electronic considerations are identical for internal 1,2 and 1,4 addition of the latent carbon nucleophile to the activated enone in **17** (Scheme IV). A priori analysis of this carbon–carbon bond-forming operation would suggest that either 1,2 or 1,4 addition could be the favored mode. That direct 1,2 addition could occur was shown in the cyclizative reaction of 6-substituted cyclohexenone **20**, prepared via alkylation of 3-dimethylaminocyclohexanone with 1-iodo-4-trimethylstannylbutane[9] (KH, THF, 0 °C), followed by quaternization (MeI) and β elimination (DBU, benzene, 20 °C; 70% overall).[13]

When confronted with internal cyclization either transannularly via the conjugate addition mode to a strained, eight-membered ring **21**[14] or via the direct addition mode to a fused, six-membered ring (e.g., **22**), cyclohexenone **20** prefers the latter. The intermediate, direct addition product(s), octalinol(s) **22**, generated a mixture of octalinyl chlorides **23**[6e] (63%). In addition, the conjugate addition product, bicyclic ketone **21**,[15] was observed (10%). These data demonstrate that direct carbonyl, nucleophilic addition will occur when entropic (or presumably other) features of the cyclization substrate inhibit the intrinsically preferred, conjugate addition process and when 1,2 addition is a favorable ring closure.[12] However, medium-sized carbocyclic rings, often synthetically inaccessible through direct annulation processes, can be prepared via this carbocyclization scheme.

Owing to the ease of tetraalkyltin unit incorporation into the precyclization molecule, to the stability of the alkyltin unit, and to the possible polyfunctionality generated in the cyclization product, we anticipate that alkyltin-enone carbocyclization will have broad utility in complex molecule synthesis. The principal constraint would appear to be the stereoelectronic, enthalpic, and entropic requirements for ring closure.[12] We are currently examining the use of different carbon-centered electrophiles and carbon–tin nucleophiles in this carbocyclization process and the implementation of this annulative strategy in natural product synthesis.

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Supplementary Material Available: Appendix I, spectral characteristics of compounds **3**, **8**, **9**, **12**, **14**, **15b**, **17**, and **20** (2 pages). Ordering information is given on any current masthead page.

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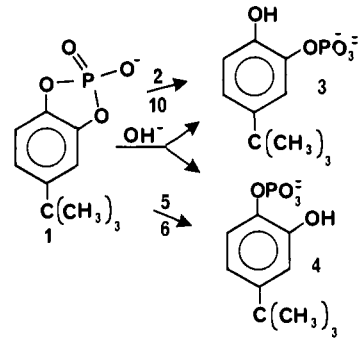
Timothy L. Macdonald,* Sankaran Mahalingam
Department of Chemistry, Vanderbilt University
Nashville, Tennessee 37235
Received November 7, 1979

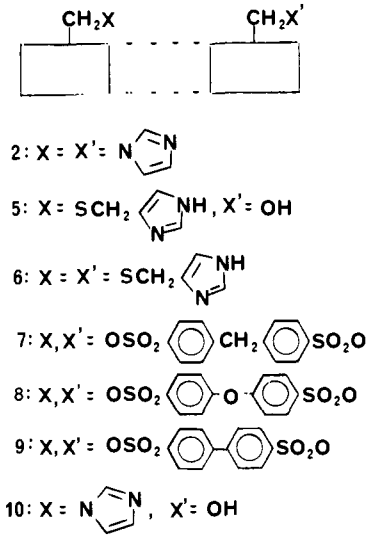
Reversing the Selectivity of Cyclodextrin Bisimidazole Ribonuclease Mimics by Changing the Catalyst Geometry

Sir:

We have described[1] the catalytic cleavage of the cyclic phosphate (**1**) of 4-*tert*-butylcatechol on complexing with a



β-cyclodextrinyl-6,6′-bisimidazole (**2**). The kinetics showed a bell-shaped pH vs. rate profile, indicating that there was cooperative catalysis by a basic imidazole group and an acidic imidazolium group. The enzyme ribonuclease[2] also catalyti-



cally hydrolyzes certain cyclic phosphates using these two catalytic groups in this way. Most strikingly, our enzyme

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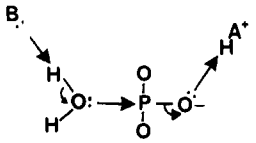

Figure 1. A top view of the catalyzed hydrolysis, showing that linear displacement does not imply that the catalyst groups be on opposite sides of the cavity.

