

BINDING FORCES AND CATALYSIS: RATE ENHANCEMENTS THROUGH CHELATION AT A REMOTE SITE

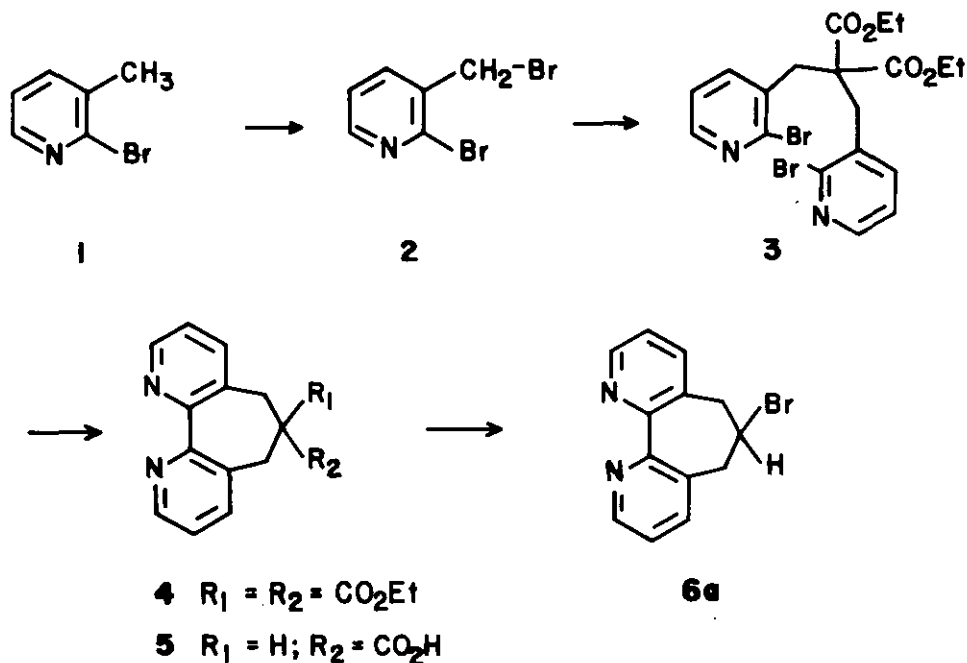
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Abstract - The rate of an elimination reaction is increased by more than three decades through distortions induced by binding at a remote site.

One means by which enzymes increase reaction rates is through binding to transition states more effectively than to ground states.¹ In an effort to reduce this principle to practice in model systems, we have prepared the bipyridyl halide **6a** as shown in Scheme 1. We report here how the binding of transition metals to the bipyridyl function, as in **6b** alters the reactivity of the halide function.

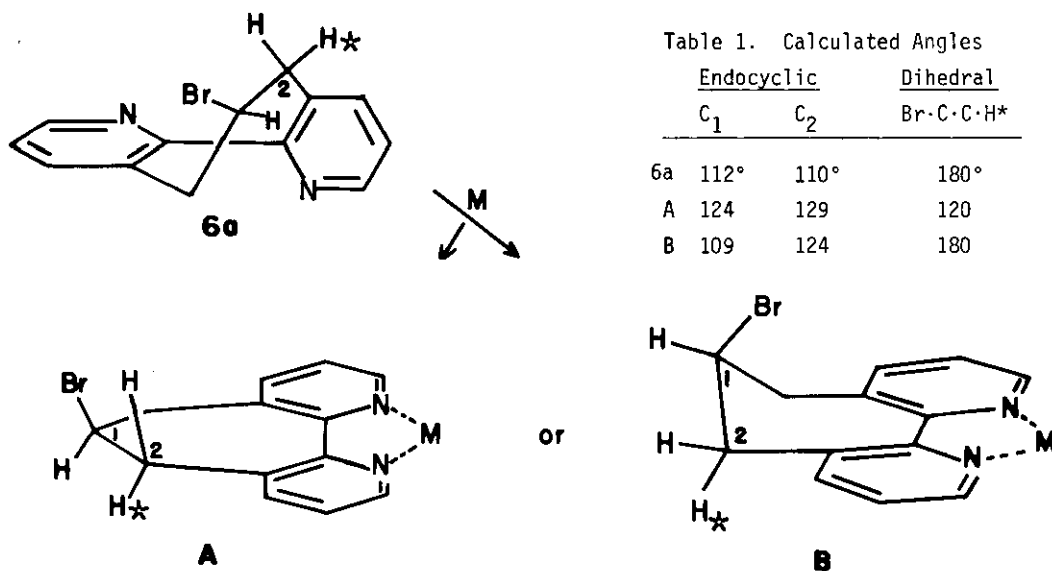
SCHEME 1



Scheme 1. **1** \rightarrow **2**; NBS/ CCl_4 , reflux 24 h (78%); **2** \rightarrow **3**; Malonic ester, NaH/THF (54%); **3** \rightarrow **4**; Cu/DMF, reflux, 3 h (77%); **4** \rightarrow **5**; 6NHCl , reflux, 12h (68%); **5** \rightarrow **6**; Ac_2O , 130°C , 1 h, then HgO , $\text{Br}_2/\text{CH}_2\text{Br}_2$, 50°C , 4 h (54%).

