was conditioned to Na^+ or K^+ by soaking overnight in a 0.01 M solution of the desired salt in the solvent to be used for the titration.

Typically, 20 mL of a 0.01 M salt solution was placed in a sealed chamber fitted with the cation electrode along with the appropriate reference electrode. Titration was accomplished with a 2 molar excess of the crown ether dissolved in the same solvent (5 mL of solution was usually added in 0.5-mL aliquots). After each addition, the solution was stirred for 4 min then allowed to sit unstirred for 1 min. Readings were taken until 2 successive readings differed by less than 0.2 mV.

Crown 1 Complexation by Mercuric Cyanide. An NMR sample was made from the crown ether and $Hg(CN)_2$ in 50% acetone-d_6/benzene-d_6 v/v so that the final concentrations were $[C_T] = 0.0069$ M and $[Hg(CN)_2] = 0.0174$ M. The solution was degassed by 2 freeze–pump–thaw cycles to remove oxygen. The NMR spectra were recorded at 300 MHz at five degree intervals from 235 to 280 K. The most downfield region of the spectra showed separate signals for the aromatic doublets of each of the crown ether species in solution (free 7.74 ppm, singly bound 7.71 and 7.87 ppm, and doubly bound 7,82 ppm at 280 K). These chemical shifts are simewhat temperature dependent, as can be seen in the matched spectra of Figure 5,

Typical NMR Experiments for Complexation of 2, 3, 8, and 9. The metal and crown (5–100 mg) were weighed into separate 1-mL volumetric flasks and diluted with the appropriate solvent. Known volumes of each solution were added to a clean, dry NMR tube by syringe and, if necessary, pure solvent was added to bring the total volume to 0.4 mL. In mixed solvent systems, the solvent was premixed. The reference standards (Me_4Si, $CFCl_3$) were added, and the tubes were capped and wrapped with Teflon tape. When long reaction or equilibrium times were necessary (as in slow rate determinations), the tube contents were flash frozen and sealed by an oxygen torch. When variable temperature spectra were obtained, a minimum equilibration time of 5–10 min was used at each temperature.

Complex of Dimethyl 22-Cr-6, 9, and $Hg(CF_3)_2$ (15). To 1 equiv of the crown in MeOH was added 1 equiv of $Hg(CF_3)$ in MeOH. After stirring 10 min and evaporation of the solvent, a white solid was obtained. Slow recrystallization from Et_2O afforded crystals suitable for X-ray analysis, mp 150–157 °C.

Complex of Macrobicyclic Crown 1 with 2 $Hg(CN)_2$ (11). The crown **1** (250 mg, 0.4237 mmol) and $Hg(CN)_2$ (214 mg, 0.8474 mmol) were combined in MeOH–Et_2O solution. After stirring 10 min, the solvent was removed in vacuo, and the resulting white solid was recrystallized from EtOAc to afford crystals suitable for X-ray analysis, mp starts 175–181 °C, then no further change until an amber melt at 280 °C.

Complex of 2 with $Hg(CF_3)_2$ (12). A solution of **2** (17.8 mg 0.26 mmol) in 3 mL of MeOH/H_2O (1:1, v/v) was combined with $Hg(CF_3)_2$,[12] (178 mg 0.053 mmol). The white precipitate which formed was collected and dried, mp 147–150 °C. Anal. Calcd for $C_{36}H_{54}O_{12}\cdot 1.88Hg(CF_3)_2$: C, 36.30; H, 4.13; F, 16.30; Hg, 28.68, Found: C, 36.30; H, 4.13; F, 15.11; Hg, 28.58.

X-ray Diffraction. Crystals suitable for diffraction were obtained from EtOAc for **1**·2$Hg(CN)_2$ (**11**) and from Et_2O for **9**·$Hg(CF_3)_2$ (**15**). Data were collected at room temperature (~21 °C) on a Syntex $P2_1$ automated diffractometer by using nickel-filtered Cu Kα radiation (λ = 1.5418 Å). Cell dimensions were determined from least-squares refinement of several independently measured reflections well-separated in reciprocal space. The θ–2θ scanning technique with variable scan rate was used to measure intensities to 2θ of 100° for **11** and to 130° for **15**. Cell dimensions and other experimental parameters are given in Table VI (see Supplementary Material). Empirical absorption corrections were made by using ψ scan data,

The structures were solved by the heavy atom technique by using XRAY76.[29] Non-hydrogen atoms were refined, first isotropically, subsequently anisotropically, by full-matrix least squares.[30] Unique reflections with $I \geq 2\sigma(I)$ were used in the refinement (3482 of 4527 observations for **11** and 4261 of 4604 observations for **15**). Hydrogen atoms, except for those on the methyl groups of **15**, were included at calculated positions with $U = 0.051$ Å^2 but were not refined. Atomic scattering factors for non-hydrogen atoms were taken from Cromer and Waber,[31] those for hydrogen from Stewart, Davidson, and Simpson.[32] The function minimized was $w(|F_o| - |F_c|)^2$, where the weights, w, were determined as follows: $w^{1/2} = 1$ when $|F_o| \leq X$ and $w^{1/2} = X/|F_o|$ when $|F_o| > X$. For **11**, $X = 80.0$; for **15**, $X = 25.0$.

Acknowledgment. We acknowledge financial support from the National Institutes of Health, and we thank Professor H. Cooper for stimulating correspondence.

Supplementary Material Available: Tables of anisotropic thermal parameters for non-hydrogen atoms, calculated positional parameters for hydrogen atoms, tables of bond lengths, valency and torsion angles, and lengths and angles involved in the coordination spheres (25 pages). Ordering information is given on any current masthead page.

(29) The XRAY system—version of 1976, J. M. Stewart, Ed., Technical Report TR-446 of the Computer Science Center, University of Maryland, College Park, Maryland,

(30) Least-squares calculations with use of FMLS, anisotropic full-matrix least-squares refinement, Ganzel, P. L.; Sparks, R. A.; Trueblood, K. N., UCLA; modified by McPhail, A. T., Duke University; illustration with ORTEP, Johnson, C. K., Oak Ridge, ORNL-3794.

(31) Cromer, D. T.; Waber, J. T. *Acta Crystallogr.* **1965**, *18*, 104–109.

(32) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175–3187.

Binding Forces and Catalysis. The Use of Bipyridyl–Metal Chelation to Enhance Reaction Rates

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Abstract: The application of a binding force (the chelation of a metal by a 2,2′-bipyridyl) to enhance reaction rates is examined with three systems. Metals are shown to increase the rate of *cyclization* of certain 3,3′-disubstituted, 2,2′-bipyridyl derivatives. Similar effects are seen in the *elimination* reaction of an appropriate halide and the *racemization* of asymmetric bipyridyl crown ethers. The last case involves catalysis according to the Pauling principle of maximum binding to the transition state. The relevance of these findings to biochemical processes is discussed.

One of the central issues in catalysis, particularly in enzyme catalysis, is the relationship between binding forces and rate enhancements. In organic chemistry, enzyme models are devised to explore this relationship, and any number of such models have evolved to emphasize the use of binding forces to reduce activation *entropies*.[1] Attempts to reduce activation *enthalpies* are much less common.[2] Here, the goal has been to achieve maximum binding to a transition state for a reaction, a notion originating with Pauling,[3] who anticipated that active site structure would

(1) Bruice, T. C. *Annu. Rev. Biochem.* **1976**, *45*, 331–373. Jencks, W. P. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1975**, *45*, 219–409.