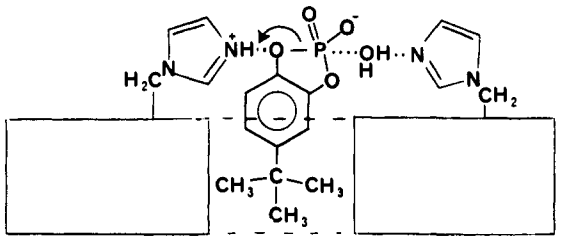

Figure 2. The specific cleavage of **1** bound in the cavity of catalyst **2** in the half-protonated state. For catalyst **10** the imidazolium ion, which is shown protonating the leaving group, is missing.

mimic was very selective,[1] cleaving only[3] the P-O(1) bond of substrate **1** to form the 2-phosphate (**3**) of 4-*tert*-butylcatechol. By contrast, hydrolysis of **1** in solution in the absence of the catalyst gave[1] a 50:50 mixture of **3** and **4**, the 1-phosphate of 4-*tert*-butylcatechol. We have now obtained further evidence on the process involved and have found that we can completely reverse the direction of catalyzed cleavage in the substrate **1** with new ribonuclease mimics (**5** and **6**) having different geometric requirements.

Our original catalyst **2** was obtained from Tabushi's[4] "capped cyclodextrin" **7**, which we found[1] to be a mixture of isomers in which the sulfonate groups were on positions 6A,6C and on 6A,6D. To establish the geometric requirements of this catalysis we have now synthesized[5] the capped cyclodextrins **8** and **9**, in which the sulfonyl groups are progressively further apart[5] than in **7**; this should lead to progressive enrichment of the 6A,6D substitution. We find that the bisimidazole **2'** prepared from **8** has 75% of the catalytic activity of **2**, while **2''** prepared from **9** has 52% of the catalytic activity of **2** at its pH optimum.[6] Thus the 6A,6C placement of catalytic groups is better, in which the catalysts are not on opposite sides of the cavity containing the bound substrate. This is still consistent with an in-line displacement at phosphorus, with attacking and leaving oxygens 180° apart, as models and Figure 1 indicate.

The regioselective cleavage of **1** by our catalyst **2** was also expected by this mechanism, since H_2O being delivered by an imidazole group attached directly to the cyclodextrin must approach in line with the P-O(1) bond, and cannot get far enough out from the catalyst to allign with the P-O(2) bond (Figure 2). Consistent with this, we find that simple β-cyclodextrinyl-6-imidazole (**10**) at pH 7.75 also cleaves **1** catalytically to form at least 90% **3** rather than **4**. In the pH (pD) region of 7.9-8.1 (9.1-9.4), where the rate shows a pH-independent plateau, we find an H_2O/D_2O isotope effect with **10** of 2.5 ± 0.7 (three kinetic points each in H_2O and D_2O), consistent with the general base delivery of H_2O. We also find that simple cyclodextrin (cycloheptaamylose) at 5 mM suppresses the rate of uncatalyzed cleavage of **1** (1 mM) but does not change the ~50:50 random ratio by which **3** and **4** are produced. Thus the regioselectivity indeed seems to reflect the geometry of approach of H_2O in the catalyzed process.

