EXAFS results also demonstrate that oxidative addition to form a six-coordinate Pt(IV)-DNA adduct with the retention of both ammines and chlorides does not occur. From the EXAFS spectra, no appreciable differences were detected at this stage *in the platinum coordination spheres* of the complexes formed by *cis*- and *trans*-DDP with DNA. This result, however, should not be taken to indicate that subtle differences do not exist.

In conclusion, this work provides, for the first time, strong structural evidence against the possibility of distinct metal-metal bonding in the complexes of both *cis*- and *trans*-DDP with calf thymus DNA. The data are consistent with the presence of four Pt-N (or -O) bonds in a presumably square-planar Pt(II) coordination sphere. Further stereochemical details from EXAFS study must await determination of interatomic distances other than those in the coordination shell using spectra of higher signal-to-noise ratio (in progress).

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(15) The fitting error quoted here for each parameter is calculated by changing that particular parameter (while least-squares refining the others) until the χ^2 doubled. The systematic errors (not included) due to background removal, Fourier filtering, and chemical bonding effects may amount to $\lesssim$0.5, 10, and 20% in distance, Debye–Waller factor, and coordination number, respectively.
(16) The Pt–Cl bonds differ drastically from the Pt–X (X = N or O) bonds in phase shift and backscattering amplitude[9e,f] which is easily discernible in EXAFS spectroscopy. The EXAFS spectra of *cis*- and *trans*-$Pt(NH_3)_2Cl_2$, for example, exhibit an interference pattern characteristic of two types of distances (Pt–N and Pt–Cl) with a "beat mode" at $k \approx 10.4$ Å^{-1}. Fourier transforms of these spectra result in two peaks at $r' = 1.48$ and 1.86 Å with an intensity ratio of ~0.8:1.0. Nonlinear least-squares curve fitting of the Fourier filtered $k^3\chi(k)$ data with a two-distance model gave Pt–N and Pt–Cl distances at 2.05 and 2.33 Å, respectively, which compare favorably well with the observed values of 2.01 (4) and 2.33 (1) Å (G. H. W. Milburn and M. R. Truter, *J. Chem. Soc.* A, 1609 (1966)).

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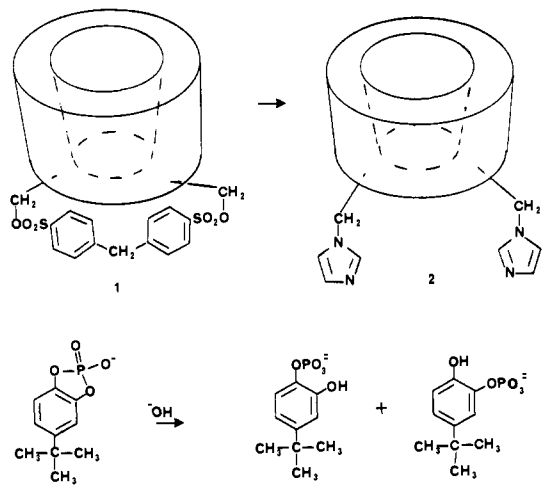
β-Cyclodextrinylbisimidazole, a Model for Ribonuclease

Sir:

Tabushi has reported[1] the preparation of **1**, in which β-cyclodextrin (cycloheptaamylose) is capped as a disulfonate derivative. We had been interested[2] in such selectively difunctionalized cyclodextrins for the synthesis of bifunctional catalysts. As an example, we find that on heating with imidazole in DMF at 85–90 °C for 96 h **1** is converted to the bisimidazole derivative **2**.[3] Tabushi has recently described[4] several other displacement reactions of **1**. We now wish to report that **2** has the ability to catalyze the hydrolysis of a cyclic phosphate