(2) (a) Breslow, R.; Fairweather, R.; Keana, J. *J. Am. Chem. Soc.* **1967**, *89*, 2135–38. (b) Boger, J.; Knowles, J. R. *Ibid.* **1979**, *101*, 7631–7633. (c) Breslow, R.; Czarniecki, M. F.; Emert, J.; Hamaguchi, J. *Ibid.* **1983**, *105*, 2739–2745.

(3) Pauling, L. *Nature (London)* **1948**, *161*, 707–709.

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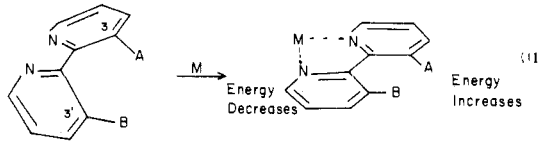
Table I. Half-Lives for Cyclization in Me_2SO

compd	temp, °C	time, min
1	110	15
9	110	26
1 + $NiCl_2$	45	60
9 + $NiCl_2$	120	140

be complementary to transition structure. The problems in reducing the Pauling principle to practice have been the following: (1) finding a binding interaction with well-defined geometrical consequences, (2) arranging reacting centers so that binding and reaction share a common coordinate, and (3) knowing enough about the transition structure so that maximum binding occurs uniquely to it. In this paper we describe some progress we have made on these issues.

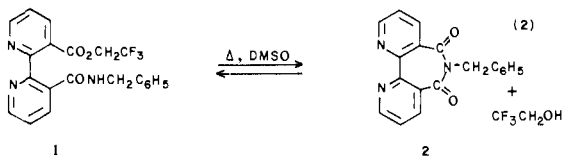
The chelation of metals by 2,2′-bipyridyl derivatives (eq 1)



forces the aromatic nuclei toward coplanarity and brings together substituents in the 3,3′-positions. The predictability of this motion suggested its use as a vehicle to approach the problems above. Could the force of chelation apply a mechanical stress (in the sense of a pair of pliers) through the interannular bond to the reacting centers A and B? If so, binding could overcome some of the nonbonded interactions which contribute to the activation enthalpy for cyclization reactions involving the 3,3′-positions.

Cyclization

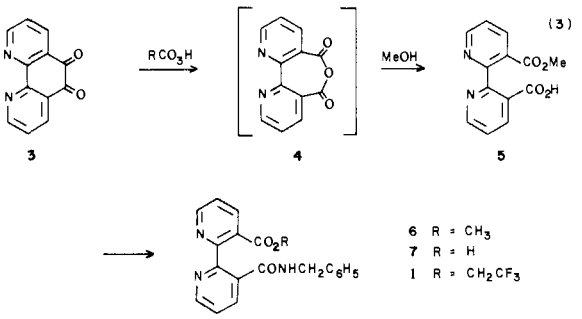
After some experimentation, we settled on the reaction of a modest electrophile (trifluoroethyl ester) and nucleophile (benzyl amide) to an imide (eq 2). This pair cyclized at a conveniently



1 2

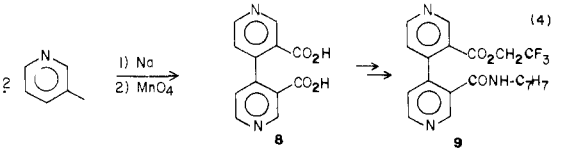
measured rate and represented a compromise between too reactive partners and those which were inert.

The test substance **1** was prepared as outlined in eq 3. Since attempts to dehydrate 2,2′-binicotinic acid to the corresponding anhydride **4** led to decomposition, the latter was generated in situ through Baeyer–Villiger oxidation of the quinone[4] **3** in MeOH. The resulting monofunctionalized derivative **5** was condensed with benzylamine by using DCC then saponified to **7** and esterified with $CF_3CH_2OH/SOCl_2$ to yield **1**.



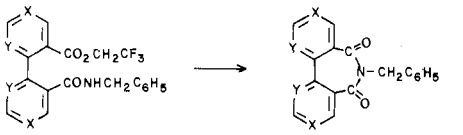
3 4 5

In order to remove ambiguities in interpretation, the 4,4′-bipyridyl derivative **9** was prepared as a control. This substance has the same relationships between ring nitrogens and reactive centers but cannot *chelate* metals. Binding of metals at either pyridyl nitrogen of **9** should result in inductive effects on the reacting centers comparable to those experienced during similar binding of **1**. Even though the special effects experienced by simultaneous binding of a metal to *both* pyridyl nitrogens of **1** are not reproduced in **9**, no better control could be envisioned. The material was prepared from β-picoline through reductive coupling[5] then oxidation to 4,4′-binicotinic acid **8** (eq 4). The



8 9

corresponding cyclic anhydride could be generated with hot Ac_2O, from which the monofunctionalized derivative was prepared by opening with CF_3CH_2OH. Coupling to benzylamine was accomplished by using a mixed anhydride procedure.



1 X = CH, Y = N
9 X = N, Y = CH

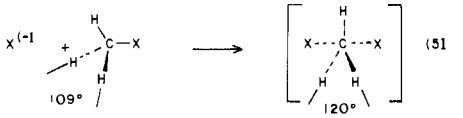
The results of the cyclization experiments are given in Table I. Unfortunately, our attempts to extract reliable activation parameters from the data were thwarted by experimental difficulties. The combination of high temperatures and long reaction times caused sufficient decomposition to render equilibria determinations uncertain. The values shown are obtained from a least-squares fit to experimental data by using 5–10 runs for each determination and represent approximate half-lives for the reversible cyclization to the imides.

Qualitatively it was observed that the 2,2′-bipyridyl derivative cyclizes slightly faster than the 4,4′ isomer even in the absence of metal ions. On the addition of $NiCl_2$, the rate of cyclization of the 4,4′ isomer is actually *slowed*. This may be the result of metal binding at the amide function or the inductive effect arising from metal binding at a pyridyl nitrogen. The cyclization of the 2,2-isomer **1** is, however, considerably accelerated by the metal. In this case cyclization occurs at a conveniently measured rate at 45 °C. Without metal ions, no cyclization could be observed at this temperature.

The cyclization to the imide, however, is a complicated reaction involving several intermediates, and while it is likely that metal binding *increases* as these intermediates are formed, it is unlikely that we shall discover which transition state responds to the "compression". Our intent to find a simpler system led us to the case described below.

Substitution and Elimination

The few chemical reactions for which the transition structure can be assumed involve S_N2 processes. In the special case of substitution of methyl halides with the corresponding isotopically labeled halides the transition state is reached when the carbon center becomes sp^2 hybridized. For other cases, X ≠ Y, the transition structure deviates from this ideal (eq 5), but it is rea-

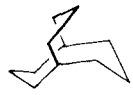


sonable to assume that the reactions could be catalyzed if the carbon bearing the leaving group could be forced toward the sp^2 geometry.

It has generally been easier to distort tetrahedral carbon toward *smaller* bond angles—as in small ring compounds—than toward larger ones.[6] Those structures, e.g., manxanes[7] **10**, where the

(4) Gillard, R. D.; Hill, R. E. E.; Maskill, R. *J. Chem. Soc. A* **1970**, 1447–1451.

