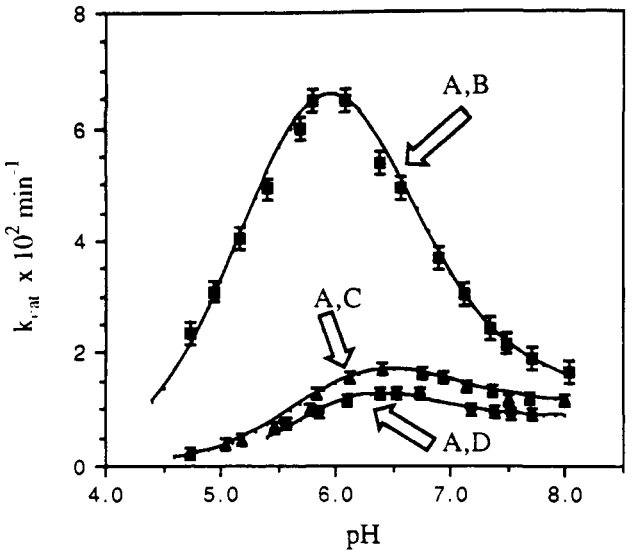


**Figure 2.** The $k_{cat}$ at 25.0 °C for the hydrolysis of **2** (1.0 mM) complexed within the cavity of 5.0 mM β-cyclodextrin A,B (■), A,C (▲), and A,D (●) bis(imidazoles).

showed[9] that the $ImH^+$ acts to protonate the phosphate anion group of the substrate, not just the leaving group. Much evidence in the literature is consistent[9,10] with a similar mechanism for ribonuclease A itself: the $ImH^+$ group of the enzyme first hydrogen bonds to the $O^-$ of the substrate phosphate, and the proton is transferred as the enzyme Im delivers a nucleophile to form an intermediate phosphorane *monoanion*. The key step is related to that shown in Figure 1B.

This led us to wonder about the mechanism of catalyzed hydrolysis of **2** by cyclodextrin-bis(imidazoles). Did they indeed perform bifunctional catalysis by the mechanism of Figure 1A, or was Figure 1B the true mechanism as we suggest for the enzyme? The geometric differences among the isomeric cyclodextrin-bis(imidazoles) allow us to choose between these possibilities. They demonstrate that in this system, too, the function of the $ImH^+$ is to protonate the phosphate anion so as to promote the formation of an intermediate phosphorane.

The mechanism of Figure 1A requires the Im and $ImH^+$ to interact with groups that are 180° apart, the attacking $H_2O$ and the leaving $O^-$. Although the angles made by groups attached to oxygen mean that the catalytic groups need not themselves be 180° apart on the cyclodextrin framework,[2] the 6A,6D isomer would be well suited to this mechanism. By contrast, there seems to be no way for the 6A,6B isomer to use the mechanism of Figure 1A; the two catalytic groups are next to each other, not on opposite sides of the bound substrate. The mechanism of Figure 1B requires the Im and $ImH^+$ to interact with groups that are ca. 90° apart, the attacking $H_2O$ and the phosphate $O^-$. This seems possible (models) for all three isomers but particularly easy for the 6A,6B bis(imidazole) and difficult for the A,D isomer. The A,C isomer can fit either mechanism of Figure 1.

We have now studied the kinetics of cleavage of **2** by all three isomers of β-cyclodextrin-bis(imidazole). All show kinetic saturation with increasing concentration of catalyst and a bell-shaped pH vs rate profile for $k_{cat}$. As Figure 2 shows, the A,B isomer is much more effective than is the A,D isomer, with the A,C bis(imidazole) in the middle. The preference for the A,B isomer means that this system indeed uses the mechanism of Figure 1B, just as we have suggested for the enzyme.

The A,B isomer is quite a good catalyst. At the pH optimum the $k_{cat}$ for the hydrolysis of **2** is 0.0014 $s^{-1}$, and $K_m$ is 0.18 mM. The resulting specificity constant $k_{cat}/K_m$ (7.8 $s^{-1}$ $M^{-1}$) is only 230 times smaller than that (1800 $s^{-1}$ $M^{-1}$) for the hydrolysis of cytidine-2,3-cyclic phosphate by ribonuclease A;[13] of course the substrates are different.