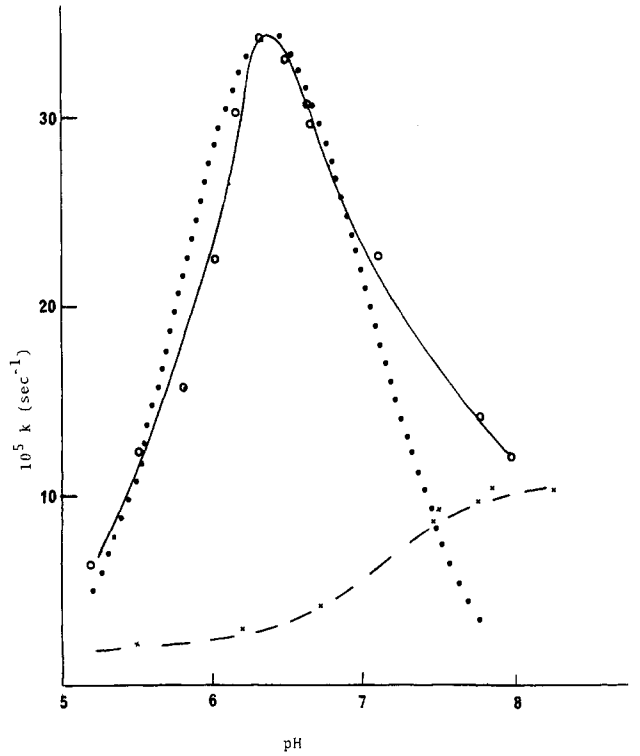


Figure 1. The observed pseudo-first-order rate constants for hydrolysis of 3 at kinetic saturation with 2 (O, —) or with 6β-cyclodextrylimidazole (x, - -) as a function of pH at 25.0 °C. Each rate is corrected for a few percent buffer catalysis. The dotted curve is that calculated for bifunctional catalysis by an acidic and a basic group, each with $pK_a = 6.3$.

substrate, in a selective manner, with bifunctional catalysis by a neutral imidazole and an imidazolium cation. The enzyme ribonuclease also hydrolyzes cyclic phosphate substrates by a similar mechanism.[5]

Sulfonate **1** was prepared as described.[1] Although by most criteria it was homogeneous, careful HPLC[6] showed that it is a mixture of two very similar isomers.[7] Molecular models suggest that with one end attached to carbon 6 of glucose residue A, the other end can reach carbon 6 of either residue C (or F) or D (or E). Thus **2** may also be a mixture of the 6A,6C and the 6A,6D isomers.

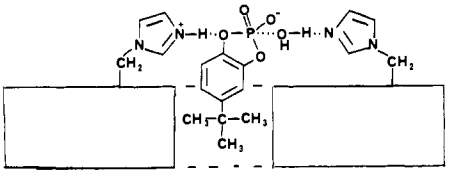
As substrate for **2** we have prepared the cyclic phosphate **3** (as the *N*-methylpyridinium salt) from 4-*tert*-butylcatechol, as described for catechol.[8] Molecular models show that, when the *tert*-butylphenyl group of **3** is hydrophobically bound into the cyclodextrin cavity,[9] the cyclic phosphate group is accessible to the imidazole rings of **2.** Specifically, one imidazole ring can act as a general base to deliver H_2O to the phosphorus of **3** and the other imidazole ring, *N*-protonated, can transfer the proton to O(1) of the cyclic phosphate to assist hydrolysis of the P-O(1) bond. If the catalyst uses the same in-line mechanism without pseudorotation used by the enzyme, with the two catalytic groups hydrogen bonded to the nucleophilic H_2O and the leaving oxygen on apical positions of a phosphate trigonal bipyramid, it is impossible to cleave **3** to produce **4.** Thus with this mechanism we expect only **5** from **3.**

Kinetic studies show that a bifunctional catalytic mechanism indeed operates. The hydrolysis of **3** (1.0 mM) with **2** (5.0 mM) at 25.0 °C with μ of 0.45 (KCl) was followed in the UV at 290 nm at various pH's obtained with acetate, phosphate, and Tris buffers. Good pseudo-first-order rate data were obtained and corrected for a few percent buffer-catalyzed rates. Doubling the concentration of **2** has no further effect on the rate, showing that **3** and **2** form a complex. Such kinetic saturation at 5 mM **2** shows that the binding of **3** by **2** has a strength typical of that for other *tert*-butylbenzene derivatives with cyclodextrins.[9]

The resulting rate constants are plotted vs. pH in Figure 1. β-Cyclodextrinyl-6-monoimidazole was also prepared[3] from known monotosylate[10] and examined as a catalyst for the hydrolysis of **3**; the data at kinetic saturation are also in Figure 1. β-Cyclodextrin itself did not catalyze the hydrolysis of **3.** The bell-shaped pH-rate profile with **2** shows that the catalytically most active form is monoprotonated, as expected for a mechanism with bifunctional acid–base catalysis. Similar profiles have been observed with ribonuclease,[5] with pH-rate maxima near pH 7. The pH-rate profile for the monoimidazole catalyst shows that it can function as either an acidic *or* a basic catalyst, with the latter somewhat more effective. As expected from this, the experimental points for **2** fit the calculated curve (Figure 1) for bifunctional catalysis by two groups of $pK_a = 6.3$ over much of the pH range, but deviate at either end since the unprotonated form is still an appreciable basic catalyst and the fully protonated form can still act as an acidic catalyst.

