Scheme I

$$[Rh(L)_2(CO)I] + I^- \underset{}{\overset{K_1}{\rightleftharpoons}} [Rh(L)(CO)I_2]^- + L$$

slow $\downarrow CH_3I$; very fast $\downarrow CH_3I$

$$[CH_3Rh(L)_2(CO)I_2] + I^- \underset{K_2}{\overset{L}{\rightleftharpoons}} [CH_3Rh(L)(CO)I_3]^-$$

or

$$[CH_3Rh(L)(CO)I_2] + I^-$$

yl iodide, that we were unable to obtain accurate kinetic data; it is still possible to place a lower limit for the relative rates of $>10^5$; i.e., the anionic species are far more reactive than the neutral rhodium species in this type of oxidative addition.

We therefore propose that the catalytic effect of halide ions in these systems arises from the type of mechanism shown in Scheme I.

The liberation of free halide ion from a rhodium(III) complex is necessary in the above scheme. Now it is well known that the alkyl group on a transition metal is a powerful trans labilizing ligand, and indeed the reaction of $[Rh(Ph_3P)_3Cl]$ with CH_3I results in formation of a five-coordinated rhodium(III) complex with the coordination position trans to the methyl group being vacant.[6] Thus it is reasonable to assume that the halide ion is liberated from an anionic rhodium(III) species with sufficient speed that the catalytic effect is produced. In agreement with this scheme the addition of excess triphenylstibine to the $[Rh(Ph_3Sb)_2(CO)I]$-CH_3I reaction inhibits the catalytic effect of halide. Also the reaction is first order in added halide ion and methyl iodide, at least during the first part of the reaction in the stibine complex system. The gradual loss of rate which occurs in the stibine complex system at high conversions (see Figure 2) is not accompanied by any marked spectroscopic change and it seems likely that an equilibrium between the rhodium(III) species, as shown in Scheme I, is reducing the amount of free halide in the system and hence the overall reaction rate.

It is apparent from this study that trace levels of halide ion can play an important role in reactions involving nucleophilic behavior by a labile metal complex. The lack of halide catalysis with the phosphine complex presumably results from the position of the equilibrium between neutral and anionic rhodium(I) species in the presence of halide ion (vide supra). This is not to imply that ionic species are not also important in the reaction of methyl iodide with $[Rh(Ph_3P)_2(CO)I]$ since we find that the conductivity of the solutions steadily increases over the course of the reaction. By contrast no evidence of halide catalysis in the reaction of $[Ir(L)_2(CO)X]$ complexes with methyl iodide is observed and neither is there an appreciable increase in conductivity during these reactions.

Acknowledgments. The author wishes to express his appreciation for the experimental assistance of Messrs. W. O. Weinreis and T. Moore.

References and Notes

(1) I. C. Douek and G. Wilkinson, *J. Chem. Soc. A*, 2604 (1969).
(2) P. B. Chock and J. Halpern, *J. Am. Chem. Soc.*, **88**, 3511 (1966).
(3) $[Rh(PH_3Sb)_2(CO)I]$ was charged as the solid complex $[Rh(Ph_3Sb)_3(CO)I]$ which is apparently completely dissociated into $[Rh(Ph_3Sb)_2(CO)I]$ + Ph_3Sb in methylene chloride and chloroform as judged from molecular weight determinations. This dissociation phenomena has also been documented for the arylstibine chloro–rhodium complexes by P. E. Garrou and G. E. Hartwell, *J. Organomet. Chem.*, **69**, 445 (1974). We also studied methyl iodide addition to the chloro complex and find the same behavior as described here for the iodo complex. Detailed studies of chloro complexes were not performed, however, after it was observed that halide exchange was occurring in the system $[Rh(Ph_3P)_2(CO)Cl]$ + CH_3I. Similarly we observed that chloride and bromide salts would catalyze the reactions as described above for $[Bu_4N]I$.
(4) The products of methyl iodide addition to $[Rh(Ph_3P)_2(CO)X]$ and $[Rh(Ph_3As)_2(CO)X]$ are mixtures of compounds containing both methyl–rhodium bonds and acetyl–rhodium as indicated by both infrared and NMR data.[1] The reaction product of $[Rh(Ph_3Sb)_2(CO)I]$ + CH_3I can be isolated as an orange solid by evaporation and recrystallization from CH_2Cl_2–CH_3OH. This material analyzes as the simple adduct $[RhI_2$-$CH_3(CO)(Ph_3Sb)_2]$. Anal. Calcd for $C_{38}H_{33}I_2ORhSb_2$: C, 41.28; H, 2.98; I, 22.96. Found: C, 41.23; H, 3.15; I, 23.65. The infrared spectrum shows γCO at 2049 cm^{-1} and the PMR spectrum of this material shows the CH_3–Rh at δ − 1.30 ppm (downfield from TMS) with $J(RhH)$ = 2 Hz. The compound shows no tendency to isomerize to an acetyl-containing species. The same product is formed with or without the halide catalyst.
(5) Salts of the anions $[Rh(L)(CO)X_2]^-$ have been prepared by D. E. Morris et al. by reaction of compounds of the type $[Rh(L)(CO)X]_2$ with halide salts (private communication).
(6) P. G. H. Troughton and A. C. Skapski, *Chem. Commun.*, 575 (1968).