We are studying the product selectivities and isotope effects in those hydrolyses to characterize them further. However, it is already clear that the geometric catalyst preference we have discovered is further support for our proposal that the best way for bifunctional catalysts to hydrolyze substrates related to RNA is by protonation of the phosphate anion group. This may well apply to the enzyme ribonuclease also. In any case this mechanistic idea has guided us to a particularly effective enzyme mimic.[12]

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## Rates for 1,2 Migration in Alkylchlorocarbenes

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Alkylcarbenes, in cases where they have a singlet ground state, can undergo rearrangement with migration of alkyl or hydrogen, and much work has been expended on the studies of carbene rearrangements.[1-4] The isomerizations of alkylcarbenes are so rapid that the additions to multiple bonds are precluded, and, consequently, there has been no report on the intermolecular capture of dialkyl carbenes. Moss and co-workers[5-7] demonstrated that the presence of a chlorine atom on the carbene markedly affects the stability and reactivity, enabling intermolecular reactions to compete with intramolecular 1,2 shift. To our knowledge, there has been no direct measurements of rate constants for 1,2-H migration in alkylcarbenes at ambient temperature because they do not absorb intensively in a region where they can be monitored. We now wish to report the 1,2-H migration rate constants for a series of alkylchlorocarbenes in an effort to understand the migratory aptitudes in this rearrangement. Semiempirical MINDO/3 calculations for the same series of carbenes are in agreement with the observed migratory aptitude.

The alkylchlorodiazirines are synthesized by Graham's method.[8] The decomposition products are well-known and have been reported previously.[5-7,9,10] Laser flash photolysis of diazirines in isooctane at 25 °C in the presence of pyridine produces transient species with a maximum absorption in the 360-380-nm range. These transients are not present in the absence of pyridine and are attributed to pyridinium ylides. Plots of the observed pseudo-first-order rate constants for the growth of the absorption of ylides, $k_{growth}$, vs [pyridine] are linear and allow the measurements of the rate constant for 1,2-H migration, $k_i$, in alkylchlorocarbenes. The slopes give the rate constants for reaction of the carbenes with pyridine, $k_y$, and the intercepts yield $k_i$. The values of $\tau = 1/k_i$ are given in Table I as $\tau$(exp). The analysis of $k_{growth}$ vs [pyridine] gives only approximate values of $k_i$ (≈10 ns) for ethyl-, propyl-

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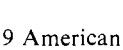
**Table I.** Experimental Data on Alkylchlorocarbenes

| carbene | $\tau$(exp) (ns) | $\tau$(calc) (ns) | $k_y/k_i$ ($M^{-1}$) | $k_y \times 10^{-9}$ ($M^{-1}$ $s^{-1}$) | reaction product |
|---|---|---|---|---|---|
| $CH_3$-C-Cl | 330 | | | 8.86 ± 0.1 | $CH_2$=CHCl[6] |
| $CH_3$-$CH_2$-C-Cl | ≈10 | 7.8 | 70 | *a* | $CH_3CH$=CHCl[b,9] |
| $C_2H_5$-$CH_2$-C-Cl | ≈10 | 11.7 | 105 | *a* | $C_2H_5CH$=CHCl[b,9] |
| $(CH_3)_2$CH-C-Cl | ≈10 | 11.3 | 125 | 11 ± 3 | $(CH_3)_2C$=CHCl[9] |
| Ph-$CH_2$-C-Cl | 16.5 | | | 7.5 ± 0.5 | Ph-CH=CHCl[b,9] |
| Ph-CH($CH_3$)-C-Cl | <3 | ≈1.5 | 13 | *a* | Ph-C($CH_3$)=CHCl[b,10] |
| $(CH_3)_3$C-C-Cl | ≈90[11] | | | 2.4 ± 0.2 | $(CH_3)_2C$=C($CH_3$)Cl[9] |
| c-$C_3H_5$-C-Cl | 1670<br>2600[c] | | | 0.47 ± 0.3 |  Cl[7] |

[a] Assumed to be equal to $9 \times 10^9$ $M^{-1}$ $s^{-1}$, mean value of the three $k_y$ values measured for >CH-C-Cl type carbenes. [b] *Z* and *E* isomers are produced: $k_i = 1/\tau$ represents an average for the two competing H-shifts. [c] From the direct observation of the carbene decay at 250 nm, after correction for a second-order process which significantly shortens the apparent lifetime of this carbene as measured by the pyridine ylide technique. The second-order process (dimerization) is important in this case because the carbene concentrations produced in LFP are large and the rearrangement to cyclobutene is particularly slow.

**Table II.** Calculated Activation Parameters $E_a$ (kcal/mol) and $\Delta S^{\ddagger}$ (cal/mol·K)

| carbene | hydrogen migration | | | methyl migration | |
|---|---|---|---|---|---|
| | $E_a^{MNDO}$ | $E_a^{MINDO/3}$ | $\Delta S^{\ddagger}$ MNDO | $E_a^{MNDO}$ | $E_a^{MINDO/3}$ |
| $CH_3$-C-Cl | 30.3 | 9.4 | -3.5 | | |
| $CH_3$-$CH_2$-C-Cl | 28.2 | 6.0 | -3.1 | 37.6 | 15.4 |
| $(CH_3)_2$CH-C-Cl | 24.5 | 2.5 | -3.8 | | |
| $(CH_3)_3$C-C-Cl | | | | 29.0 | 1.0 |
| Ph-$CH_2$-C-Cl | 26.1 | 4.3 | -3.6 | | |
| Ph-CH($CH_3$)-C-Cl | 22.8 | 2.3 | | | |

