributed into cyclic, C_i, and linear, M_i, species as illustrated in Scheme ESI1 and eqn (ESI1).

$$[M_1]_o = \sum_1^\infty i\,[C_i] + \sum_1^\infty i\,[M_i] \tag{ESI1}$$

If the two functional groups reversibly react with each other only and if the equilibrium constant, K_{inter}, for this reaction is independent of the length of the chain to which the two groups are attached, it is possible to derive eqn (ESI2) for cyclic species and eqn (ESI3) for linear species.[2]
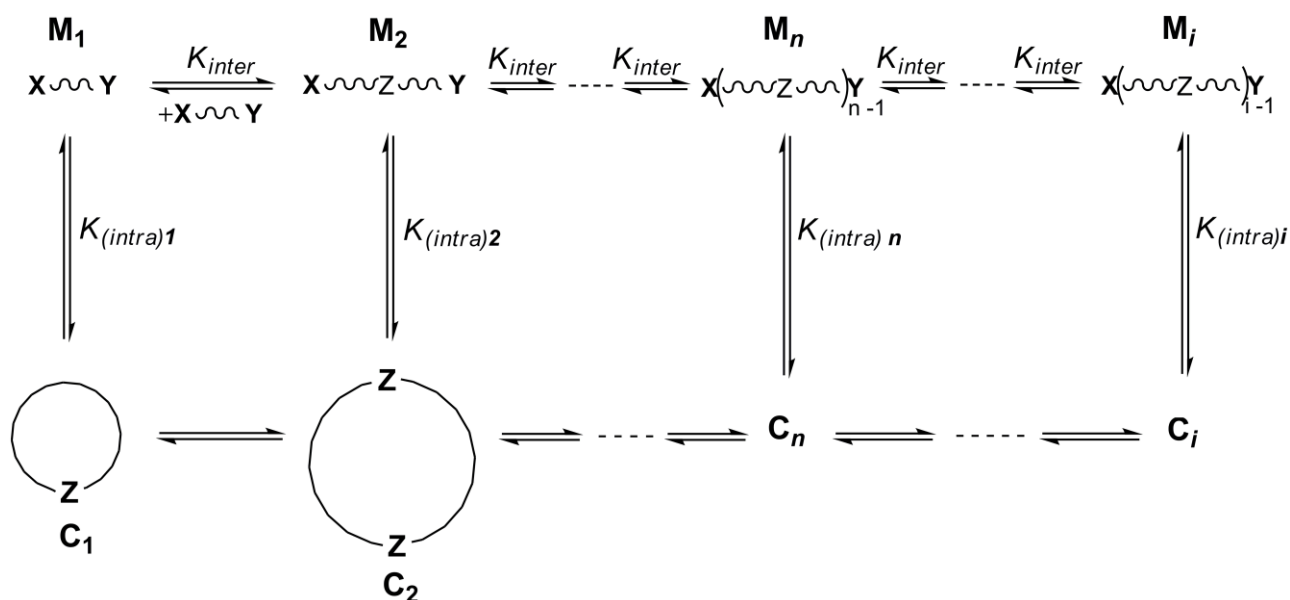
Scheme ESI1. A Macrocyclization Equilibrium.

ESI2

$$[C_i] = EM_i \, x^i \qquad\qquad (ESI2)$$

$$[M_i] = \frac{x^i}{K_{inter}} \qquad\qquad (ESI3)$$

In eqns (ESI2) and (ESI3), x is the extent of reaction in the linear fraction defined in such a way that it approaches 1 when the reaction is nearing completion, and EM_i is the Effective Molarity of the i-th cyclic oligomer, defined by the ratio $K_{(intra)i} / K_{inter}$ (Scheme ESI1). The EM_i coincides with the macrocyclization constant K defined in eqn (ESI4)[3] and is a measure of the thermodynamic ease of formation of the given cycle.

