Effective Molarities in Supramolecular Catalysis of Two-Substrate Reactions

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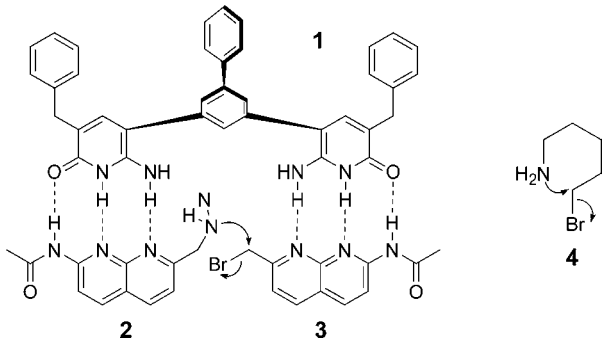
ABSTRACT

Reactivity data related to processes in which molecular receptors promote the reaction of two simultaneously complexed reactants have been surveyed and analyzed in terms of effective molarity (EM). Methods and criteria for the calculation of reliable EM's have been highlighted. Extension of a previous extrathermodynamic treatment of intramolecular reactions of bifunctional chains to the intracomplex reactions of the ternary complexes involved in two-substrate catalyzed reactions has provided a sound framework for a comparative analysis of reactivity and catalytic efficiency in structurally diverse and apparently unrelated systems.

Introduction

Catalysis plays a central role in the domain of chemical and biochemical sciences. One approach to develop new catalysts, clearly inspired by the mode of action of the natural enzymes, has been the design and synthesis of molecular receptors endowed with catalytic properties.[1] This approach has taken advantage of the considerable degree of understanding of the weak forces involved in molecular recognition processes accumulated in the past quarter of a century.[2]

The majority of reported examples refer to supramolecular catalysts which act on a single bound substrate. In recent years, however, a number of receptors designed in such a way as to promote the reaction of two simultaneously complexed reactants have been developed. The simple concept underlying the design of two-substrate catalytic receptors consists of the conversion of an otherwise bimolecular reaction into a monomolecular reaction within a ternary complex, as illustrated by template **1**,[3] which binds to **2** and **3** and promotes alkylation of the nitrogen. Clearly, the intracomplex reaction in **1·2·3** is strictly related to the cyclization of **4**, with the obvious difference that, in addition to covalent bonds, noncovalent bonds are an integral part of the backbone of the cyclic transition state involved in the former case.



Intramolecular reactions sometimes proceed at much faster rates than analogous intermolecular reactions.[4] To set intramolecular reactivity on a quantitative scale, the effective molarity (EM) parameter has been widely used by several workers.[4,5] The EM is defined in eqs 1−3, and

$$EM = k_{\text{intra}}/k_{\text{inter}} \quad (1)$$

$$v_{\text{intra}} = k_{\text{intra}}[A\sim\sim B] \quad (2)$$

$$v_{\text{inter}} = k_{\text{inter}}[A\sim\sim][\sim\sim B] \quad (3)$$

represents the (sometimes hypothetical) concentration of one of the reactants needed for the intermolecular reaction to proceed with a pseudo-first-order specific rate equal to that of the intramolecular reaction. More generally, the EM can be viewed as an intramolecular reactivity corrected for the inherent reactivity of end groups. As such, the EM sets on a common scale reactivity data for different intramolecular reactions.[5a]

Several hundreds of EM data are available for intramolecular reactions of bifunctional molecules,[4a,5] but calculation of EM's is not yet a normal practice in quantitative works on supramolecular catalysis of two-substrate reactions. Out of a few dozen reports available on the subject, EM's have been given for only a handful of cases, but it is fortunate that kinetic data suitable for the calculation of EM's are sometimes available even when no such data were calculated by the authors.

This Account aims to collect quantitative information related to two-substrate supramolecular catalysis in the form of EM data, and to show that a comparison of such

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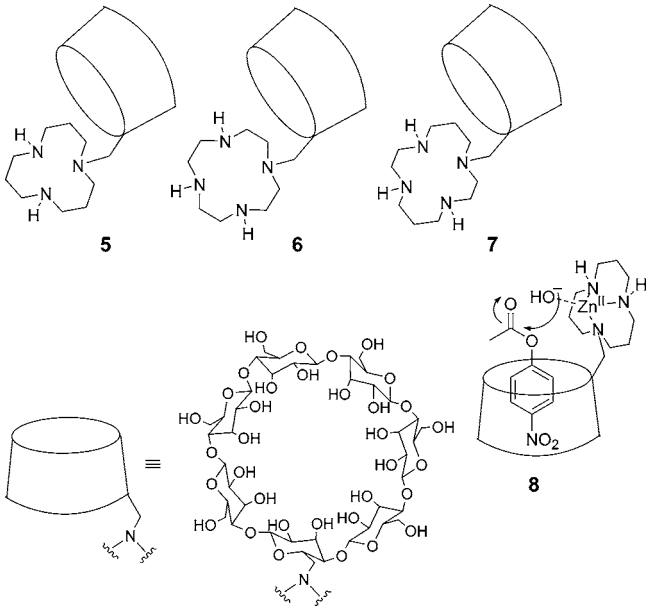
data is a valuable source of new insight into the factors relating structure to catalytic efficiency.

Calculation of Effective Molarities

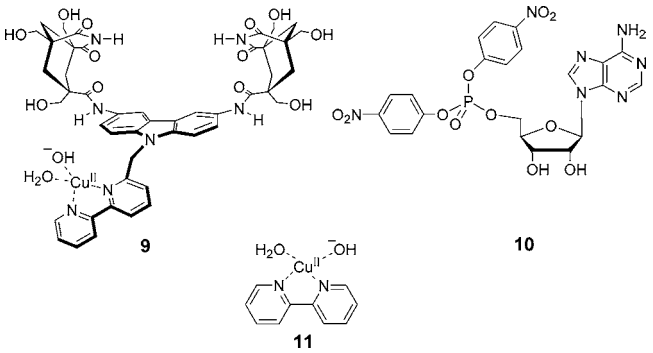
Translation of kinetic data for intramolecular reactions into EM's critically depends on a somewhat arbitrary choice of the model reactions needed for the measurement of k_{inter}. This is a general problem which poses not only experimental but also conceptual difficulties.[4a,5a] The measurement of accurate EM's in the field of supramolecular catalysis is no exception. The composition and structure of the productive (Michaelis) complex must be known and its kinetics of decomposition into products accurately measured. The quantity k_{inter} must be obtained under identical conditions on a model reaction chosen in such a way that the immediate environments of reacting functionalities resemble as close as possible those found in the Michaelis complex.