Hydrolysis of **3** can yield either the 1-phosphate (**4**) or the 2-phosphate (**5**). With simple alkaline hydrolysis by 0.01 N NaOH, a mixture of **4** and **5** is produced which is 60% **4** and 40% **5**, identified by 220-MHz ^1H NMR (downfield shift for H ortho to phosphorylated O). HPLC[11] also shows that the product is a 60:40 mixture of the two isomers. By contrast, the hydrolysis of **3** by the bisimidazole **2** produces only the minor one of these isomers (a few percent of the other, detected by HPLC but not by NMR, is ascribable to concomitant uncatalyzed hydrolysis and some contamination of **3**) which is assigned structure **5** based on the NMR evidence. This is the expected product if the catalyst protonates O(1), as models suggest. Chromatographic isolation demonstrates that **3** goes only to **5** and a trace of **4,** and in particular also that **3** does not become covalently attached to the catalyst **2.**

Catalysis of the hydrolysis of **3** by the enzyme model **2** is slow compared with typical ribonuclease catalyses. However, this model resembles the enzyme in binding a substrate, performing bifunctionally catalyzed hydrolysis with the same catalytic groups used by ribonuclease to cleave a related substrate, and carrying this out in a regioselective manner to



produce one isomer of the product. It thus shows many of the properties of an enzyme.

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(13) On leave from CNRS during 1976–1977, supported in part by a U.S.–France exchange award of the NSF.

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Stereochemistry of Acrylonitrile Dimerization

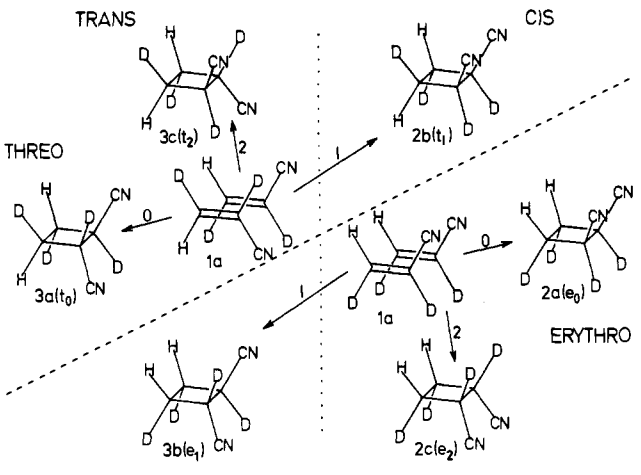
Sir:

Cycloaddition of two olefins and its reverse, cycloreversion or the cleavage of cyclobutane, have been the object of extensive theoretical[1] and experimental studies,[2,3] in which prediction and elucidation of stereochemistry have been the dominant theme. We now report the first stereochemically complete profile of a cycloaddition and the emergence of a simple statistical model as an adequate representation of the results.

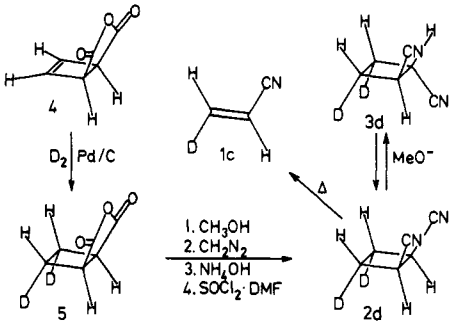
In the dimerization[4] of *cis*-1,2-dideuterioacrylonitrile (**1a**, Scheme I) two, not necessarily equal, modes of formation of the β,β' bond lead to a threo (t) and an erythro (e) set of three products each, which may be further characterized by the minimum number (indicated at each arrow) of 180° $[1 + 2n]$ rotations about the α,β and α',β' bonds required to generate the observed stereochemistry. These processes, formally involving zero, one, and two internal rotations (subscripts 0, 1, and 2), correspond in Woodward-Hoffmann notation to s + s, s + a, and a + a cycloadditions, respectively.