Chelation of metals by **6** forces the aromatic nuclei toward coplanarity and applies stress to the 7-membered ring. *A priori* this ring might respond by flattening toward the extreme A or folding toward B (Scheme 2). In A, the endocyclic bond angles of the halide-bearing carbon **increase** and torsional interactions maximize; this should lead to enhanced rates of **substitution** at this center. In B the benzylic carbon's angles increase and torsional strain is minimized; this arrangement should enhance **elimination** reactions. The table shows the relevant angles for **6a**, A and B which are obtained from molecular mechanics calculations³; these calculations show B to be some 20 kcal/mole more stable⁴ than A.

SCHEME 2



The calculations imply that binding of metals to **6a** will effect elimination reactions rather than substitution reactions of the halide. These anticipations are borne out by experiment (Scheme 3). The Finkelstein reaction of **6a** leads to **7a** along with 5% olefin **8a**. As Table 2 indicates, the rate of this reaction is scarcely affected by chelation. Thus the PdI₂ complex **6b** (prepared from **6a** by treatment with [C₆H₅CN]₂PdCl₂ followed by halide exchange with NaI in Me₂CO) gave **7b** at nearly the same rate under these conditions.

The presence of metal has a dramatic effect on the elimination reaction. The complex **6c** (prepared from **6a** with one equiv. $\text{Pd}(\text{OAc})_2$) gives **8c** instantly under conditions where **6a** eliminates to **8a** at an unexceptional rate. Even at 0°C the reaction of **8c** is too fast to measure by conventional techniques. Assuming reasonable activation parameters, the rate enhancement afforded by the metal is at least 10^3 .

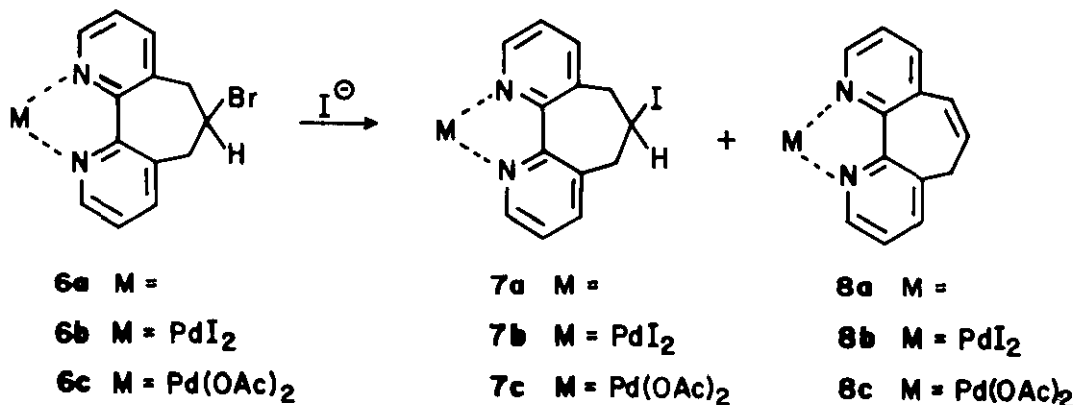


Table 2.

Substitutions	Rate Constants	Conditions
6a → 7a	$1.3 \times 10^{-3} \text{ M}^{-1}\text{sec}^{-1}$ ($\pm 10\%$)	75°C , NaI in MEK
6b → 7b	$3.1 \times 10^{-3} \text{ M}^{-1}\text{sec}^{-1}$ ($\pm 15\%$)	" " "
Elimination		
6a → 8a	$3.4 \times 10^{-2} \text{ M}^{-1}\text{sec}^{-1}$	80°C , KOAc in DMSO(95%) D ₂ O(5%)
6c → 8c	$>3.0 \text{ M}^{-1}\text{sec}^{-1}$	" " "

The enhancement observed here might well arise from the factor intended, viz. increased binding between metal and bipyridyl as the complex moves from ground state toward transition state. In earlier studies with closely related compounds, we have shown that chelation of metals with such bipyridyl derivatives substantially lowers the energy of the coplanar state.⁵ While the **ground** states of such metal complexes are not coplanar, the chelates are undoubtedly closer to coplanarity than the free bipyridyls. Illumination of these structural details must await crystallographic determination. In the meantime, we note that despite control experiments⁶ the case at hand, like those

of others⁷, is not without alternative interpretations. We are examining the mechanistic details of this elimination reaction with the aim of removing these ambiguities.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

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2. F. H. Case, J. Am. Chem. Soc., 1946, 68, 2574. All new compounds were characterized by elemental analyses and a full complement of spectra.
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6. For example, the Pd(OAc)₂ complex of the diester 4 in DMSO/D₂O and excess acetate ion showed no exchange of the benzylic protons under these, and even more vigorous conditions. This excludes an effect in which the Pd catalyzes the elimination through enhancing the acidity of the benzyl hydrogens. In addition, Pd(OAc)₂ showed no effect on the rate of elimination of either cyclohexyl bromide or β-phenethyl bromide with KOAc under any of these conditions.
7. a) R. Breslow, R. Fairweather and J. Keana, J. Am. Chem. Soc., 1967, 89, 2135; b) J. Boger and J. R. Knowles, ibid., 1979, 101, 7631; c) R. Breslow, J. Czarniecki and J. Hamaguchi, ibid., 1980, 102, 762; d) R. Breslow, G. Trainor and A. Ueno, ibid., 1983, 105, 2739.

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