In this section some of the strategies which have been followed to achieve catalysis by design in two-substrate reactions are outlined, with the main aim at illustrating methods and results involved in the calculation of EM's.

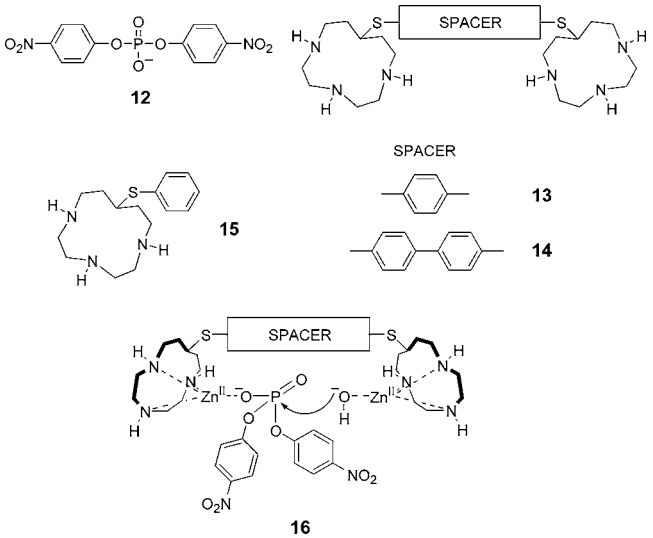
A common strategy underlying the design of the majority of two-substrate supramolecular catalysts combines a substrate recognition site with a catalytic site. The carboxypeptidase mimics **5**-Zn, **6**-Zn, and **7**-Zn[6] combine a β-cyclodextrin, whose cavity recognizes the arene portion of *p*-nitrophenyl acetate, with the Zn^{II}-complexes of polyazamacrocycles [12]ane-N_3, [12]ane-N_4, and [14]ane-N_4, respectively. The reported EM's of 0.21, 0.35, and 0.17 M for the reactions catalyzed by **5**-Zn, **6**-Zn, and **7**-Zn, respectively, are based on measurements of k_{cat} for the decomposition of the productive complex (e.g., **8**) and k_{inter} for the reaction of *p*-nitrophenyl acetate and the Zn^{II}-complexes of [12]ane-N_3, [12]ane-N_4, and [14]ane-N_4. The reliability of the calculated EM's is based on the implicit assumptions (i) that the pK_a and nucleophilicity of the Zn^{II}-bound water are unchanged upon linking the macrocyclic ligand to the cyclodextrin and (ii) that the reactivity of *p*-nitrophenyl acetate is the same in the free and complexed states.



A Kemp's triacid-derived cleft-like receptor unit was used by Rebek[7] as the recognition site for the adenine moiety of **10**. The kinetics of hydrolysis of **10** catalyzed by **9**, and by the model complex **11**, were carefully investigated, but the EM was not given. Using the reported data, we calculate EM* = 0.58 M for the intracomplex reaction of the Cu^{II}-bound hydroxide in **9** with the fully complexed phosphate triester **10**. The symbol EM* denotes from now onward quantities calculated by us.

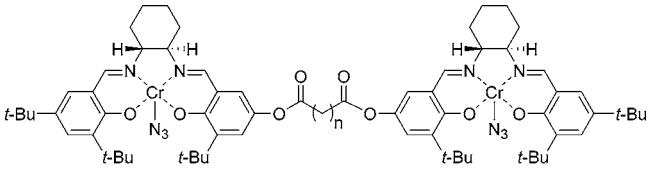


The mechanism proposed by Breslow[8] for the bifunctional catalysis of the hydrolysis of phosphate diester **12** by the bis-zinc(II) complexes **13**-Zn_2 and **14**-Zn_2 is shown in **16**. The dinuclear catalysts were superior to **15**-Zn, with a moderate synergism. From the first-order specific rates obtained under a standard set of reactant concentrations, we calculate EM* = 1.3×10^{-3} M for **13**-Zn_2, and EM* = 2.4×10^{-3} M for **14**-Zn_2.

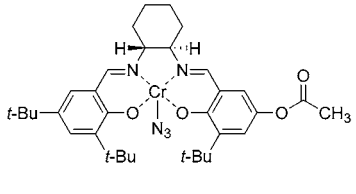


Jacobsen's dimeric complexes **17** are highly enantioselective catalysts of the asymmetric ring-opening of meso epoxides,[9] whose mechanism is shown in **19**. Analysis of initial rates for the ring-opening of cyclopentene oxide afforded the k_{inter} and k_{intra} values in Table 1. Odd features in such data are the marked dependence of k_{inter} on the number of methylene groups in the linker, and the much smaller k_{inter} based on the monomeric catalyst **18**. Whereas

the latter discrepancy is partly attenuated by a statistical factor of 4 favoring the dimers over the monomer, it has been suggested[9] that highly reactive multimetallic assemblies may play a role in the intermolecular reactions of dimeric complexes. It appears therefore that instead of combining the k_{intra} and k_{inter} pairs obtained for each dimeric catalyst,[9] more reliable EM's are calculated using the k_{inter} based on **18** for the whole series. Such values are listed in the last column of Table 1.



17a: n=2, **17b-f**: n=4-8, **17g**: n=10



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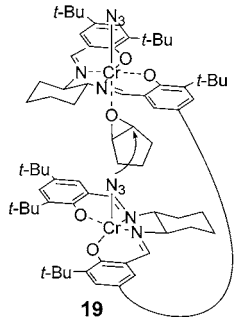

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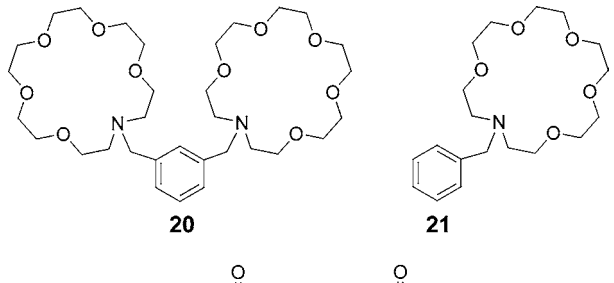
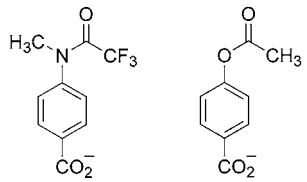
Two identical metal ions are again involved in the dinuclear complex **20**-Ba_2, in which one of the metal ions binds and activates an ethoxide nucleophile, and the other binds to the distal carboxylate of **22** and **23**, as shown in **24**.[10] On the basis of a comparison of rates of ethanolysis in the presence of **20**-Ba_2 and **21**-Ba, EM = 0.078 M and EM = 0.041 M were calculated for the reactions of **22** and **23**, respectively.