and isopropylchlorocarbenes because of the short lifetime of these species: with low [pyridine], the yield of ylide formation is low, and therefore the measured absorptions are weak; with high [pyridine], $k_{growth}$ is so large that it cannot be measured accurately with our setup. In Ph-CH($CH_3$)-C-Cl, the 1,2-H migration is so fast that the determination of $k_i$ by this method is beyond the capability of our detection system. In these cases, the ratio $k_y/k_i$ has been determined from the linear plots of 1/OD vs 1/[pyridine] with OD being the absorbance of the ylide. Assuming that $k_y$ is very similar for all these carbenes and close to $9 \times 10^9$ $M^{-1}$ $s^{-1}$, the values for $\tau = 1/k_i$ can be calculated ($\tau$(calc) in Table I) for the alkylchlorocarbenes and for Ph-CH($CH_3$)-C-Cl.

Activation parameters calculated by MNDO and MINDO/3 methods are presented in Table II. By using configuration interaction we find that, in the case of $CH_3$-C-Cl, the triplet surface does not play a role in the 1,2 H migration. Therefore the calculations have been performed for all carbenes at the singlet RHF level along the reaction path, in the same way as in ref 12. The geometries for the stationary points (carbene and transition state) are fully optimized. The calculated $\Delta S^{\ddagger}$ are similar for all carbenes suggesting that the difference in carbene lifetimes is due to their respective $E_a$. Both methods indicate that the $E_a$ are running parallel to the experimental migratory aptitudes. A known deficiency of MNDO is that it disfavors nonclassical structures, producing high $E_a$ for migrations. On the other hand, MINDO/3 which favors small rings[13] (such as the transition state for the 1,2-H migration) gives more realistic values for barriers to rearrangement, e.g., the calculated $E_a$ for rearrangement in Ph-$CH_2$-C-Cl is in excellent agreement with the experimental values of 6.4[9] and 4.5[14] kcal/mol.

It is clear from the present results that 1,2-H migration is enhanced by substitution on the $\alpha$-carbon. Thus, the hydrogen migration in $(CH_3)_2$-CH-C-Cl is 30 times faster than in C-$H_3$-C-Cl, and in Ph-CH($CH_3$)-C-Cl it is 10 times faster than in Ph-$CH_2$-C-Cl. Since electronic effects are cumulative as shown in our calculations, we find it surprising that the H migratory aptitudes are similar in $CH_3$-$CH_2$-C-Cl, $C_2H_5$-$CH_2$-C-Cl, and $(CH_3)_2$CH-C-Cl. This suggests either that the maximum enhancement in rate is reached by the addition of one methyl group on the $\alpha$-position or the occurrence of an alternative reaction pathway.

It is generally accepted that hydrogen migration is faster than methyl migration. This is confirmed by the fact that only 1,2-H shifts are observed for $CH_3$-$CH_2$-C-Cl. However, we must be cautious when comparing the 1,2-H shift and the 1,2 alkyl shift between carbenes in the same series: for example, the methyl shift in $(CH_3)_3$C-C-Cl is three times faster than the hydrogen shift in $CH_3$-C-Cl due to the inductive effects of the methyl groups. The 1,2 migration of the cyclopropyl C-C bond in c-$C_3H_5$-C-Cl to give 1-chlorocyclobutene is particularly interesting. Moss and Fantina[7] have argued that the efficient intermolecular capture of c-$C_3H_5$-C-Cl is due to an increased stability of this carbene. Our observed rate constants for this series certainly support this idea.

Experimental determination of activation parameters for alkylchlorocarbenes is underway.

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## Ligand Oxidation in a Nickel Thiolate Complex

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Recent interest in the factors that stabilize formally Ni(III) sites in many hydrogenases ($H_2$ases) and carbon monoxide dehydrogenases has stimulated investigations of Ni(II) thiolates.[1-5] Studies of the redox chemistry of Ni(II) complexes reveal that oxidations to Ni(III) or reductions to Ni(I) typically occur at potentials outside those accessible in biological systems.[6-8] Coordination environments incorporating thiolate ligands might be expected to stabilize Ni(III); however, recent studies suggest that ligand oxidation leading to the formation of disulfides may occur in preference to metal oxidation.[1] Detailed knowledge of these redox processes is important in understanding the mechanism(s) involved in small-molecule activation in the metalloenzymes and is currently limited by the paucity of well-characterized oxidation products. We report the first study of the oxidation of nickel thiolates involving three oxidation levels where the initial and final

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