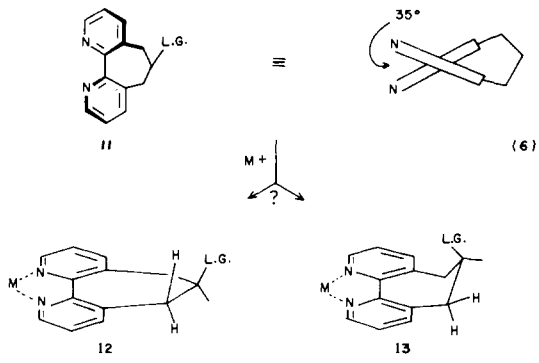
(5) (a) Stoehr, C.; Wagner, M. *J .Prakt. Chem.* **1983**, *48*, 1–17. (b) Becker, H. P.; Newman, W. P. *J. Organomet. Chem.* **1972**, *37*, 57–67.



10 manxane

desired distortion has been achieved, are generally rigid, static, or otherwise unsuitable for substitution studies. The possibility that reversible distortion toward a transition structure could be realized within the bipyridyl metal system proved irresistable.

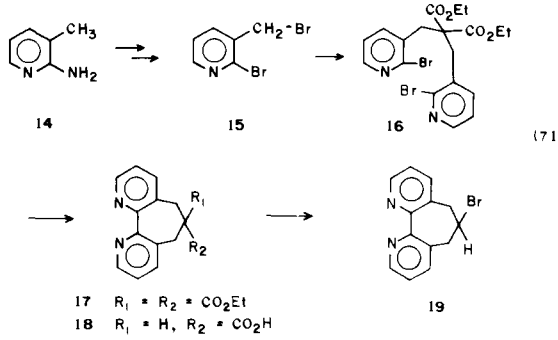
Consider the *bridged*, 2,2′-bipyridyl **11** of eq 6. Its ground state is relatively free of angle and torsional strain because the aromatic nuclei are not coplanar. When these rings are forced toward coplanarity through metal chelation, what stresses are created in the seven-membered ring? One extreme is represented in **12**,



where flattening of the seven-membered ring maximizes its torsional strains, and its endocyclic bond angles increase. Molecular mechanics calculations[8] of this conformation give the geometries indicated and imply that substitution (S_N2 or S_N1) reactions at the carbon bearing a leaving group (L.G.) should be favorable, as should those elimination reactions which prefer syn-periplanar arrangements.

The second possibility is shown in **13**, wherein a folding of the central carbon atom out of the plane minimizes torsional strain but increases the endocyclic bond angles of the benzylic carbons. This geometry is ideal for the stereoelectronic requirements of elimination reactions. This structure was initially deduced by Mislow[9] as the lowest energy for the racemization of bridged biaryls (about which more later).

The test substance **19** was prepared as outlined in eq 7, wherein modified malonic ester and Ullman and Hunsdiecker syntheses played consecutive roles. Specifically, NBS bromination of 2-bromo-β-picoline[10] **14** gave the benzyl bromide **15**, which was used



to twice alkylate malonic ester. The resulting dihalide **16** underwent intramolecular Ullman coupling to **17** in very good (>75%) yield when the copper was heated with the solvent (DMF)

(6) Gassman, P. C.; Hoye, R. C. *J. Am. Chem. Soc.* **1981**, *103*, 215–217.
(7) Leonard, N. J.; Coll, J. C. *J. Am. Chem. Soc.* **1970**, *92*, 6685–6686.
(8) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127–8134. (b) Allinger, N. L.; Yuh, Y. H. *QCPE* **1980**, *12*, 395. For our preliminary communication see: Rebek, J., Jr.; Costello, T. *Heterocycles* **1984**, *22*, 2191–2194.
(9) Mislow, K.; Hyden, S.; Schaefer, J. *J. Am. Chem. Soc.* **1962**, *84*, 1449–1455.
(10) Case, F. H. *J. Am. Chem. Soc.* **1946**, *68*, 2574–2577.

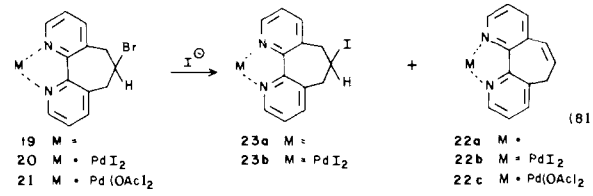
Table II

	rate constants	conditions
	substitutions	
19 → **23a**	1.3×10^{-3} M^{-1} s^{-1} (±10%)	75 °C, NaI in MEK
20 → **23b**	3.1×10^{-3} M^{-1} s^{-1} (±15%)	75 °C, NaI in MEK
	elimination	
19 → **22a**	3.4×10^{-2} M^{-1} s^{-1}	80 °C, KOAc in Me_2SO (95%), D_2O (5%)
21 → **22c**	>3.0 M^{-1} s^{-1}	0 °C KOAc in Me_2SO (95%), D_2O (5%)

before the substrate **16** was added.[11] Hydrolysis/decarboxylation gave the monoacid **18** which, as the mixed anhydride with acetic acid, underwent smooth Hunsdiecker reaction in CH_2Br_2 as solvent[12] to give **19**.

A number of nucleophiles were screened which acted on the test substance to give largely the elimination product. Only thiocyanate and iodide gave substitution products, and some considerable effort was expended in finding metal complexes of **19** which were compatible with the presence of these nucleophiles. Tungsten tetracarbonyl [$W(CO)_4$] appeared promising since its zero valent state was least likely to affect the reaction center through mere inductive effects. To be sure, the benzyl carbons can be regarded as reasonable "insulators", but transmission of such effects is more likely if the positive charge on the metal center is large. Unfortunately, the $W(CO)_4$ complex was easily oxidized to an intractable solid. Zinc chloride or acetoacetate formed complexes with **19** but these were too labile in the presence of nucleophiles. Even the $Pd(SCN)_2$ complex, prepared by precipitation from solutions of **19** with $K_2Pd(SCN)_4$, failed to hold together. In solutions containing excess SCN^-, it reversed to palladate and free **19**. Ultimately, the PdI_2 complex **20** proved suitable. The method of its synthesis was indirect, but at least its stability for the substitution study was ensured. Thus **19** was converted to its $PdCl_2$ complex with $(PhCN)_2PdCl_2$,[13] thence to **20** with excess NaI in acetone.

The effect of metal ion on the rate of the substitution reaction proved minimal (Table II). The rates shown were followed by NMR using excess NaI in MEK. Since small amounts (~5%) of the olefin **21a** were invariably formed, the data were treated appropriately for a competitive, pseudo-first-order reaction, and excellent plots were obtained. The twofold rate enhancement (**19** → **23a**, vs. **20** → **23b**) (eq 8), while reproducible, does not permit



facile interpretation. That the rate was faster in the presence of the metal confirmed, at the very least, that inductive effects were not involved. The conformational changes induced by the metal may have been small or, as predicted by the molecular mechanics calculations, the conformation of the complex tended toward the folded structure **13**, in which little change in rate is anticipated.

Next, the elimination reaction was examined. It had already been shown that acetate acted on bromide **19** to give exclusively the elimination product. This occurred at a convenient rate in wet Me_2SO at 80 °C (Table II). The $Pd(OAc)_2$ complex **21a** was generated in situ from **19** and $Pd(OAc)_2$. This proved quite sensitive to elimination. Even on standing overnight, complete dehydrohalogenation to **22c** occurs. Even so, we were unprepared for the dramatic effect that the metal complex had on the elim-

(11) Karminski, W.; Kulichi, Z. *Chem. Abstr.* **1965**, *63*, 18018d.
(12) Cristol, S. J.; Firth, W. P. *J. Org. Chem.* **1961**, *26*, 280.
(13) Kharasch, M. S.; Seyler, R. C.; Mayo, F. R. *J. Am. Chem. Soc.* **1938**, *60*, 882–884.