20 **21**



22 **23**

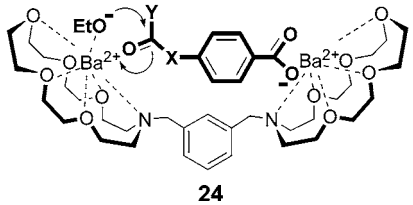


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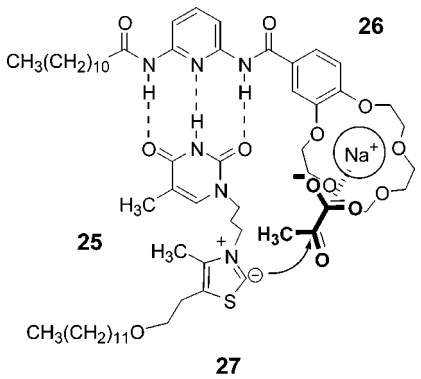
Table 1. Ring Opening of Cyclopentene Oxide Catalyzed by (salen)Cr−N_3 Complexes[a]

catalyst	k_{inter} (M^{-1} min^{-1})	k_{intra} (min^{-1})	EM* (M)
18	1.2		
17a	16	4.4×10^{-2}	0.037
17b	15	5.4×10^{-2}	0.045
17c	27	0.43	0.36
17d	16	0.32	0.27
17e	7.9	0.21	0.17
17f	10	0.15	0.12
17g	4.4	3.8×10^{-2}	0.032

[a] Data from ref 9.

The thymine moiety linked to the thiazolium in **25** and the 2,6-diaminopyridine linked to the benzo-crown ether in **26** have appropriate donor−acceptor sequences to ensure complex formation via three hydrogen bonds. The Na^+ complex of adduct **25·26** catalyzes the oxidative decarboxylation of pyruvate, as depicted in **27**.[11] On the basis of a comparison of the rate of oxidative decarboxylation of pyruvate in **27** with that measured in the presence of **25** alone (plus NaI), we calculate EM* = 0.16 M.



25 **26**

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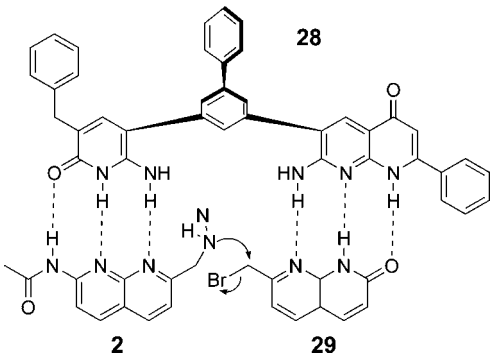
Hydrogen bonding plays a key role in supramolecular catalysts devoid of metal centers. Notable examples are receptors **1** and **28**,[3] endowed with two identical and different binding sites, respectively, for the simultaneous complexation of reaction partners. From the reported initial rates in the absence and in the presence of template and equilibrium constants for binding of reactants to monotopic model receptors, and using a general treatment of multiple complexation equilibria,[12] we calculate EM* = 0.14 and 0.11 M for reaction of ternary complexes **1·2·3** and **28·2·29**, respectively.



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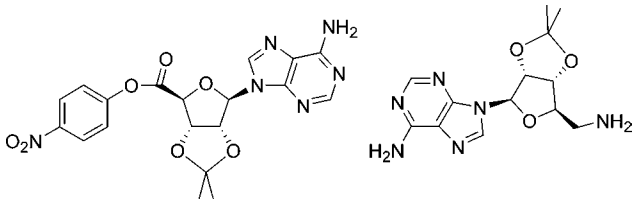
2 **29**

The aminolysis of *p*-nitrophenyl ester **30** by aminoadenosine **31** is catalyzed by template **32**, in which substrate recognition relies on chelation of purine units in **30** and **31**.[13] High binding affinities result from a



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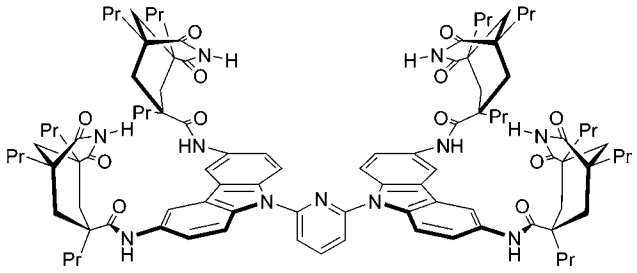

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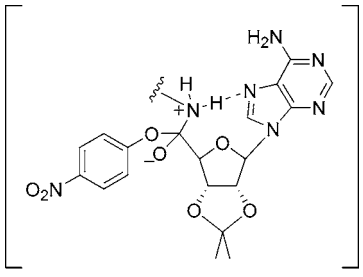
combination of hydrogen bonding and aromatic stacking. An EM value of 0.035 M within the termolecular complex **32·30·31** was calculated by the authors, with reference to the model reaction **30** + **31** in the absence of template. It was reported[13] that **30** is about 10^3 times more reactive than *p*-nitrophenyl acetate due to stabilization of intermediate **33** by hydrogen bonding to the purine N3 nitrogen. However, the template can accommodate in its cavity the tetrahedral intermediate "with conformations of the purines at the anomeric carbon that do not allow the intramolecular stabilization". We believe, therefore, that the value of 0.035 M is underestimated, and use the aminolysis of the 10^3-fold less reactive *p*-nitrophenyl acetate to calculate EM* = 35 M.



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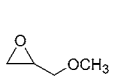
Ring opening of oxirane **34** with 4-*tert*-butylthiophenol **35** is catalyzed by the phosphonium-appended 2-ureido-4-pyrimidone **36**.[14] The proposed structure of the productive intermediate **(36·34·35)$_2$** shows simultaneous Brönsted base activation of thiol and Lewis acid activation of epoxide. From a comparison of the reaction rate measured in the presence of **36** with that measured in the presence of an equimolar mixture of **37** and **38**, we calculate EM* = 0.057 M.



