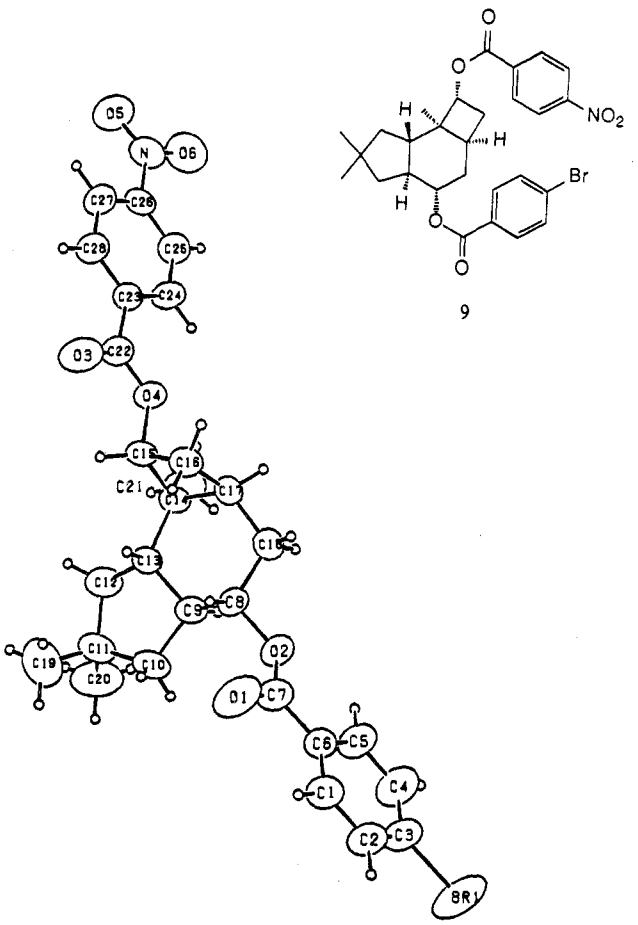

Figure 1. ORTEP representation and Chemtext diagram of 9.

dation, gave aldehyde **2**. One-carbon homologation through sequential Wittig reaction and hydrolysis of the enol ether product mixture furnished an aldehyde that was converted by [(ethoxycarbonyl)ethylidene]triphenylphosphorane to the corresponding α,β-unsaturated ester (>95% *E*). Its reduction provided alcohol **3**, which was elaborated by standard methods to the cyclization substrate **4**. Gratifyingly, this enediyne was rearranged by $CpCo(CO)_2$ directly to the highly air sensitive diene **5** as the only diastereomer (^{1}H NMR analysis). Although not demonstrated here rigorously, it is clear from model studies[7] that this cyclization is catalytic. Remarkable are the efficiency (92%!) and stereoselectivity (complete) of this process. The relative configurations of C-1, -7a, and -7b could not be deduced from spectroscopic data, although that of the latter two was assumed to be as shown, retaining the stereochemistry of the alkene unit.[6] Since Matsumoto had demonstrated that the C-1 stereocenter could be controlled, if necessary, at a later stage,[3] diene **5** was elaborated further.

Dissolving lithium in NH_3(liq) reduced the C-2a,3 π-bond to furnish the *cis*-bicyclo[4.2.0]octane stereochemistry,[9] the remaining unsaturation being removed by regio- but (surprisingly) not stereospecific hydroboration–oxidation, generating **6** and **7** in a ratio of 2:3. The structure of **6** (and thus the stereochemical outcome of the cyclization of **4**) was confirmed through an X-ray structural analysis of its derivative **9** (Figure 1),[10] the result of 4-bromobenzoylation, desilylation, and finally, 4-nitrobenzoylation at C-1.