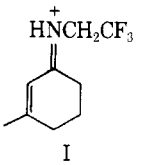
Denis Forster
Corporate Research Department, Monsanto Company
St. Louis, Missouri 63166
Received October 25, 1974

Primary Amine Catalysis of the Isomerization of a β,γ-Unsaturated Ketone to Its α,β-Unsaturated Isomer. A Possible Model for Enzymatic Double Bond Migration in Unsaturated Ketones

Sir:

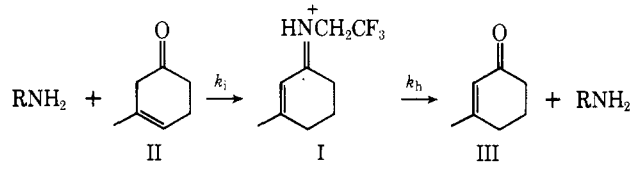
Enzymes which catalyze the interconversion of β,γ-unsaturated ketones and their α,β-unsaturated isomers have been objects of growing interest lately. The most thoroughly characterized enzymes of this type are the Δ^5-3-ketosteroid isomerases which catalyze the isomerization of β,γ-unsaturated-3-ketosteroids to their α,β-unsaturated isomers.[1] The enzyme from *Pseudomonas testosteroni* has been investigated in some detail, although little is known about the mechanism of the mammalian enzymes. The reverse reaction, α,β to β,γ isomerization, is catalyzed in the prostaglandin series by prostaglandin A isomerase.[2] In addition, Abeles[3] has postulated that the mechanism of action of 2-keto-3-deoxy-L-arabonate dehydratase includes a similar isomerization as one step. We wish to report that primary amines are capable of catalyzing the isomerization of β,γ-unsaturated ketones to their α,β-isomers. This reaction, involving the intermediate formation of a Schiff base, is very efficient and may represent a model for the corresponding enzymatic isomerizations.[4]

When 3-methyl-3-cyclohexenone is added to an aqueous solution of a 2,2,2-trifluoroethylamine buffer, the formation of 3-methyl-2-cyclohexenone can be monitored at 240 nm (the λ_{max} of 3-methyl-2-cyclohexenone) by uv spectroscopy. At moderate concentrations of buffer (<0.4 *M*) the appearance of the α,β-unsaturated isomer is pseudo first order after an initial induction period. If, however, the reaction is monitored at 268 nm, a rapid initial absorbance increase is observed, followed by a slower decay which corresponds to the rate of formation of 3-methyl-2-cyclohexenone. NMR and uv spectra taken of solutions before significant decay of the absorbance at 268 nm indicated the presence of the protonated Schiff base (I) of 3-methyl-2-cyclohexenone and trifluoroethylamine.[6] We were able to isolate I from the reaction of trifluoroethylamine and 3-methyl-3-cyclohexe-



I

Scheme I



none in carbon tetrachloride and its uv and NMR spectra were essentially identical with the transient species.[8]

The kinetics at 268 nm may be analyzed on the basis of Scheme I. Rate constants for the two reactions were evaluated from the integrated rate equation by a method similar to that used previously by Fersht and Jencks.[10] Alternatively, k_i was measured at 251 nm (the isosbestic point for the conversion of I to III) and k_h at 268 nm by using a stock solution of deprotonated I.[11] Where both methods were used, agreement was excellent.