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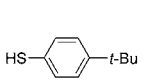

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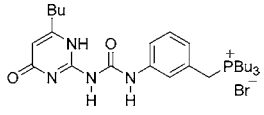

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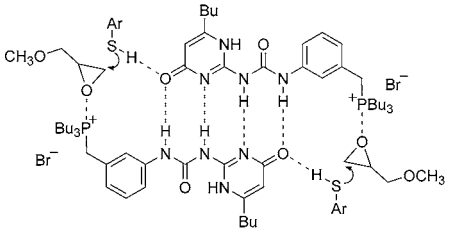
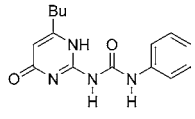


(36·34·35)$_2$



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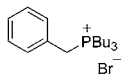

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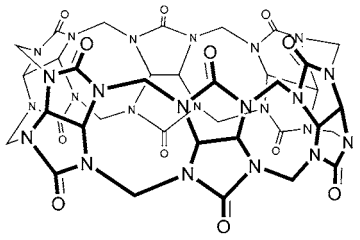
The last part of this section deals with hosts endowed with cavities roomy enough to accommodate concurrently two reactant molecules in such a way as to promote their reaction. An early study of quantitative nature was reported by Mock.[15] The 1,3-dipolar cycloaddition of alkyne **40** and alkyl azide **41** (eq 4), in the presence of cucurbituril (**39**), was markedly accelerated and became highly regioselective, yielding only **42** as a product. Kinetic analysis revealed the intermediacy of the ternary complex **39·40·41**, whose structure involves simultaneous binding of both reactants, with one $-NH_3^+$ coordinated to each set of carbonyls and with the reactive functions extending into the interior of **39**, thus providing a favorable hydrophobic contribution to complexation. From $k_{inter} = 1.16 \times 10^{-6}$ M^{-1} s^{-1} for the reaction of uncomplexed reactants, and $k_{intra} = 0.019$ s^{-1} for the reaction in the ternary complex, the remarkably high EM* value of 1.6×10^4 M is obtained.



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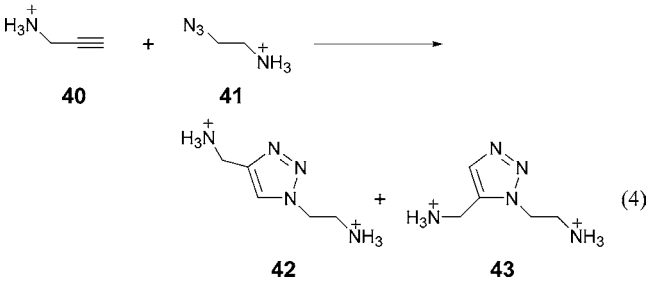
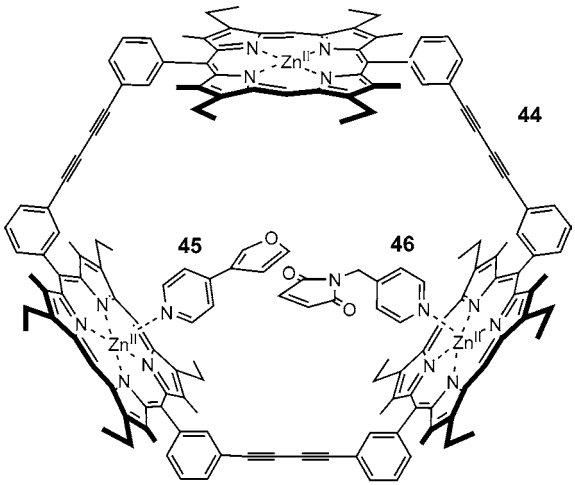


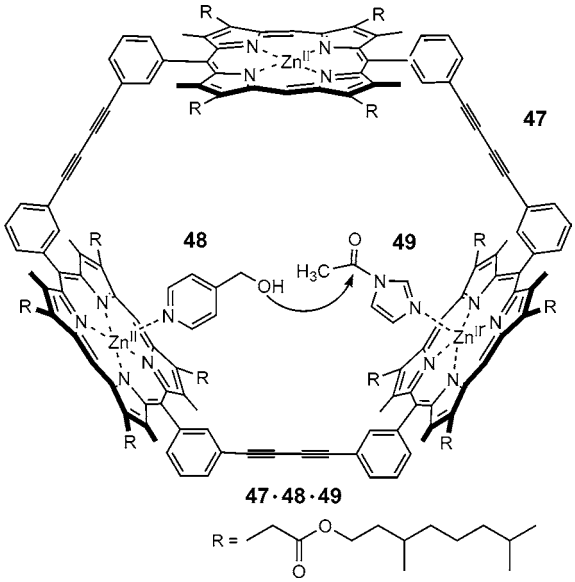
40 **41** **42** **43** (4)

The strategy adopted by Sanders to hold reaction partners in proximity is illustrated by ternary complexes **44·45·46**[16] and **47·48·49**,[17] where the hosts are porphyrin trimers and the driving force for binding is provided by Zn−N coordination. In both cases, substrates bound inside the cavity react more rapidly than uncomplexed

substrates. Translation of rate data into EM's requires an estimate of the proportion of productive trimer molecules containing both substrates in a single cavity, among a host of species of varying stoichiometry and with no preference for binding either inside or outside the cavity. The data

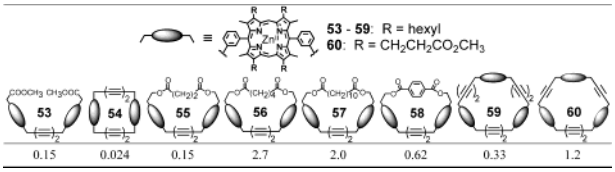


reported for the Diels–Alder reaction in **44·45·46**[16] were used[12] to calculate EM* = 8.0 M with reference to reaction between uncomplexed reactants. Similar calculations for the acetyl transfer in **47·48·49**[17] gave EM* = 16 M, based as above on the reaction between uncomplexed reactants.