Oxidation of the mixture of **6** and **7** allowed the chromatographic separation of the corresponding ketones. The subsequent base-catalyzed isomerization of the undesired isomer (equilibrium ratio 5:1) led to **8** (20% from ethyl 2-methylpropanoate), a molecule very similar to an intermediate in Semmelhack's strategy to **1**,[4] that protocol guiding the completion of the present approach. Thus, carboxylation of the enolate of **8** with CO_2, esterification with CH_2N_2, and selenium-mediated oxidation (a sequence that was not optimized in its efficiency, the relatively low yield constituting the result of incomplete conversions) generate the oxo ester precursor to **1**, whose reduction with sodium bis(methoxyethoxy)aluminum hydride gave rise to a mixture of C-4 isomeric diols, that containing the desired 4α-OH configuration predominating (37:17). Finally, deprotection of the C-1 hydroxy group supplied illudol (**1**), spectroscopically identical with the naturally occurring material.[11]

The assembly of **1** is the first in which all three rings are constructed in a step that features CpCo as a mediator in the completely stereospecific generation of a strained tricycle. The selective elaboration of the diene unit in **5**, a functional moiety that is the product of many related cyclizations, points to other applications of this strategy to the synthesis of complex molecules.

Acknowledgment. This work was supported by the National Institutes of Health (GM22479).

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond angles, and bond distances for **9** and ^{1}H NMR, ^{13}C NMR, IR, HRMS, and combustion analysis data for **1–9** and intermediates (16 pages). Ordering information is given on any current masthead page.

(9) (a) Maksic, Z. B.; Eckert-Maksic, M. *J. Mol. Struct.* **1983**, *91*, 295. (b) Spelbos, A.; Mijlhoff, F. C.; Bakker, W. H.; Baden, R.; van den Enden, L. *J. Mol. Struct.* **1977**, *38*, 155.

(10) Executed by Dr. F. J. Hollander, Chexray facility, University of California at Berkeley: triclinic; space group $P\bar{1}$, a = 8.8169 (10) Å, b = 11.6852 (19) Å, c = 14.3025 (19) Å, α = 69.878 (10)°, β = 78.541 (10)°, γ = 85.512 (11)°, V = 1356.0 (4) Å^3, Z = 2, μ_{calcd} = 15.4 cm^{-1}, ρ_{calcd} = 1.36 g cm^{-3}; Enraf-Nonius CAD4; Mo Kα radiation [λ(Kα) = 0.71073 Å]; 3° ≤ 2θ ≤ 45°; 3546 unique reflections, of which 2352 were treated as observed [$F^2 \geq 3\sigma(F^2)$]; an absorption correction was not applied; R = 0.0403, R_w = 0.0536.

(11) We thank Professors T. C. McMorris and M. F. Semmelhack for providing us with a sample of natural illudol and spectral data of synthetic illudol, respectively.

Complexation Control of Pericyclic Reactions: Supramolecular Effects on the Intramolecular Diels–Alder Reaction†

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The development of artificial enzyme-like catalysts is being pursued from two directions, the immunological[1] and the synthetic.[2] Critical to the success of these catalysts is their ability to selectively bind and stabilize the transition state of the reaction.[3] Pericyclic processes are attractive targets for catalyst design due to their widespread use in synthesis, their uncomplicated mechanisms, and the possibility of using specific binding interactions to overcome the entropic demands of their ordered transition states.[4] In this paper we demonstrate that synthetic receptors with carefully positioned binding groups can modulate the rate of a cycloaddition reaction by selectively binding to different structures on the reaction pathway.

Our target reaction was the intramolecular Diels–Alder (IMDA) reaction of disubstituted *N*-furfurylfumaramide derivatives[5] **1** (Scheme I). This process is characterized by substantial

† Presented in part at the 200th National ACS meeting, Washington, DC, August 1990.

(1) Janda, K. D.; Benkovic, S. J.; Lerner, R. A. *Science* **1989**, *244*, 437. Schultz, P. G. *Acc. Chem. Res.* **1989**, *22*, 287.

(2) For reviews see: Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245. Cram, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009. Lehn, J. M. *Angew. Chem., Intg. Ed. Engl.* **1988**, *27*, 89.

(3) Kraut, J. *Science* **1988**, *242*, 533.

(4) For examples of antibodies able to catalyze a Claisen rearrangement see: Jackson, D. Y.; Jacobs, J. W.; Sugasawara, R.; Reich, S. H.; Bartlett, P. A.; Schultz, P. G. *J. Am. Chem. Soc.* **1988**, *110*, 4841. Hilvert, D.; Nared, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 5593.