Deuterium-labeled acrylonitrile **1a** is synthesized by reduction of propiolamide-d_3 with lithium aluminum hydride,

Scheme I



Scheme II



with D_2O workup, and dehydration of the resulting acrylamide with P_2O_5 ($D_\alpha \geq 98\%$). The NMR spectrum (δ) of the purified product exhibits two 1:1:1 triplets at 6.14 (CCl_4) (5.18 (C_6D_6)) and 5.99 (CCl_4) (4.78 (C_6D_6)) in the ratio 94.3 (**1a**) to 5.7 (**1b**), respectively. Addition of Eu(fod)$_3$ causes the signal of the major component to shift downfield faster (1.00:0.66).[5] These data on chemical shifts,[6] coupling constants, and the lanthanide response are all consistent with assignment of the cis dideuterio configuration to the major isomer, **1a.**

NMR analysis of the dimerization products **2** and **3** is based upon the nonequivalence of protons cis or trans to a vicinal cyano group. For example, the spectrum of **2** in benzene-d_6 exhibits a singlet for **2a,** a different singlet for **2c,** and an AB pattern for **2b,** resolved only upon deuterium decoupling[7] (similarly for **3**). Assignments are based upon the lanthanide shift response of independently synthesized deuterated cyclobutanes (Scheme II). Exo deuteration (≥96%) of the anhydride **4**[8] is confirmed by a lanthanide shift study of unlabeled **5,** in which it is assumed that those β protons with the larger response are endo. The NMR spectrum ($CDCl_3$) of **2d** exhibits two doublets at 3.52 and 2.55. Base-catalyzed deuteration of **2d** affords a mixture of **2a, 2c,** and **3b.** In the NMR of the **2a** + **2c** mixture the assignments 2.55 ($CDCl_3$) (1.48 (C_6D_6)) to **2a** and 2.48 ($CDCl_3$) (1.01 (C_6D_6)) to **2c** are confirmed upon showing that the **2a** signal is indeed shifted downfield faster (1.00:0.71) by addition of Eu(fod)$_3$. A lanthanide shift study in benzene-d_6 on the dideuterio trans isomer **3d** permits assignment of the faster moving β signal (1.00:0.73) to the protons cis to the vicinal cyano group (as in **3a**).

Dimerization is effected by heating 100–200-mg samples in the liquid phase in silanized Pyrex ampules at 209.5 °C for 15 h or at 246.4 °C for 2 h. (Under these conditions decomposition of the cyclobutane products is negligible.) With diphenylamine as inhibitor, conversion to cyclobutanes is 9.3% at 209.5 and 10.0% at 246.4 °C, with acrylonitrile being recovered in 65.5 and 57.2% of theory, respectively.

Recovered acrylonitrile contains 19.0% at 209.5 and 20.3% at 246.4 °C of the trans dideuterio isomer, **1b,** corresponding to 15 and 16.5% isomerization, respectively. When heated at 208 °C for 24 h at 225 mm, **1a** is recovered unchanged.

Dimerization products **2** and **3** are separated by GC for

Table I. Dimerization of *cis*-1,2-Dideuterioacrylonitrile at 209.5 and 246.4 °C

		209.5 °C				246.4 °C			
Product	Process[a]	% (exptl)[b]	% (cor)[c,d]	k_{rel}	% (stat)[e]	% (expt)	% (cor)	k_{rel}	% (stat)
2a	e_0	19.8	22.3 (21.4)	1.00	22.1	18.4	20.4	1.00	20.3
3b	e_1	28.1	28.9 (28.5)	0.65	27.0	28.0	29.0	0.71	28.2
2c	e_2	6.9	6.2 (7.1)	0.28	8.3	9.0	8.7	0.43	9.8
3a	t_0	17.5	18.3 (17.1)	1.00	18.6	16.4	17.0	1.00	17.1
2b	t_1	20.1	18.4 (18.5)	0.50	19.1	20.5	18.7	0.55	19.3
3c	t_2	7.6	6.0 (7.4)	0.33	4.9	7.6	6.0	0.35	5.4

[a] Erythro and threo processes are denoted by e and t; subscripts denote the minimum number of rotations. [b] Total dimers from a single experiment. [c] Corrected to 100% **1a** at zero time. [d] The values in parentheses are the result of combining two experiments, one at 205 ± 4 °C for 20 h, the second at 210 ± 4 °C for 13 h. [e] Predicted by statistical model (see text).

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