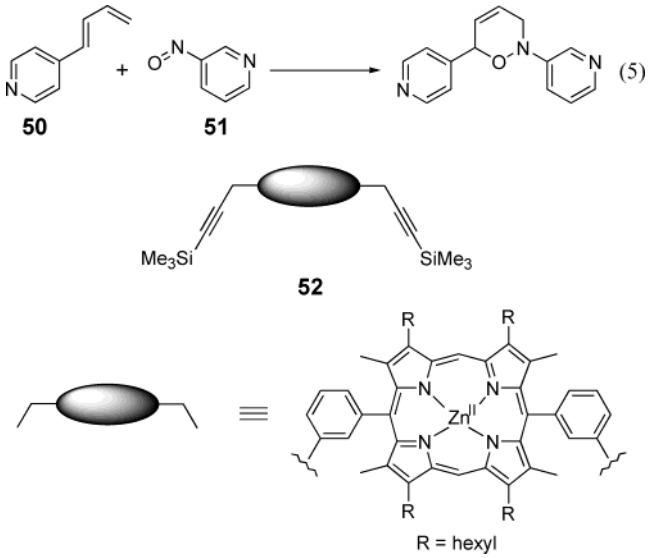
However, unlike the above Diels–Alder reaction, the transacylation reaction is sensitive to Lewis acid activation, as shown by the finding that porphyrin units in monomeric form gave a small but definite rate increase.[17] In the language of Kirby,[1a] inclusion of reactants into the host cavity provides not only passive binding but also dynamic binding. If the reaction between reactants complexed to monomeric porphyrin is taken as the model intermolecular reaction, a more realistic EM* = 0.67 M is calculated. The ratio between the two values, 16/0.67 = 24, quantifies the reactivity increase of acetylimidazole due to zinc coordination.

Table 2. Effective Molarities (EM*, M) in the Hetero-Diels–Alder Reaction of 50 + 51 Promoted by Metalloporphyrin Hosts (Dichloromethane, 25 °C)[a]



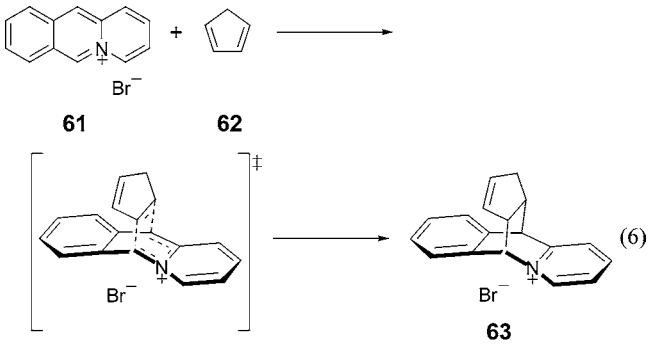
[a] Data from ref 18.

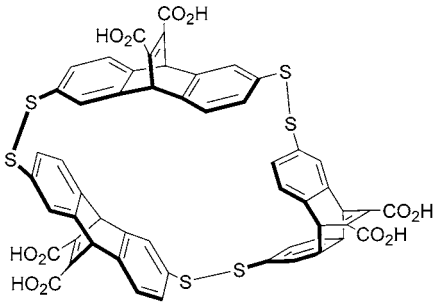
An extensive investigation of the influence of host geometry changes on acceleration rates obtained in the hetero-Diels–Alder reaction of **50** and **51** (eq 5) was carried out by Sanders et al.[18] Using the published rate and equilibrium data, we calculate[12] as before the set of EM* values in Table 2, based on the reaction between the reactants complexed to the monomeric porphyrin **52**, to allow for Lewis acid activation of the dienophile **51**.



The notion of affinity for a stable transition-state analogue (TSA), on which the development of catalytically active imprinted polymers and catalytic antibodies was based, has been very recently used for the selection of a catalyst from a dynamic combinatorial library (DCL).[19] The chosen reaction is the Diels–Alder reaction between acridizinium bromide **61** and cyclopentadiene **62** (eq 6), the product of which was reasoned to be a good TSA for the reaction itself. A DCL in the presence of the reaction product **63** resulted in the selection and amplification of cyclophane **64** that was found to induce a modest acceleration of the given Diels–Alder reaction. It was established that **64** binds strongly **61** and that there is enough room for the weaker binding of **62** in the same cavity. Kinetic analysis yielded the k_{cat} for reaction of **64·61·62**, from which EM = 0.08 M.

Shape-complementary molecules that, upon reversible dimerization via hydrogen bonding, form pseudospherical capsules have been shown to reversibly encapsulate smaller molecules. One of such molecular containers, the so-called "hydroxy softball" **(65)$_2$**, encapsulates diene and





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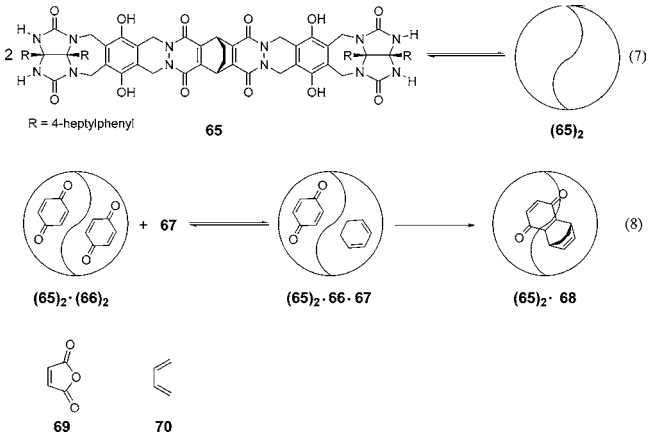
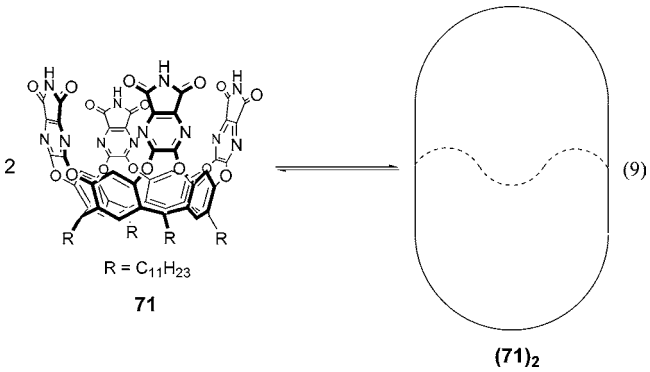
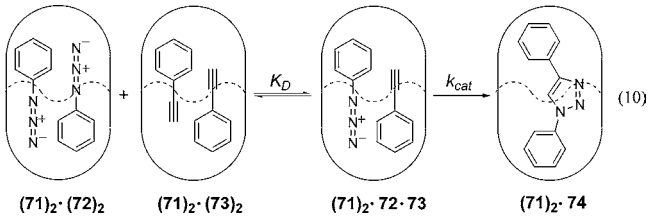
dienophile and promotes the Diels–Alder reaction.[20] Analysis of equilibrium and rate data indicates that the reaction of *p*-benzoquinone (**66**) with cyclohexadiene (**67**) takes place as shown in eq 8, where the precursor to **(65)$_2$·68** is the unsymmetrically loaded encapsulation complex **(65)$_2$·66·67**. The reported data were translated into EM