4(5)-Mercaptomethylimidazole[7] reacted with β-cyclodextrin 6-tosylate to afford 6β-cyclodextrinyl 4-imidazolylmethyl sulfide (**5**).[8] In a similar fashion the bisimidazole derivative **6**[8] was prepared from capped cyclodextrin bissulfonate **8**. Both were catalysts for the hydrolysis of **1**, and the bisimidazole derivative **6** showed a bell-shaped[9] pH-rate profile for catalysis

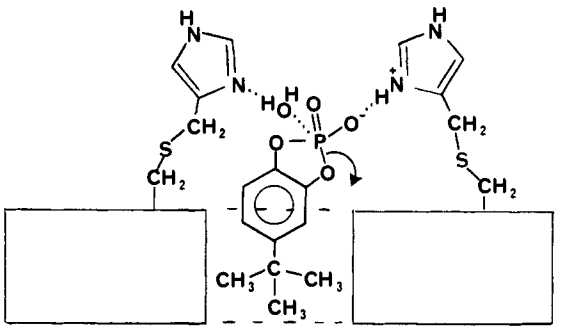

Figure 3. The specific cleavage of **1** bound in the cavity of catalyst **6** in the half-protonated state. The imidazolium ion is shown hydrogen bonding the phosphate anion, although it can also curl back to reach the leaving group. In catalyst **5** this imidazolium ion is missing.

as **2** had done, although here with the pH maximum at 7.0. Again this indicates cooperative catalysis by an imidazole and imidazolium group. These more flexible catalysts show less rate acceleration[10] than did **2** or **10**, with k_{cat}/k_{un} of 8 for **6** at pH 7.0 and of only ~2 for **5** at pH 7.25. However, with catalyst at 5 mM and substrate at 1 mM, the random hydrolysis in solution is completely suppressed by binding, and only the specific geometry of the catalyzed process is seen. This specific geometry is opposite that which was observed with **2** and **10**: the product is now exclusively **4**, the 1-phosphate of 4-*tert*-butylcatechol. Less than 2% **3** can be detected by LC[1] with either **5** or **6** as catalyst.

Attack to cleave the P-O(2) bond in a complex of **1** with **5** or **6** is now possible with H_2O delivery by a catalytic imidazole since the longer link moves the imidazole further from the binding site.[11] Thus the result is completely reasonable, as models and Figure 3 indicate. The striking reversed regioselectivity between the **2,10** and the **5,6** sets of catalysts, operating on the same substrate, again[12] reveals that even modest catalytic rate enhancements can combine with suppression of the uncatalyzed reactions to lead to highly selective chemical processes.[13]

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(2) For a review see Richard, F. M.; Wyckoff, H. W. *Enzymes*, **4**, Chapter 24 (1971).

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(5) Compounds **8** and **9** were synthesized from the corresponding bissulfonyl chlorides and cyclodextrin in a similar manner to that described[1,4] for **7**. Compound **8** had the expected ^1H NMR spectrum, was "homogeneous" by LC, and analyzed for a nonahydrate. Anal. Found (calcd for $C_{54}H_{76}O_{40}S_2 \cdot 9H_2O$): C, 40.48 (40.75); H, 5.63 (5.91); S, 3.98 (4.03). Compound **9** had the expected ^1H NMR spectrum, was "homogeneous" by LC, and analyzed for an octahydrate. Anal. Found (calcd for $C_{54}H_{76}O_{39}S_2 \cdot 8H_2O$): C, 41.48 (41.65); H, 6.05 (5.91); S, 3.98 (4.11). From CPK molecular models assuming sp^2 hybridization in the diphenyl ether oxygen, the sulfur–sulfur distances in **7**, **8**, and **9** are, respectively, 9.7, 10.2, and 10.8 Å. The 6A,6C oxygen–oxygen distances for β-cyclodextrin range from 5.5 to 9.9 Å, while the 6A,6D distances are 7.8 to 13.7 Å.

(6) At the kinetic maximum, with pH 6.3–6.4, at kinetic saturation in catalyst the k_{cat} values for **2**, **2'**, and **2''** were 36.2, 27.0, and 18.9 × 10^{-5} s^{-1}, respectively.

(7) Schneider, F. *Z. Physiol. Chem.* **1967**, *348*, 1034-1042.