$$M_{i+j} \;\xrightleftharpoons{K}\; C_i \;+\; M_j \qquad\qquad (ESI4)$$

$$[M_1]_o = \underbrace{\sum_{1}^{\infty} i \, EM_i \, x^i}_{cyclic\ species} + \underbrace{\frac{1}{K_{inter}} \sum_{1}^{\infty} i \, x^i}_{linear\ species} \qquad\qquad (ESI5)$$

Eqn (ESI5) is easily obtained by substitution of eqns (ESI2) and (ESI3) into Eqn (ESI1). The two terms in the right-hand side of eqn (ESI5) represent the amounts of monomer, in concentration units, that have been converted into cyclic and linear fractions, respectively. If the cyclic species are strain-free,[4] their EM_i values are given by J&S equation, eqn (ESI6), where B represents the EM of the – often hypotethical – strain-free monomeric ring.[2]

$$EM_i = B \, i^{-\frac{5}{2}} \qquad\qquad (ESI6)$$

The term $i^{-5/2}$ in eqn (ESI6) is the product of the two factors $i^{-3/2}$ and i^{-1}. The former factor directly derives from J&S theory and relates to the probability that a Gaussian chain composed of i repeating units has one end coincident with the other, and the latter factor relates to the number of equivalent bonds available to the ring-opening of a cyclic i-mer.[5]

Eqn (ESI6) can be entered into eqn (ESI5) to give eqn (ESI7) where C_{n+1} is the smallest strain-free cyclic species.

ESI3

$$[M_1]_o = \underbrace{\sum_1^n i EM_i\, x^i}_{\text{strained rings}} + \underbrace{B \sum_{n+1}^{\infty} i^{-\frac{3}{2}}\, x^i}_{\text{strianless rings}} + \underbrace{\frac{1}{K_{\text{inter}}} \sum_1^{\infty} i\, x^i}_{\text{linear}} \qquad \text{(ESI7)}$$

When the reaction is almost complete (high concentrations of monomer) x approaches 1. Under these conditions both the first two series in the right-hand side of eqn (ESI7) are convergent. This mathematical result translates into the physical fact that only a finite number of monomer units can be hosted in the cyclic fraction of the system. On the contrary, under the same conditions the third series in eqn (ESI7), related to linear species, is divergent. This means that the linear fraction of the equilibrating polymer can host, in principle, an infinite number of monomer units. Furthermore, if K_{inter} in eqn (ESI7) is high enough, let us say larger than $10^5\ \text{M}^{-1}$, there will be a well defined critical concentration ($c_{\text{mon}}*$) of monomer units, below which only cyclic species will be present at equilibrium and above which only the linear fraction of the system will increase on increasing of the monomer concentration. Above the $c_{\text{mon}}*$, the concentration of each macrocycle assumes the value of its EM [eqn (ESI2), $x^i \rightarrow 1$] and does not increase anymore on increasing the total monomer concentration. In a pictorial representation the EM_i's of the various macrocycles can be viewed as an infinite number of communicating vessels of finite total capacity, where the material is collected until the $c_{\text{mon}}*$ is reached.[6] Above the $c_{\text{mon}}*$, these vessels are completely full and the material in excess overflows into the open-chain polymer box of infinite capacity.

[1] H. Jacobson and W. H. Stockmayer, *J. Chem. Phys.* 1950, **18**, 1600–1606.

[2] G. Ercolani, L. Mandolini, P. Mencarelli and S. Roelens, *J. Am. Chem. Soc.* 1993, **115**, 3901–3908.

[3] P. J. Flory, "Statistical Mechanics of Chain Molecules" Wiley-Interscience: New York, 1969; Appendix D.

[4] For a detailed discussion on strain energy see: (a) L. Mandolini, *Adv. Phys. Org. Chem.* 1986, **22**, 1–111; (b) C. Galli and L. Mandolini, *Eur. J. Org. Chem.* 2000, 3117-3125.

[5] The effective molarity of macrocycle C_i clearly decreases when i increases, because the longer is the linear precursor the higher is the conformational entropy lost in the ring closure to generate the macrocycle.

[6] S. Di Stefano, *J. Phys. Org. Chem.* 2010, **23**. 797–805.