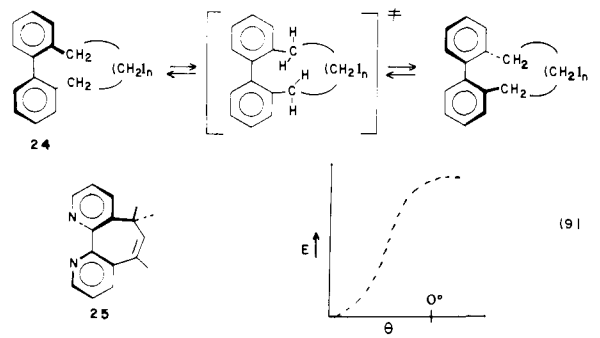
ination reaction in the presence of excess acetate. Mere addition of an equiv of KOAc to a solution of **21** at room temperature gave instantaneous elimination. Even at 0 °C we were unable to follow the rate since the half-life for the elimination reaction was less than 1 s.

While it is tempting to attribute this enhancement to the distortion toward the elimination-prone conformation **13**, other interpretations are possible. First, the presence of the metal has a deshielding effect on one of the benzylic protons in the Pd complexes: for **19** vs. **20** the shift is from δ 2.9 → δ 3.6 and for **19** vs. **21** δ 2.19 → δ 3.25. Similar shifts were observed in the $Pd(Br)_2$, $Pd(Cl_2)$, and $Pd(SCN)_2$ complexes of **19**, a feature which suggests that the *acidity* of this proton is enhanced by the metal. Attempts to expose this acidity by exchange reactions failed. For example, the $Pd(OAc)_2$ complex of the diester **17** did not show any exchange in hot D_2/Me_2SO-d_6 after 24 h. However, this does not rule out an inductive effect of the metal which moves the transition state for the reaction of the complex more toward the E_1Cb end of the elimination spectrum than might be the case in the metal-free **19**.

A second possibility, that of direct palladium involvement in the elimination reaction, was also considered. While very closely related controls could not be devised, we were able to show that $Pd(OAc)_2$ was without effect on the KOAc-induced elimination reactions of either β-phenethyl bromide or cyclohexyl bromide under these conditions. It will be difficult to establish with certitude the origins of the rate acceleration in the elimination reaction; it may well arise from the factor intended, viz angle distortion of the benzyl carbon toward the transition state. To what degree the ground state of the complex **21** resembles **13** cannot, unfortunately, be established without crystallographic data. The inductive effect of the Pd in **21** is also uncertain, and we hope that spectroscopic evidence, e.g., ^{13}C NMR, will provide information on this point in the future.

Racemization

For most chemical *reactions* the transition structure is not known, but the trajectories of the atoms undergoing changes in bonding can be plotted in their motions from, say, a ground state to an intermediate. There are some *physical* processes, however, for which reasonable assumptions concerning the transition structure may be made. The racemization of biaryls is such a case. In cyclic systems, e.g., **24**, the transition state is reached when the aromatic rings become coplanar, because the steric effects involving the ortho,ortho' groups are then maximal. When only a few bridging atoms are involved, the racemization coordinate is merely the dihedral angle defined by the aromatic ring planes, and the transition state occurs when this angle is 0° (eq 9). Since many unimolecular isomerization reactions tend to have



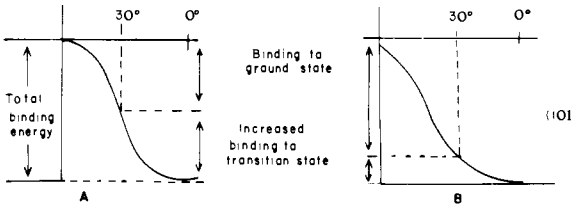
(91)

activation entropies close to zero, the free energy of activation is almost exclusively enthalpic; for the case at hand, these potential energy terms come from steric compression and angle strain terms.

The energetics of bipyridyl racemization can be expected to be quite similar. Our preliminary studies on such systems have shown the bipyridyl barriers to be slightly lower, a result that indicates the lone-pair/lone-pair repulsions and the attendant dipole–dipole interactions in a planar bipyridyl are of less enthalpic consequence than the C–H/C–H interactions in the corresponding biphenyl. A priori, the entropy of activation in bipyridine racemization might be expected to be nonzero because of differential solvation. The dipole moment of a planar vs. a twisted bipyridine must differ, and the reorganization of solvent that could occur in response to this difference may result in $\Delta S^{\ddagger}$ being either positive or negative. However, we have found in related cases **25** that the barrier to racemization is essentially solvent independent,[14] so such reorganizations must be negligibly small.

An enormous volume of structural information exists concerning metals chelated with 2,2'-bipyridyl derivatives.[15] The crystallographic structures available indicate that the ground states of such complexes are nearly coplanar—i.e., maximum binding between metal and nitrogen atoms exists in this conformation. It is an inescapable conclusion that metal ions catalyze the racemization of 2,2'-bipyridyls and that they *do so in the Pauling sense of maximum binding to the transition state.*

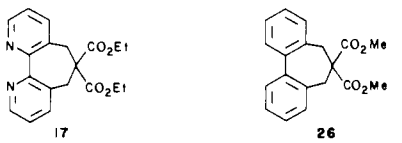
The degree of catalysis is less predictable. The total binding energy available—ca. 12–14 kcal for typical transition metals with the parent 2,2'-bipyridyl in H_2O[16]—sets the upper limit, but some of this is expended during initial binding at one nitrogen, a process which is not represented on the reaction (racemization) coordinate. There is evidence, however, that most of the binding energy involved is due to *chelation*,[17] a process which shares this coordinate. Even so, some of this is consumed in complex formation, i.e., binding to the ground state. This amount will depend on the shape of the binding curve (about which little is known) and the dihedral angles of the ground-state complex. Two possibilities are shown in eq 10.



(101)

In A, the coplanar chelate is in a well with steep sides, and binding energy is lost rapidly with small deviations from coplanarity. In B, binding is relatively insensitive to such deviations. For a ground-state complex with dihedral angle of say 30° (shown), the two cases lead to different degrees of catalysis. In A, poor binding exists in the ground state and much is gained in becoming coplanar, whereas in B the situation is reversed. The catalysis observed would be greater in A, and binding to the ground state is greater in B. Even on a given curve, the partitioning of the total binding between ground state and transition state will depend on the geometry of the complex. An entirely parallel situation exists in enzymic catalysis, in which the total intrinsic binding between enzyme and substrate[18] is partitioned between K_m and k_{cat}.

The availability of two very different bipyridyl structures permitted experimental examinations of both situations described above. The first was the diester product of the Ullman reaction **17**. Since molecular mechanics calculations on the corresponding biphenyl compound indicated a dihedral angle of only about 35°, considerable binding to metals was expected to the ground state.