(8) Characterized by TLC and NMR. Compound **5** analyzed as a tetrahydrate. Anal. Found (calcd for $C_{46}H_{74}O_{34}N_2S$): C, 42.47 (42.40); H, 6.58 (6.34); N, 1.80 (2.15); S, 2.13 (2.46).

(9) The curve resembled that in Figure 1 of ref 1 and had seven points over the pH range 6.2–7.5 with a maximum rate at pH 7.0.

(10) With catalyst at 5 mM k_{cat} for **5** was 4.5 × 10^{-5} s^{-1} at pH 7.25, while k_{cat} for **6** was 15.5 × 10^{-5} s^{-1} at pH 7.0.

(11) Of course the imidazolium ion in **6** can also be further out in space, but the bell-shaped pH-rate profile shows that it plays a catalytic role as well. It

may curl back to protonate the leaving group or it may be hydrogen bonded to the charged phosphate oxygens. Evidence that the roles of the imidazolium ions are those shown in Figures 2 and 3 is the finding that the pH–rate maximum for **2** comes at approximately its titration pK_a, but that for **6** is almost 1 pH unit higher than its titration pK_a of 6.1. This would indicate stabilization of the imidazolium ion by the bound phosphate anion in **6**, but not in **2**. If the imidazolium ion in **6** catalyzes the hydrolysis by such phosphate binding, it would be playing the role of lysine-41 in ribonuclease. Because of the flexibility in **5** and **6**, the specificity in the cleavage of **1** is particularly striking.

(12) For an earlier example in which high specificity accompanied relatively modest catalytic acceleration, cf. Breslow, R.; Campbell, P. *Bioorg. Chem.* **1971**, *1*, 140–156.

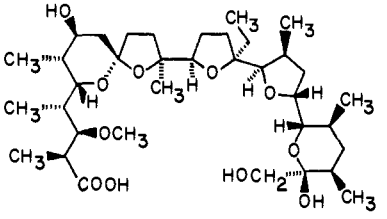
(13) Support of this work by the National Institutes of Health is gratefully acknowledged.

Ronald Breslow,* Philippe Bovy, Carol Lipsey Hersh
Department of Chemistry, Columbia University
New York, New York 10027
Received November 9, 1979

Synthesis of the Polyether Antibiotic Monensin. 1. Strategy and Degradations[1]

Sir:

The polyether antibiotics constitute a growing class of naturally occurring ionophores having a variety of useful biological properties and a degree of stereochemical complexity as yet unsurpassed by other natural products with an all-carbon backbone.[2] One of these materials, a compound named monensin (**1**), has acquired special significance since it was the first



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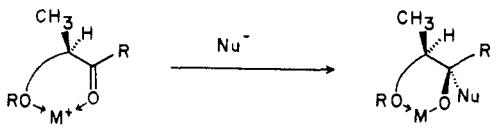
polyether antibiotic to have its structure determined and also to find its way to the marketplace.[3] The utility of monensin, as well as its challenging array of 17 asymmetric centers, has attracted considerable attention since its discovery, and during the years 1977–1978 serious synthetic programs started up at Harvard and here at Columbia. Earlier this year Kishi and co-workers reported their results.[4] In this series of papers we describe our work on a highly convergent synthesis of monensin starting from simple optically active compounds.