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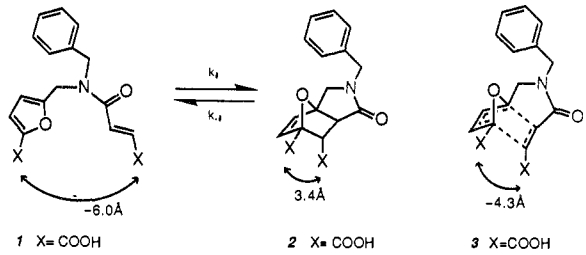
Scheme I



1 X= COOH 2 X= COOH 3 X=COOH

Table I. Rate Constants for the Intramolecular Diels–Alder Reaction of **1** in $CDCl_3$ at 25 °C

receptor	10^5k_1, s^{-1}	10^5k_{-1}, s^{-1}	K
4	0.48 ± 0.13	1.37 ± 0.32	0.35
7	14.0 ± 1.3	2.67 ± 0.52	5.2
none[b]	3.96 ± 0.41	4.34 ± 0.50	0.91
none[c]	3.68 ± 0.2	3.89 ± 0.1	0.94

[a] All values are the average of several runs. [b] Dimethyl ester of **1**. [c] **1** in DMSO-d_6:$CDCl_3$ (1:9).

structural changes in going from starting material to product. Specifically, the two substituents (X in Scheme I) move from ~6.0 Å apart[6] in the required s-cis starting material[7] to 3.4 Å apart in the tricyclic product.[8] Thus, a synthetic receptor that can bind to the two substituents (e.g. carboxylic acids in **1**) in an intermediate position (e.g. ~4.3 Å) should selectively stabilize the transition state **3** over **1** and **2** and so accelerate the reaction.[9,10]

We have recently shown[11] that simple diamide receptor **4** (derived from terephthaloyl dichloride and 6-amino-2-picoline) can effectively bind aliphatic dicarboxylic acids, as seen in the X-ray structure of the complex with adipic acid (**5**). Molecular modelling studies[8] suggested that the separation of the aminopyridine groups in **4** was appropriate for complexing not transition state **3** but the s-cis conformer of the *N*-furfurylfumaramide starting material **1**. This, in turn, should lead to a slowing down of the IMDA reaction. The ^1H NMR spectrum of a 1:1.6 mixture of **1**[12] and **4** in $CDCl_3$ shows large downfield shifts of the receptor amide–NH resonances, as expected[11] for the formation of a tetrahydrogen bonded complex of type **6**. The complementarity between **1** and **4** is further demonstrated by the complexation-induced changes in (1) the s-cis:s-trans ratio of **1** to >97:3 from an equilibrium position of 60:40 and (2) the IMDA equilibrium constant from ~1 to ~0.3. The rates of the IMDA reaction of **1** were studied with temperature jump techniques[13] and the resulting k_1 and k_{-1} values are collected in Table I. Complexation of **1** by **4** results in a ~10-fold drop in the rate of the IMDA reaction (k_1) compared to uncomplexed analogues.[15] These results are all consistent with the selective complexation and stabilization

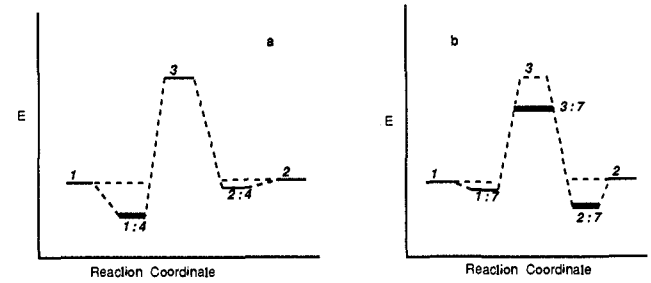
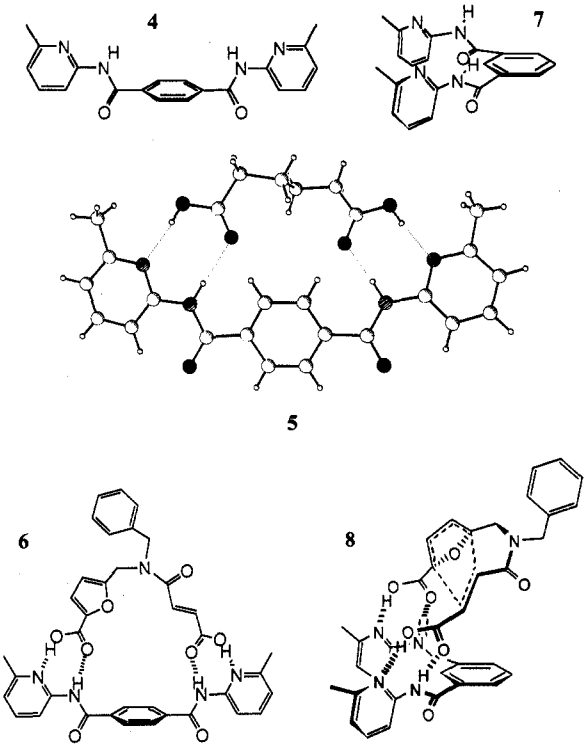