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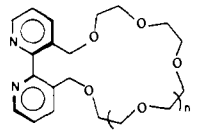
The barriers to racemization of the dimethyl or diethyl esters were determined at the coalescence temperature of the AB quartet of the benzyl protons and were found to be 11–12 kcal/mol. The analogous biphenyl **26** has been studied much,[19] with $\Delta G^{\ddagger} = 14.6$ kcal/mol $\Delta H^{\ddagger} = 11.3$, and $\Delta S^{\ddagger}$ −11 eu in $CDCl_3$. In accord with our earlier[14] findings, the barrier in the bipyridyl is lower. The $Pd(OAc)_2$ complex of **17** was prepared and proved sufficiently soluble for low-temperature NMR study. However, accidental equivalence of the chemical shifts of the benzyl protons stopped our attempts to obtain separated signals for the low-temperature extreme. From line-broadening at low temperatures a $\Delta G_c^{\ddagger}$ of ≤9 kcal/mol could be estimated. This number is similar to that previously found for **25** and is not surprising given the similarities in structure. This situation corresponds to a case where the total or intrinsic binding between $Pd(OAc)_2$ and the coplanar conformation of **17** is partitioned in such a way that the larger fraction is consumed in the formation of the crystalline complex leaving only the smaller fraction, ca. 3 kcal/mol, available for catalysis of the racemization.

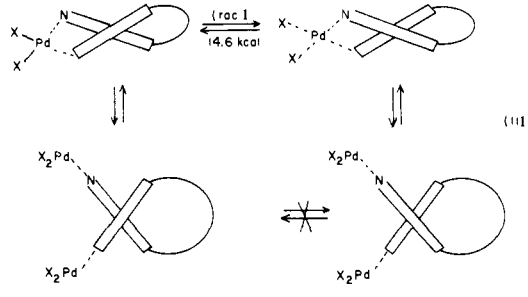
The situation was found to be reversed in the case of the bipyridyl crown ethers,[20] **27**. The barrier to racemization for these ethers was determined by DNMR by using the signals for the diastereotopic benzyl protons. While the coalescence spectra were beyond the limits of the instrument, line shape analysis was performed between 323 and 500 K. At the latter temperature racemization is reasonably rapid, and considerable broadening of the AB quartet occurs. The E_{act} for the racemization can be calculated as 25.7 kcal/mol.



27 M = —
n = 0, 1 or 2 (a, b or c)
28 M = $PdCl_2$

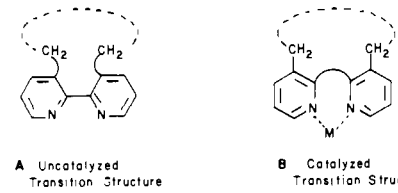
M =	n =	$\Delta G_c^{\ddagger}$ (kcal/mol)
—	0, 1 or 2	≥ 25.7
$PdCl_2$	0	14.6
"	1	14.0
"	2	13.9

The $PdCl_2$ complexes **28**, on the other hand, showed rapid racemization for which the $\Delta G_c^{\ddagger}$ was found to be 14.6 kcal/mol. The energy barriers are lowered by more than 11 kcal corresponding to a factor of $\sim 10^8$ in rate enhancement at room temperature. Formation of the ground-state complexes consumed very little of the total binding, a fact reflected by the ready displacement of the metal in these complexes by *o*-phenthroline and the easy addition of a *second* metal[21] to form a 2:1 complex (eq 11). This leaves a larger fraction of the intrinsic binding energy for catalysis at coplanarity.



(11)

An additional factor which may contribute to the enormity of the observed rate enhancement may arise from the molecular mechanics of the racemization process. Westheimer[22] concluded that racemization of related biphenyls requires that the ortho and ortho′ substituents bend *away* from each other in a manner shown (with some exaggeration) in eq 12A. Indeed, this conclusion led



A Uncatalyzed Transition Structure B Catalyzed Transition Structure ?

(12)

to the discovery of buttressing effects. For the corresponding complex, B, the metal may force in-plane distortions of the *bipyridyl* nucleus in a manner that substituent bending (and its energetic cost) is much reduced. This possibility is unavailable to the diester **17** wherein the seven-membered ring limits such in-plane distortions of the bipyridyl.

Evidence for this interpretation may be found in the preference for square-planar binding in Pd^{2+} complexes. This suggests that N–Pd–N angles which are larger than, for example, the 60° of *o*-phenanthroline will lead to better binding. Such would be the case in B vs. A. Some structural evidence that supports this reasoning has been provided by Brown,[23]

The forgoing also raises a more abstract question of comparing catalyzed and uncatalyzed reactions. If eq 12 accurately represents the situation, then it may be concluded that *the catalyst changes the mechanism.* Is this generalizable? If so, it may lead to despair among model builders concerned with the Pauling principle but hope for those who would rather discover reactions effected by catalysts which have no uncatalyzed counterpart.

Experimental Section

2,2′-Binicotinic Acid 3-Methyl Ester (5). A solution of 1,10-phenanthroline-5,6-quinone,[4] 3.10 g (14.8 mmol), in MeOH (50 mL) was stirred at room temperature while 85% *m*-chloroperbenzoic acid, 4.20 g (24.4 mmol), in 10 mL of MeOH was added dropwise, followed by addition of 2 drops of 6 N HCl. The color of the reaction mixture darkened then faded to yellow during this time. After the color changes were complete (1 h), the solution was allowed to stir for another hour. Then 100 mL of $CHCl_3$ was added, and the crude product was extracted into 1 N HCl (3 × 75 mL). The aqueous acidic extracts were combined, $CHCl_3$ was added, and the pH of the aqueous phase was adjusted to 4 with 2.5 N NaOH. After extraction of the aqueous layer with $CHCl_3$ (3 × 100 mL), the combined organic phases were dried over $MgSO_4$, and the solvent was removed to give the product as a solid. Recrystallization from hot CH_2Cl_2 afforded 2.7 g (70%) of the white crystalline product, mp 182–185 °C: NMR ($CDCl_3$) δ 3.6 (s, 3), 7.4 (d of d, J_{CB} = 8 Hz, J_{CA} = 5 Hz, 2), 8.3 (d of d, J_{BC} = 8 Hz, J_{BA} = 2 Hz, 2), 8.6 (d of d, J_{AC} = 5 Hz, J_{AB} = 2 Hz, 2); IR ($CHCl_3$) 1721 cm^{-1}; mass spectrum, *m/z* 258, 242, 227, 214.

2,2′-Binicotinic Acid 3-*N*-Benzylcarboxamide 3′-Methyl Ester (6). Dicyclohexylcarbodiimide, 0.58 g (2.81 mmol), was added to a solution of the acid ester, 0.31 g (1.20 mmol), and 0.13 mL of benzylamine (1.20 mmol) in CH_2Cl_2 at 0 °C. After stirring at room temperature for 2 h, the dicyclohexyl urea was suction filtered, and the filtrate was evaporated to a yellow oil. Crystallization from $CHCl_3$/hexane afforded 0.7 g (90%) of the amide ester as pale yellow crystals, mp 132 °C: NMR 60 MHz ($CDCl_3$) δ 3.7 (s, 3), 4.4 (d, *J* = 6 Hz, 2), 7.3 (m, 2), 8.3 (m, 2), 8.7 (m, 2); IR ($CHCl_3$) 1751, 1686 cm^{-1}; mass spectrum, *m/z* 348, 317, 289, 257, 243.