= 0.48 M for the above reaction, and EM = 0.36 M for the reaction of maleic anhydride (**69**) with **67**. Interestingly, the almost identical value of 0.35 M was obtained for the much slower reaction of **66** with butadiene (**70**). Unlike the previous examples, direct observation of the "Michaelis" complex was possible when the 1,3-dipolar cycloaddition of phenyl azide (**72**) to phenylacetylene (**73**) was carried out in the presence of capsule **(71)$_2$**, reversibly self-assembled from two identical resorcinarene subunits (eq 9).[21] The cylindrical cavity of **(71)$_2$** can accommodate simultaneously two different aromatic guest molecules. The background second-order rate constant for cycloaddition is very low ($k_{inter} = 4.3 \times 10^{-9}$ M^{-1} s^{-1}), and in the presence of 5 mM **(71)$_2$**, the initial rate of product



formation is 1.3×10^{-9} M s^{-1}. The disproportionation equilibrium of encapsulated reactants could be monitored by ^{1}H NMR in deuterated mesitylene. From the reported $K_D = 9 \pm 3$, we calculate that one-half of the capsules are in the form of the "Michaelis" complex **(71)$_2$·72·73**, which translates into $k_{cat} = 5.2 \times 10^{-7}$ s^{-1}, EM* = 120 M.



Discussion

To the extent that the intermolecular reference reactions reproduce to a good precision all of the basic interactions featured by reactant and transition-state complexes involved in the related intracomplex reactions, the EM data summarized in Table 3 provide a measure of catalytic efficiency which is independent of the chemical activation possibly provided by catalytic groups (dynamic binding[1a]), but solely depends on the way in which the catalytic template assembles the two simultaneously complexed reactants in a position suitable for the reaction to occur. Unlike the frequently reported rate acceleration, the EM is independent of the working concentrations, and its numerical value is determined by the usual choice of molarity as concentration unit.

The EM's in Table 3 span the wide range of 7 orders of magnitude, from 10^{-3} to 10^4 M. The higher the EM, the more efficient the catalyst, at least as long as reactivity is concerned. Other measures of catalytic efficiency, such as low product inhibition and high durability (high turnover number), and specific regio- and stereochemical features are immaterial to the present context. In fact, many of the processes listed in Table 3 are stoichiometric rather than catalytic because of severe product inhibition, and even when turnover catalysis is observed, none of the catalysts has reached the degree of ripeness for use in laboratory-scale syntheses, with the notable exception of Jacobsen's catalysts.[9]

A convenient starting point in a discussion of why the EM's are so high in some cases and so low in others is the consideration of the number of rotatable single bonds in the ternary complexes. The ease of cyclization of α,ω-

Table 3. Effective Molarities

entry	reaction	catalyst	reaction conditions	ref	EM (M)	EM* (M)
1	*p*-nitrophenyl acetate hydrolysis	**5**-Zn	H_2O, 25 °C, pH 7	6	0.21	
		6-Zn			0.35	
		7-Zn			0.17	
2	hydrolysis of phosphotriester **10**	**9**	H_2O, 25 °C, pH 6−9.5	7		0.58
3	hydrolysis of phosphodiester **12**	**13**-$(Zn)_2$	20% DMSO, 55 °C, pH 8.36	8		0.0013
		14-$(Zn)_2$				0.0024
4	ring-opening of cyclopentene oxide	**17a**−**g**	23 °C	9		0.032−0.36[a]
5	ethanolysis of anilide **22**	**20**-$(Ba)_2$	EtOH, 25 °C	10	0.078	
	ester **23**				0.041	
6	pyruvate decarboxylation	**26**-Na	$CDCl_3$−CD_3CN 9:1 (v/v), 25 °C	11		0.16
7	S_N2 alkylation of **2** by **3**	**1**	$CDCl_3$, 25 °C	3		0.14
	2 by **29**	**28**				0.11
8	aminolysis of *p*-nitrophenyl ester **30** by **31**	**32**	$CHCl_3$, 25 °C	13	0.035	35
9	ring-opening of glycidyl methyl ether **34** by **35**	**(36)$_2$**	$CDCl_3$, 50 °C	14		0.057
10	1,3-dipolar cycloaddition between **40** and **41**	**39**	88% HCOOH−H_2O 1:1 (v/v), 40 °C	15		16,000
11	Diels−Alder reaction **45** + **46**	**44**	$C_2H_2Cl_4$, 60 °C	16		8.0
12	acetyl transfer from **49** + **48**	**47**	toluene, 70 °C	17		0.67
13	Diels−Alder reaction **50** + **51**	**53**−**60**	CH_2Cl_2, 25 °C	18		0.024−2.7[b]
14	Diels−Alder reaction **61** + **62**	**64**	H_2O, 25 °C, pH 9	19	0.08	
15	Diels−Alder reaction **66** + **67**	**(65)$_2$**	*p*-xylene-d_{10}, 22 °C	20	0.48	
	66 + **70**				0.35	
	69 + **67**				0.36	
16	1,3-dipolar cycloaddition **72** + **73**	**(71)$_2$**	mesitylene-d_{12}, rt	21		120

[a] Individual EM* values in Table 1. [b] Individual EM* values in Table 2.

bifunctional chain molecules is strongly influenced by the length of the chain connecting the end groups.[5] The number of single bonds in the chain determines not only the size and hence the strain of the ring being formed but also the amount of torsional entropy lost upon cyclization.[5] It is instructive to compare the efficiency of the template-assisted S_N2 reaction in **1·2·3**, EM* = 0.14 M, with that of the corresponding six-membered ring formation from **4**, EM = 100 M.[4a] Since the number of single bonds (five) is the same in both systems, it is concluded that the relative positioning of the guest reactants in the ternary complex is far from ideal, and that a geometrical distortion in the transition-state structure is responsible for the loss of efficiency by nearly 3 orders of magnitude compared with the reaction of **4**.