Figure 1. Postulated changes in the free energy profile for the IMDA reaction upon complexation by (a) **4** and (b) **7**.

Chart I



of starting material **1** and the resultant increase in the activation energy of the IMDA reaction (Figure 1a).[16]

Selective complexation of the transition state (**3**) requires a closer positioning of the carboxylate binding groups in the receptor. This can be readily achieved by moving the aminopicoline sites around the periphery of a benzene ring, as in diamide receptor **7** (formed from the reaction of 6-amino-2-picoline with isophthaloyl dichloride). Addition of **1** to a $CDCl_3$ solution of **7** leads to the normal ^1H NMR shifts associated with diacid complexation. There is also a 15-fold increase in the IMDA equilibrium constant (to more than 5) compared to **1**/**4**, confirming the preferential complexation of product **2** over **1**. That the transition state (**3**) is also stabilized (as shown in **8**) is seen by the almost 30-fold increase in the rate of the IMDA reaction (k_1), compared to **1**/**4**. The absence of any large effect on the retro-IMDA (k_{-1}) suggests that **2** and **3** are stabilized to similar extents by **7** (Figure 1b). This is a likely consequence of the relatively close positioning of their carboxylate groups, compared to **1**. These effects, while modest, show that a simple receptor molecule can influence the rate of a pericyclic reaction by selectively complexing the starting material, transition state, and/or product.

Acknowledgment. We thank the National Institutes of Health (GM35208) for their support of this work and Shyamaprosad Goswami for his synthesis of **4**.

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(6) Distance based on a BzN–Cfuran torsion angle of 111°.
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(8) Distances estimated using Macromodel v.2. (Still, W. C., Columbia University) as well as CPK models.
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(11) Garcia-Tellado, F.; Goswami, S.; Chang, S. K.; Geib, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 7395.
(12) Synthesized from 5-hydroxymethylfurfural by protection (DHP, TsOH), reductive benzylamination ($NaBH_4$), acylation (fumaric acid monomethyl ester, DCC), deprotection (HCl), oxidation (Swern + Ag_2O), and hydrolysis (2.5% aqueous NaOH).
(13) The reaction mixture in $CDCl_3$ was heated at 60 °C and rapidly cooled to 25 °C. Changes in the integration of the ^1H NMR resonances of **1**, its s-trans conformer, and **2** were used to moniter the return to equilibrium. The total furan concentration was used and rate constants were calculated using the kinetic expression for first-order reversible reactions $1/\tau = k_1 + k_{-1}$ where τ is the relaxation time.[14]
(14) Laidler, K. J. *Chemical Kinetics*, 3rd ed.; Harper and Row: New York, 1987; p 36.
(15) The choice of a control reaction is difficult due to the insolubility of diacid **1** in $CDCl_3$. Comparisons are made to **1** in 10% DMSO-d_6 in $CDCl_3$ and the dimethyl ester derivative (**1**, X = CO_2CH_3).
(16) Activation parameters for the simple IMDA reaction, measured for a more soluble derivative of **1** (*N*-octyl in place of *N*-benzyl), were $\Delta G^{\ddagger}$ = 25.9 kcal mol^{-1}, $\Delta H^{\ddagger}$ = 19.6 kcal mol^{-1}, and $\Delta S^{\ddagger}$ = 12.2 cal K^{-1} mol^{-1}.