2,2′-Binicotinic Acid 3-*N*-Benzylcarboxamide (7). The amide ester **6**, 0.47 g (1.35 mmol), in 10 mL of MeOH was saponified by the addition of 1.09 mL of 2.5 N NaOH solution (2.73 mmol) followed by stirring for 1 h. The volatiles were evaporated under reduced pressure, and 10 mL of H_2O were added, followed by adjustment of the pH to 4.0 with 3 N HCl. Several extractions with $CHCl_3$ were pooled, dried over $MgSO_4$, and then evaporated to yield 0.42 g (93%) of the white amorphous solid product, mp 130–150 °C dec: NMR (Me_2SO-d_6) δ 4.2 (d, *J* = 6 Hz, 2), 7.1 (m, includes singlet, 7), 7.9 (m, 2), 8.5 (m, 2); IR (Nujol mull) 1667 cm^{-1}; mass spectrum, *m/z* 315, 288, 228, 182.

2,2′-Binicotinic Acid 3-*N*-Benzylcarboxamide Trifluoroethyl Ester (1). The amide acid, **7**, 0.4081 g (1.23 mmol), in benzene (25 mL) along with a few drops of pyridine and 5 mL of trifluoroethanol (64.4 mmol) were cooled to 0 °C, under N_2, and treated with 0.088 mL (1.23 mmol) of $SOCl_2$. After 1 h the reaction mixture was evaporated under reduced

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pressure, $CHCl_3$ (25 mL) was added, and the solution was washed twice with saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and evaporated to give 0.26 g (51%) of the product which crystallized on the addition of ether, mp 120 °C: NMR 60 MHz ($CDCl_3$) δ 4.2–4.7 (overlapping q and d, 4), 7.0–7.5 (m, includes singlet, 7), 8.2 (m, 2), 8.7 (m, 2); IR ($CHCl_3$) 1745, 1669 cm^{-1}.

Anal. Calcd for $C_{21}H_{16}O_3N_3F_3$: C, 60.72; H, 3.88; N, 10.12; F, 13.72. Found: C, 60.71; H, 3.94; N, 10.10; F, 13.76.

3,3′-Dimethyl-4,4′-bipyridine.[5] To a solution of 1.94 mL (20 mmol) of β-picoline and 2.17 g (20 mmol) of Me_3SiCl in 10 mL of dry THF under an N_2 atmosphere was added a slurry of 1.32 g of a 40% mineral dispersion of sodium (23 mmol) in 5 mL of THF. The rate of addition was controlled so that the reaction flask was never warm to the touch. After complete addition, the mixture was stirred at room temperature for 4 h. The THF was removed by evaporation, and the residue was treated with hot benzene. The mixture was filtered hot, and the filtrate was cooled and then evaporated. The residue was immediately dissolved in 75% acetone/water (v/v). To this stirred solution was added solid $KMnO_4$, and the temperature was maintained at below 50 °C with cooling when required. The addition was continued until the MnO_4^- color persisted. The excess MnO_4^- was decomposed with sucrose, and the MnO_2 was removed by filtration through Celite. The acetone was removed by evaporation, and the aqueous solution was made alkaline with 2.5 N NaOH. The aqueous portion was extracted twice with $CHCl_3$, and then the organic phases were dried with Na_2SO_4 and evaporated. The remaining picoline was removed by high vacuum, and the residue was recrystallized from hexanes, yielding 40% white crystals, mp 121–121.5 °C. ^1H NMR 2.5 (s, 3), 7.08 (d, J = 5 Hz, 2), 8.50 (d, J = 5 Hz, 2), 8.55 ppm (s, 2); mass spectrum, m/z 184, 169.

4,4′-Binicotinic Acid (8). A suspension of 0.739 g of recrystallized 4,4′-bipicoline in 50 mL of water was heated to 95 °C, whereupon the solid completely dissolved. To this was added 1.27 g (2 equiv) of $KMnO_4^-$ taking care that the temperature in the reaction flask did not exceed 96 °C. Another 2 equiv of MnO_4^- was then added, and the mixture was stirred at 95 °C for 2.5 h. Another equivalent was then added, and the mixture was heated overnight at 90–95 °C. While the solvent was still hot, the MnO_2 was filtered through Celite, and the residue was washed with two 75-mL portions of boiling water. The filtrate was then concentrated to about 10 mL, and 6 N HCl was added to adjust the pH of the solution to approximately 4. At this point a fine white precipitate formed. This was collected and vacuum dried to give 600 mg (61%) of the diacid, mp >250 °C dec: ^1H NMR (Me_2SO-d_6/10% trifluoroacetic acid) 7.48 (d, J = 4.3 Hz, 2), 8.98 (d, J = 4.3 Hz, 2), 9.30 ppm (s, 2); mass spectrum, m/z 244, 199, 154.

4,4′-Binicotinic Anhydride. The vacuum dried diacid **8** was suspended in Ac_2O in a ratio of 0.3 mL/mg. The mixture was heated to 139 °C under a reflux condenser equipped with a drying tube. A dark brown solution developed, and the heating was continued for 8 h. After high vacuum evaporation of the solvent, the residue was used in the next step without purification. ^1H NMR ($CDCl_3$) 7.6 (d, J = 6.1 Hz, 2), 8.97 (d, J = 6.1 Hz, 2), 9.1 ppm (s, 2); IR $CHCl_3$) 1840, 1765 cm^{-1}; mass spetrum, m/z 226, 182, 154.

4,4′-Binicotinic Diacid Monotrifluoroethyl Ester. The crude anhydride above was suspended in a minimum of trifluoroethanol, and the mixture was stirred for 2 h. The excess trifluoroethanol was removed by evaporation, and the resulting brown residue was used without further purification. ^1H NMR (acetone-d_6) 4.62 (q, J = 7.6 Hz, 2), 7.72 (d, J = 4.5 Hz, 1), 7.34 (d, J = 3.1 Hz, 1), 7.99 (2d, J_1 = 4.5 Hz, J_2 = 3.1 Hz, 2), 9.14 (s, 1), 9.19 ppm (s, 1).

3-(Benzylamido)-3′-(trifluorocarbethoxy)-4,4′-bipyridine (9). The residue of the previous reaction was combined with 1 equiv (calculated from the weight of the starting diacid) of isobutyl chloroformate in dry CH_2Cl_2 at 0 °C. The solution was allowed to warm to room temperature after 1 equiv of benzylamine was added. A tan precipitate was formed and was filtered off. The organic filtrate was washed with saturated aqueous $NaHCO_3$, dried, and evaporated. The brown residue was eluted down a silica column with EtOAc to yield 281 mg of a clear glass (from 460 mg of diacid, 36%). The glass could be crystallized from ether/petroleum ether to give a white solid, mp 121–122 °C: ^1H NMR ($CDCl_3$) 4.3 (overlapping q, d, 4), 6.87 (2d, over-lapping t(N–H), 3), 7.18 (br s, 5), 8.58 (d, J = 4.5 Hz, 1), 8.6 (d, J = 6.0 Hz, 1), 8.66 (s, 1), 8.94 ppm (s, 1); IR ($CHCl_3$) 1742, 1665 cm^{-1}; mass spectrum, m/z 415, 316, 309, 288. Anal. Calcd for $C_{21}H_{16}N_3O_3F_3$: C, 60.72; H, 3.88; N, 10.12; F, 13.72. Found: C, 60.83; H, 4.06; N, 10.15; F, 13.95.

General Thermolysis Procedure. In a typical experiment, 20 mg (0.048 mmol) of the 4,4′-bipyridyl model **9** was combined with 10 mg of triphenylmethane in 0.5 mL of dry Me_2SO-d_6 and placed in a dry NMR tube under N_2. The tube was capped and sealed with Teflon tape, and then an initial NMR spectrum was recorded. The tube was then immersed in an oil bath at 110 °C such that the reaction solution was entirely beneath the bath surface. After 5 min, the tube was removed from the oil bath and quickly plunged into a dry ice/acetone bath unitl frozen. The solution was then thawed just before the NMR spectrum was recorded. The imide and amide signals were integrated against the trityl hydrogen as an internal standard. The tube was then replaced in the hot oil bath and the procedure was repeated at various time intervals.