It is unfortunate that, for most reactions, the intramolecular counterpart in which the two reactants are connected by a chain of covalent bonds not only is not available but cannot even be envisaged. We propose therefore to resort to the extrathermodynamic treatment of EM's set forth many years ago.[5a] Application of transition-state theory to eq 1 leads to eq 11, which is conveniently written in the compact form of eq 12, where the quantities EM_H and EM_S, defined in the given order by the exponential terms of eq 11, are the enthalpic and entropic component of the EM.

$$EM = \exp[-(\Delta H^{\ddagger}_{intra} - \Delta H^{\ddagger}_{inter})/RT] \exp[(\Delta S^{\ddagger}_{intra} - \Delta S^{\ddagger}_{inter})/R] \quad (11)$$

$$EM = EM_H \times EM_S \quad (12)$$

The quantity $\Delta H^{\ddagger}_{intra} - \Delta H^{\ddagger}_{inter}$ is a measure of the strain energy of the cyclic transition state. For a strainless intramolecular reaction $EM_H = 1$, and the EM is solely determined by the entropic component, $EM = EM_S$. To a useful approximation, the quantity $\Delta S^{\ddagger}_{intra} - \Delta S^{\ddagger}_{inter}$ turned out to be independent of intrinsic factors such as the nature of the reacting groups, reaction mechanism, and solvent, but strongly dependent on the number of essential single bonds in the bifunctional chain. A large number of experimental $\Delta S^{\ddagger}_{intra} - \Delta S^{\ddagger}_{inter}$ data related to the formation of 3- to 23-membered rings in several cyclization reaction series were averaged and smoothed to give the set of values listed in Table 4. Extension to longer chains was essentially based on the Jacobson−Stockmayer theory.[22] The dependence of log EM_S on the number of skeletal single bonds is shown graphically in Figure 1. Cyclization of the shorter chains involves an average drop of 4.0 eu per added single bond, which implies a nearly complete freezing of the torsional motion of one C−C bond, whose contribution to the entropy has been estimated as 4.4−4.8 eu.[23] Longer chains exhibit a much smaller dependence on chain length, because the incremental torsional contribution brought about by an additional single bond is largely retained in the cyclic transition state. Incidentally, the quantity 30 eu at $r = 0$ quantifies the loss of rotational−translational entropy suffered by bimolecular reactions in solution, and provides an estimate of the maximum advantage of intramolecu-

Table 4. Entropy Changes and Effective Molarities[a] in the Cyclization of Bifunctional Chains as a Function of the Number of Skeletal Single Bonds (*r*)

r	$\Delta S^{\ddagger}_{intra} - \Delta S^{\ddagger}_{inter}$ [a]	EM_S (M)	*r*	$\Delta S^{\ddagger}_{intra} - \Delta S^{\ddagger}_{inter}$ [a]	EM_S (M)
0	30	3.6×10^6	10	−1.5	4.7×10^{-1}
1	26	4.8×10^5	12	−2.7	2.6×10^{-1}
2	22	6.4×10^4	14	−3.7	1.6×10^{-1}
3	18	8.6×10^3	16	−4.3	1.1×10^{-1}
4	14	1.1×10^3	20	−5.3	6.9×10^{-2}
5	10	1.5×10^2	25	−6.0	4.9×10^{-2}
6	6	2.0×10	30	−6.5	3.8×10^{-2}
7	2	2.7	40	−7.3	2.5×10^{-2}
8	0	1.0	50	−8.0	1.8×10^{-2}
9	−0.8	6.7×10^{-1}			

[a] From ref 5a.

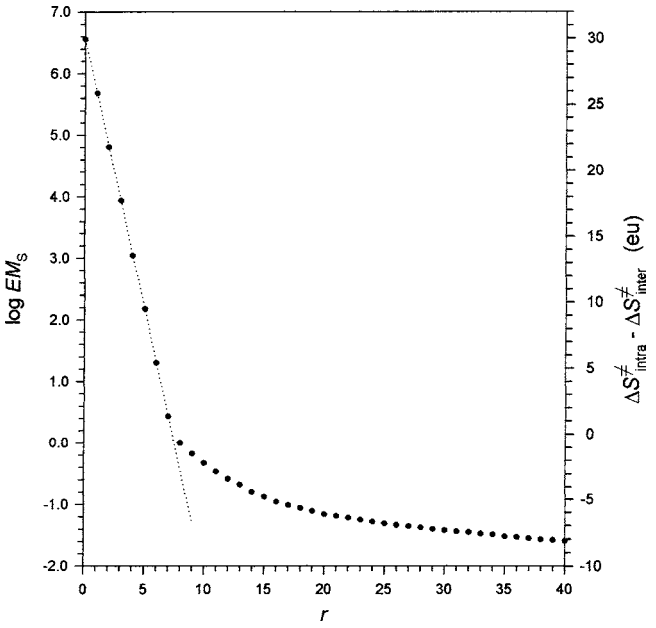
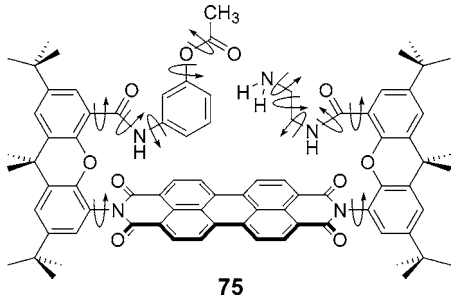


FIGURE 1. Log EM_S vs number of rotatable bonds (r) in the bifunctional chain undergoing cyclization.

larity as exp(30/R), or $10^{6.6}$ M,[5a,24] to be compared with Page and Jencks's earlier estimate[4b] of 10^8 M.

The data in Table 4 have been recently used[5b] to predict with good accuracy a large number of EM's related to the formation of strainless rings. As an additional, illustrative example, let us consider the intramolecular acyl transfer in **75**, for which EM = 0.22 M.[25] The number of single



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bonds in **75** is 12, but an estimate of the torsional entropy is complicated by restricted rotations about amide and imide bonds. A number of rotatable bonds in the range 8−12 translates into an EM_S value of 1.0−0.26 M (Table 4), which compares well with the experimental value of 0.22 M, and indicates that **75** was well designed to attain to a transition state whose strain energy does not exceed 1 kcal/mol.