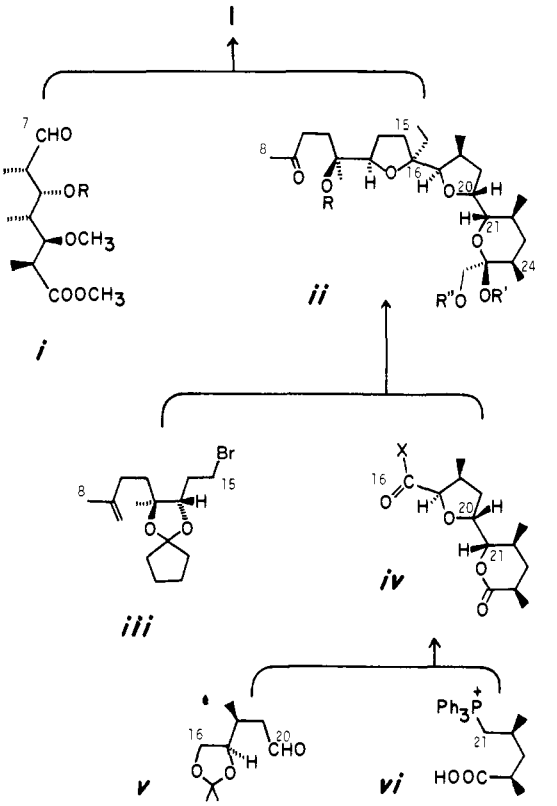
As outlined in the Scheme I, our synthesis is designed to be convergent at several levels. In addition to the usual logistical attractions of convergency, this scheme has a distinct stereochemical advantage. As applied here it allows monensin to be broken down retrosynthetically into fragments (i, iii, and v) containing only vicinal asymmetric centers so that most of the remote stereorelationships may be built up synthetically by coupling fragments having the proper absolute configuration. The remaining remote asymmetric centers (C-9 and C-24) are easily controlled by their environment on substituted six-membered rings. To avoid potentially tedious resolutions of the required intermediates, the synthesis begins with (−)-malic acid (→ iii) and (+)-β-hydroxyisobutyric acid[5] (→ i, v,[6] and vi).

The stereochemical problems in monensin are thus reduced to the formation of vicinal stereorelationships with control by preexisting asymmetric centers. One reaction which has proven especially useful in this context is the chelation-controlled nucleophilic addition shown in eq a.[7] We have studied this



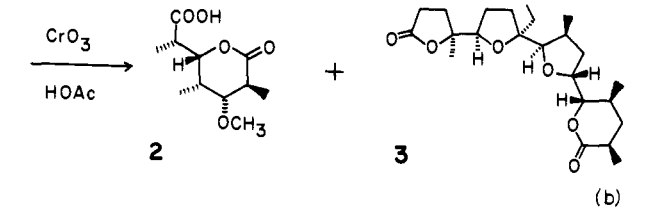
(a)

Scheme I



reaction in some detail and have found general methods for controlling the stereochemistry of the addition to the extent of ≥50:1 with Grignard reagents.[8] It should be noted that the stereochemistry produced by this type of operation is opposite to the usual Cram's rule[9] (steric control) prediction in cases where the chain bearing -OR is more sterically demanding than methyl. For this reason, stereoselection of the type shown has commonly been referred to as "anti-Cram" as well as "chelation controlled".

To secure materials for structure proof of advanced synthetic intermediates and to enrich our supplies of these valuable compounds, a monensin degradation–reconstruction program was undertaken. The primary degradation was achieved by chromic acid as reported with the original structure elucidation[10] (eq b).



(b)

The lactonic acid **2** was converted into the left fragment of monensin (i, Scheme I) in six steps. Reduction via the mixed carbonic anhydride (EtO_2CCl, Et_3N) with sodium borohydride in wet ether[11] (4 h, 25 °C) gave the corresponding primary alcohol which was protected with benzyl chloromethyl ether (*i*-Pr_2NEt). Saponification (LiOH–H_2O–THF) followed by acidification (excess NaH_2PO_4, 0 °C) and immediate in situ methylation (CH_2N_2) then gave the acylic ester **4** (78% from **2**) (eq c). Although the hindered secondary alcohol resisted protection with trialkylsilyl chlorides under the usual conditions, triethylsilyl perchlorate[12] (C_5H_5N, CH_3CN, 0 °C) added cleanly and rapidly. Finally hydrogenolysis (10% Pd/C, H_2, Et_2O) and oxidation ($CrO_3 \cdot 2C_5H_5N$, CH_2Cl_2) gave the left fragment of monensin as the triethylsilyl ether **5**[14] (86% from **4**).

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