General Thermolysis Procedure with Metal Catalyst. A combination of 100 mg of the 4,4′-bipyridyl model compound **9**, 50 mg of triphenylmethane, and 57.3 mg of $NiCl_2$–$6H_2O$ was dried under high vacuum. After drying, the solids were dissolved in 6 mL of dry Me_2SO under N_2. A 1-mL portion of this was removed, and the remaining 5 mL of solution was heated to 150 °C. After cooling, the sample was diluted with $CHCl_3$ to 5 mL. The organic phase was extracted twice with saturated EDTA, disodium salt. The $CHCl_3$ layer was dried and then evaporated. The residue was then dissolved in $CDCl_3$, and the initial spectrum was recorded. The remaining sample (in the oil bath) turned a deep blue at 150 °C. After 1 h a 1-mL sample was removed and was frozen in a dry ice/acetone bath. This sample was worked up in the same manner as above, and the spectrum was recorded and integrated. Aliquots of the remaining solution were removed and worked up at appropriate times.

2-Bromo-3-(bromomethyl)pyridine (15). A mixture of 2-bromo-3-methylpyridine **14**,[10] 10 g (58.1 mmol), and NBS, 11.4 g (64 mmol), in 250 mL of CCl_4 was heated at reflux for 24 h. The solid succinimide was removed by filtration, and the CCl_4 was washed twice with water. Removal of solvent in vacuo afforded a yellow oil. The NMR spectrum of the crude product indicated that it was a mixture of starting material, 78% desired dibromide, as well as some tribromide. **Caution**: The mixture is a lachrymator and irritant; it should be kept in the hood and handled only with gloves! Vacuum distillation provided a clear oil, bp 90–91 °C at 1 mm: ^1H NMR (90 MHz, $CDCl_3$) 4.48 (s, 2), 7.24 (dd, J = 8.25, 5.25 Hz, 1), 7.75 (dd, J = 8.25, 1.8 Hz, 1), 8.28 ppm (dd, J = 5.25, 1.8 Hz, 1).

1,3-Bis(2-bromo-3-pyrido)-2,2-dicarbethoxypropane (16). Into a dried flask was placed 3.5 g of NaH 50% paraffin dispersion. Under N_2 this was washed twice with hexanes and twice with dry THF. The remaining NaH was covered with 100 mL of dry THF, and 0.9 equiv of diethyl malonate was added slowly. The mixture was stirred for 20 min when the crude bromination product **15** (from 10.48 g of **14**) was added all at once. The new solution turns bright orange while heating under reflux overnight. The excess NaH was quenched with water, and the aqueous solution was extracted twice with ether and twice with $CHCl_3$. The combined organic phases were dried and evaporated to leave a dark brown oil. The oil was distilled under reduced pressure, and the fraction that boiled between 180 and 195 °C (13 mm) was resubmitted by the procedure with 3.5 g of NaH in dry THF. To this mixture was added another portion of dibromide **15** (prepared from 10.48 g of **14**). The mixture was again heated under reflux overnight. The reaction was then quenched with water and extracted twice with $CHCl_3$. The red organic solution was washed with several portions of aqueous 10% sodium thiosulfate in order to remove the red color. The $CHCl_3$ was dried and evaporated to yield a brown semisolid. This solid was taken up in hot EtOH from which 8.84 g of the desired compound crystallized upon cooling. An additional 0.66 g could be recovered from silica gel chromatography of the residue (30% EtOAc/hexane) for a total yield of 54% of white plates, mp 153–155 °C: ^1H NMR (90 MHz, $CDCl_3$) 1.07 (t, J = 6 Hz, 6), 3.53 (s, 4), 4.20 (q, J = 6 Hz, 4), 7.21 (dd, J = 8.0, 4.5 Hz, 2), 7.80 (dd, J = 8.0, 1.5 Hz, 2), 8.27 ppm (dd, J = 4.5, 1.5 Hz, 2). Anal. Calcd for $C_{19}H_{20}N_2O_4Br_2$: C, 45.62; H, 4.03; N, 5.60; Br, 31.95. Found: C, 45.74; H, 4.23; N, 5.52; Br, 31.81.

1,1-Dicarbethoxy-3,4,5,6-di(2,3-pyrido)-3,5-cycloheptadiene (17). To 760 mg of copper powder in a flame-dried two-necked flask under N_2 flow was added 1.5 mL of freshly dried and distilled DMF. This mixture was heated at reflux temperature for 15 min.[11] Then 1.0 g of the dibromide **16** was added as the solid, all at once. The heating was continued for 3 h until a deep red color could be seen in the solvent. The mixture was then cooled to room temperature, and the residue was diluted with 6 N HCl. This solution was transferred to another flask, and the remaining solid was washed with more acid until all the residue had been transferred (ca. 40 mL total). The remaining copper powder was removed by vacuum filtration. The pH of the filtrate was adjusted to slightly alkaline with 2.5% aqueous NaOH, and then enough saturated ammonium hydroxide was added to turn the solution green. This aqueous solution was extracted 3 times with $CHCl_3$, leaving a dark blue water layer. The pooled $CHCl_3$ extracts were dried and evaporated, and the residue was chromatographed on a silica column with EtOAc to yield 77% white crystals. Recrystallization from $CHCl_3$/hexane gave mp 116–117 °C: ^1H NMR (90 MHz, $CDCl_3$) 1.28 (t, J = 6 Hz, 6), 3.07 (s, 4), 4.24 (q, J = 6 Hz, 4), 7.30 (dd, J = 8.1, 5.7 Hz, 2), 7.79 (dd, J = 8.1, 1.5 Hz, 2), 8.79 ppm (dd, J = 5.7, 1.5 Hz, 2). Anal. Calcd from

$C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23. Found: C, 67.26; H, 6.01; H, 8.19.

1-Carboxy-3,4,5,6-di(2,3-pyrido)-3,5-cycloheptadiene (18). A solution of 500 mg of the diester **17** in 6 N HCl was heated under reflux overnight. The reaction was cooled in an ice bath, and the solution was neutralized with 10 N KOH until a white precipitate formed. The solid was removed by filtration, and the filtrate was concentrated to yield a second crop of precipitate. The combined solids were dried under vacuum to yield 238 mg (68%) of the desired product, mp >240 °C: ^{1}H NMR (90 MHz, Me_2SO-d_6/TFA) 3.12 (d, J = 6 Hz, 4), 3.75 (quintet, J = 6 Hz, 1), 7.95 (br q, 2), 8.50 ppm (d, J = 8.5 Hz, 2), 9.05 ppm (br s, 2); mass spectrum, m/z 240, 195. Anal. Calcd for $C_{14}H_{12}N_2O_2 \cdot {}^1/_4H_2O$: C, 68.70; H, 5.15; N, 11.44. Found: C, 68.71; H, 5.36; N, 11.31.