Extension of the above treatment to the reactions of supramolecular ternary complexes is not straightforward, because no information is available on the entropy of rotatable bonds other than covalent bonds, and rough approximations are required. The number of single bonds in the spacer units of Jacobsen's catalysts **17a**−**g** is $n + 5$. If the Cr−O bond in **19** is assimilated to a standard single bond, then the number of internal rotors r involved in the intracomplex reactions in **19** is $n + 6$, and the following EM_S values (M) are calculated from Table 4: **17a**, 1.0; **17b**, 0.47; **17c**, 0.37; **17d**, 0.26; **17e**, 0.21; **17f**, 0.16; **17g**, 0.11. Comparison with data in Table 1 reveals a generally good agreement between predicted and experimental values, with the exception of the shortest chains (**17a** and **17b**), for which the EM's are significantly lower than the values estimated on purely entropic grounds. This behavior may be attributed to the fact that an almost linear Cr−N−N−N−C−O−Cr arrangement cannot be accommodated in a cyclic structure without severe distortions when the linker is too short.

In all of the systems in which reaction partners are held in proximity via nitrogen coordination to the metal centers of dimeric and trimeric Zn(II)−porphyrins (Table 3, entries 11−13), there are three single bonds in the reactants plus two N−Zn bonds. The experimental EM values are 1 to nearly 4 orders of magnitude lower than the EM_S value of 150 M for a five-rotor system, suggesting that in all cases there is a more or less pronounced mismatch between transition-state guest and catalyst host.

There are many other systems among those listed in Table 3 in which rotatable bonds are involved (entries 1−3, 5, 6, 8, and 9). With the sole exception of the acyl transfer from **30** to **31** catalyzed by **32** (entry 8), the experimental EM values are lower by 1−3 orders of magnitude than the corresponding EM_S values estimated as above from Table 4, again suggesting the operation of strain effects. The number of rotatable bonds in the complex **32·30·31** is 7, and the corresponding EM_S, 2.7 M, is an order of magnitude lower than the experimental value of 35 M. A possible explanation for this discrepancy is that the value of 35 M calculated by us is overestimated, but it cannot be excluded that a tight binding of **30** and **31** to **32** due to multiple hydrogen bonding and π-stacking reduces the torsional freedom and, consequently, the entropy loss upon acyl transfer.

In the ternary complex involved in the cucurbituril-catalyzed reaction of **40** with **41**, the reactants grasp at the host's carbonyls with their $-NH_3^+$ groups and extend their reacting groups into the interior, thereby filling completely, or very nearly so, the host cavity. Indeed, the calculated[26] cavity volume of 164 Å^3 translates into an encapsulated reactant concentration of 10 M, which corresponds to the pure liquid state of a compound having molecular weight 100 Da and density 1 g/mL. It seems likely, therefore, that torsional motions of **40** and **41** are frozen in the ternary complex, and no further torsional entropy is lost upon reaching the transition state. The EM for this system is very high, 1.6×10^4 M (Table 3, entry 10). In fact, it is not only the highest value among those listed in Table 3, but it is more than 3 orders of magnitude higher than the actual concentration of functionalities in the host's cavity, where they apparently enjoy a much more favorable orientation than in the encounter complex of the uncatalyzed reference reaction. Using the language of Menger's "spatiotemporal postulate",[27] cucurbituril not only concentrates reactants but also increases the time that the reacting functions reside within a critical distance. The value of 1.6×10^4 M approaches the upper limit of $10^{6.6}$ or 4×10^6 M predicted[5a,24] for the EM of an

intramolecular (intracomplex) reaction in which the reacting functions are in the ideal condition in terms of proximity and orientation for a strain-free reaction to occur without any entropy change other than those due to bond-breaking and bond-making processes. Residual torsional motions in the ternary complex, or imperfect side-by-side alignment of the reacting functionalities, or both, might be held responsible for the finding that the experimental EM is still 200-fold lower than predicted by theory.

Even more significant in the context of a comparison between intermolecular processes is the reaction of **72** with **73** catalyzed by Rebek's capsule **$(71)_2$**, because no conventional bonds are established between reactants and host and, consequently, no torsional entropy changes are involved. Here, togetherness is ensured by imprisonment of both reactants in the same cell. The volume of the cell[21] is 450 Å^3, and the actual concentration of encapsulated reactants is 3.7 M, which is only 1/32 of the EM calculated from rate data (Table 3, entry 16). Like in the reaction of **39·40·41**, the EM is much higher than the actual concentration in the host's cavity, which again indicates a favorable directional correlation of functionalities in the complex **$(71)_2$·72·73**, but it is apparent that **$(71)_2$** is significantly less effective than **39** in promoting the 1,3-cycloaddition between azido and alkyne functionalities.

In contrast to the previous examples, the EM's of the Diels−Alder reactions catalyzed by softball **$(65)_2$** (Table 3, entry 15) are an order of magnitude lower than the actual reactant concentration of 5.3 M calculated[28] from the softball capacity of 313 Å^3. Clearly, togetherness alone does not guarantee high reactivity. The more stringent orientational requirements of Diels−Alder reactions, compared with 1,3-cycloaddition reactions between functionalities endowed with cylindrical symmetry, provide a likely explanation for the less efficient catalysis through encapsulation of the former reactions. It is apparent, therefore, that reactants of the Diels−Alder reactions listed in entry 15 of Table 3, when hosted in the cavity of **$(65)_2$**, spend a significant fraction of their time in a wrong mutual orientation. This is even more so for the Diels−Alder reaction in **64·61·62** (Table 3, entry 14), for which an EM as low as 0.08 M was calculated.

Conclusions and Outlook

A comparison of available EM's for different reaction types with the idealized EM_S values derived from a previous extrathermodynamic treatment of intramolecular reactivity data proved to be a useful source of insights into the factors affecting reactivity of two-substrate reactions catalyzed by molecular receptors. In the majority of systems, the large torsional entropy losses due to the involvement of several rotatable bonds in the ternary complexes impose severe restrictions to catalytic efficiency. A glance at Table 4 and Figure 1 shows that large EM's (>1 M) call for a limited number of rotatable bonds ($r < 8$). However, the three dozen EM's collected in Table 3 are still a limited sample of data. It is hoped, therefore, that the calculation of EM's will become an integral part of any quantitative work on intracomplex reactions. It is also felt that use of the data in Table 4 for the evaluation of the maximum EM to be obtained in the absence of strain can be useful in the design of new catalytic receptors.

Since no torsional entropy is involved in reactions between encapsulated reactants, such processes have the potential of approaching the upper reactivity limit of intramolecular (intracomplex) reactions. Accumulation of EM data will prepare the ground for testing concepts and theories of directionality of chemical reactions, such as Koshland's "orbital steering",[29] Flory's "favorable directional correlation",[30] Menger's "reaction windows",[27] and Bruice's "near-attack conformers",[31] and for comparing them with descriptions based on entropy and strain.[5,24,32]

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