1-Bromo-3,4,5,6-di(2,3-pyrido)-3,5-cycloheptadiene (19). A solution of 71.0 mg of the monoacid **18** in approximately 10 mL of Ac_2O was heated to 130 °C for 1 h, whereupon the solid dissolved and the solution darkened with the formation of the mixed anhydride. The solvents were removed under high vacuum. The brown residue was dissolved in 10 mL of CH_2Br_2 under N_2 and 164.3 mg of red mercuric oxide (2.5 equiv) was added as a solid. The stirred mixture was heated to 50 °C for 15 min. Then 60 μL (4 equiv) of bromine was added all at once. Heating was continued until the bromine color had disappeared (about 4 h). The reaction was cooled, and the reaction mixture was diluted with $CHCl_3$. A solution of 50% saturated aqueous EDTA and saturated $NaHCO_3$ was stirred rapidly with the organic phase for 15 min. The organic layer was separated and washed with fresh EDTA solution. The combined aqueous layers were back extracted with $CHCl_3$, and the combined organic layers were dried and evaporated. The crude residue was chromatographed on silica gel with $CHCl_3$/EtOH/EtOAc, and the resulting white solid was recrystallized from benzene/cyclohexane, mp 145–146 °C: ^{1}H NMR (90 MHz, $CDCl_3$) 2.9, 3.15 (ABXq, J = 13.7, 5.9 Hz, 4), 4.8 (X quintet, J = 4.8 Hz, 1), 7.3 (dd, J = 8.7, 5.8 Hz, 2), 7.62 (dd, J = 8.7, 1.5 Hz, 2), 8.91 ppm (dd, J = 5.8, 1.5 Hz, 2); mass spectrum, m/e 276, 274, 195. Anal. Calcd for $C_{13}H_{11}N_2Br$: C, 56.75; H, 4.03; N, 10.18; Br, 29.04. Found: C, 56.59; H, 4.22; N, 9.99; Br, 29.18.

Palladium Chloride Complex 19. A solution of 223 mg of palladium chloride bis(benzonitrile) complex was prepared in 25 mL of benzene.[13] Any remaining solids were removed by filtration, and 152 mg of bromide above was added to the filtrate. Immediate precipitation of a bright yellow solid resulted. The solid was isolated by filtration and used without further purification, mp >240 °C: ^{1}H NMR (300 MHz, Me_2SO-d_6) 3.16 (dd, J = 6.63, 13.95 Hz, 2), 3.52 (dd, J = 6.63, 13.95 Hz, 2), 5.30 (quintet, J = 6.63 Hz, 1), 7.79 (dd, J = 5.93, 8.72 Hz, 2), 8.27 (d, J = 8.72 Hz, 2), 9.06 ppm (d, J = 5.93 Hz, 2).

Palladium Iodide Complex 20. The crude solid above was suspended in about 2 mL of acetone. To this was added excess NaI in acetone. A purple color was immediately formed with the dissolution of the solid. The solvent was evaporated, and the residue was dissolved in $CHCl_3$. The purple solution was washed twice with water, and the organic phase was dried and then evaporated, leaving a purple solid. Attempts to recrystallize this substance from a variety of solvents all failed as did one attempt at reverse phase chromatography with H_2O/CH_3CN, mp 221–222 °C: ^{1}H NMR (300 MHz, acetone-d_6) 3.17 (dd, J = 6.76, 14.11 Hz, 2), 3.59 (dd, J = 7.76, 14.11 Hz, 2), 5.41 (quintet, J = 6.76 Hz, 1), 7.84 (dd, J = 6.35, 7.76 Hz, 2), 8.34 (dd, J = 7.76, 1.4 Hz, 2), 9.81 ppm (dd, J = 6.35, 1.4 Hz, 2).

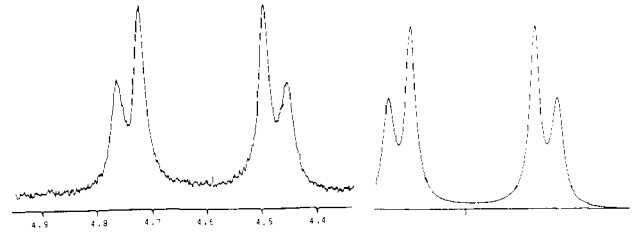
Palladium Acetate Complex 21. This substance was never isolated but generated in situ by combining 1 equiv of $Pd(OAc)_2$ with 1 equiv of bromide **19** in $CDCl_3$. (If the complex is left in solution overnight, an NMR spectrum indicates complete conversion to the olefin **22c**): ^{1}H NMR for **22** (300 MHz, $CDCl_3$) 3.25 (dd, J = 15.6, 5.07 Hz, 2), 3.48 (dd, J = 15.6, 5.07 Hz, 2), 4.95 (quintet, J = 5.07 Hz, 1), 7.51 (dd, J = 7.60, 5.50 Hz, 2), 7.95 (d, J = 7.60, 2), 8.40 ppm (d, J = 5.50 Hz, 2).

General Procedure for the Substitution Reaction. Typically, 26.6 mg of bromide **19** and 162.8 mg of NaI were combined in 2.5 mL of dried and distilled methyl ethyl ketone, under N_2. The solution was heated to 75 °C and 250-μL aliquots were removed at 1020, 2700, 5040, 7260, 9840, and 12540 s, sequentially. These samples were diluted with $CHCl_3$ and washed 3 times with water. The organic portion was dried and evaporated, and then the residue was dissolved in approximately 0.5 mL of benzene-d_6 and placed in an NMR tube. The NMR spectrum was recorded at 300 MHz by using a strong decoupling signal centered at the middle of the benzyl resonances for both the bromide **19** and iodide (~2.6 ppm). The halide methine protons then appeared as singlets that could be integrated (bromide 4.06 ppm, iodide 4.10 ppm). The olefin **22a** could also be seen as a doublet at 6.16 ppm which was also integrated. The kinetics were then treated as competitive first-order reactions to calculate the rate constant for appearance of iodide. Iodide **23a** mass spectrum, m/z 322, 195; olefin mass spectrum, m/e 193.

Substitution on Palladium Complex 20. These reactions were performed in the same way as the noncomplexed reactions, except for the workup of each aliquot. These were diluted with $CHCl_3$ and washed 1 time with H_2O, twice with 10% aqueous $Na_2S_2O_3$, and another time with water. The spectra were recorded the same way as described above.

Elimination with KOAc. Bromide **19** (23.7 mg) was dissolved in 1 mL of Me_2SO-d_6/5% D_2O (v/v), and 33.6 mg of vacuum-dried KOAc was dissolved in the same solvent system. Then 200 μL of each solution were combined in an NMR tube, the final concentrations being the following: [bromide] = 0.041 M and [KOAc] = 0.086 M. The tube was heated to 80 °C in the probe and the spectra were recorded at 1-min intervals. The data were treated according to second-order kinetics as the concentration of KOAc could not be made large enough for pseudo-first-order conditions.

Variable-Temperature Experiments with Pd-Bound Crowns. For example, the Pd bipyridyl-16-crown-4 **28a**[20] was dissolved in acetone-d_6, and the room temperature (34 °C) 90-MHz NMR spectrum was recorded. The temperature was dropped to −45 °C where the separation of chemical shift no longer increased with decreasing temperature. From this spectrum, the difference in chemical shift and coupling constant were measured to use in the formula. The temperature was then raised in 10° increments until close to the coalescence temperature, where the increment was decreased to 2° through coalescence. For the racemization studies of the free crown **27a**, spectra were recorded in nitrobenzene at 323, 403, 485, and 500 K and matched with computer-simulated spectra.



The upper limit spectra and simulation are shown below. Least-squares analysis of the rates gave E_{act} = 25.7 kcal/mol (r = 0.999).

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