The rate constant for formation of the intermediate (k_i) is second order in amine concentration and may be described by eq 1 where $k_i^{AB} = 2.2 \times 10^{-1}\ M^{-2}\ \text{sec}^{-1}$. The

$$k_i = k_i^{AB}[RNH_2][RNH_3^+] \quad (1)$$

hydrolysis of I to III has a substantial water-catalyzed term as well as a term in free amine. In the pH range studied (4.7-6.9) the observed rate constant is given by eq 2, where

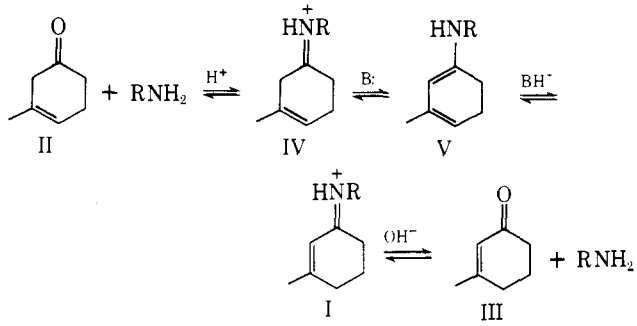
$$k_h = (k_h^{H_2O} + k_h^{OH^-}[OH^-] + k_h^{B}[RNH_2])\left(\frac{[H^+]}{[H^+] + K_a}\right) \quad (2)$$

K_a is the ionization constant of I. Evaluation of these constants gave $k_h^{H_2O} = 3.41 \times 10^{-4}\ \text{sec}^{-1}$, $k_h^{OH^-} = 4.08 \times 10^3\ M^{-1}\ \text{sec}^{-1}$, $k_i^{B} = 1.40 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$, and $K_a = 1.66 \times 10^{-7}$.

We interpret these results in terms of Scheme II. In this mechanism the second-order term in amine for the formation of the imine (k_i^{AB}) is explicable in terms of a second molecule of amine acting as either a general base in the deprotonation of IV or as a general acid in the protonation of V.[12]

The overall catalytic efficiency of trifluoroethylamine in the isomerization of 3-methyl-3-cyclohexenone is limited by the rate of hydrolysis of the protonated Schiff base (I) to the α,β-unsaturated ketone (III) since at all but very low amine concentrations $k_h < k_i$. Evaluation of k_h for 1 M amine at pH 6 gives a rate constant of $1.12 \times 10^{-3}\ \text{sec}^{-1}$. If we compare this rate constant to the rate constant for spontaneous isomerization of II ($k_{isom}^{H_2O} \leq 2 \times 10^{-7}\ \text{sec}^{-1}$)[14] we see a rate enhancement of about 10^4-fold. A comparison with the corresponding acid-catalyzed[15] and base-catalyzed[14] processes at this pH shows a rate increase of $>10^6$-fold and $>10^5$-fold, respectively, for amine catalysis. Even more strikingly, the actual rate of bond migration (k_i) at 1 M amine is about 100 times greater than imine hydrolysis (k_h). It is clear that primary amines possess enormous catalytic capabilities with respect to double bond migration in β,γ-unsaturated ketones.

Scheme II



We would like to suggest that this process might represent a model for the corresponding enzymatic isomerizations. Specifically, an ϵ-amino group of a lysine residue at the enzymatic active site might combine with the substrate to form a Schiff base, followed by general base-general acid assisted hydrogen migration. Subsequent hydrolysis would lead to the product ketone. In this connection, it is noteworthy that a Schiff base has been implicated in the mechanism of action of 2-keto-3-deoxy-L-arabonate dehydratase.[3] It was postulated that this Schiff base facillitates a double bond migration as well as an initial dehydration. On the other hand, Δ^5-3-ketosteroid isomerase of *P. testosteroni* shows no loss of activity on modification of its amino groups by methyl acetimidate,[5] suggesting that the Schiff base mechanism may not be operative for this enzyme. As far as the mammalian Δ^5-3-ketosteroid isomerases and prostaglandin A isomerase are concerned, there is at present no evidence regarding the existence of Schiff base intermediates.

Acknowledgment. We wish to thank Professors D. L. Whalen and M. W. Logue for several informative discussions and Professor Benisek for a preprint of ref 5. This work was supported by Grant No. GM20188 from the National Institutes of Health.

References and Notes

(1) P. Talalay and A. M. Benson, "The Enzymes," Vol. VI, 3rd ed, 1972, p 591.
(2) R. L. Jones, *Biochem. J.*, **139**, 381 (1974).
(3) D. Portsmouth, A. C. Stoolmiller, and R. H. Abeles, *J. Biol. Chem.*, **242**, 2751 (1967).
(4) After submitting this manuscript, we learned that Benisek has also observed primary amine catalysis of the isomerization of a β,γ-unsaturated ketone to its α,β-isomer via Schiff base formation, although no detailed kinetic analysis was carried out.[5]
(5) W. F. Benisek and A. Jacobson, *Bioorg. Chem.*, in press.
(6) Protonated forms of α,β-unsaturated imines absorb at 270–290 nm, whereas the unprotonated forms absorb at 220–230 nm.[7]
(7) R. M. Silverstein, G. C. Bassler, and T. C. Morrill, "Spectrophotometric Identification of Organic Compounds," 3rd ed, Wiley, New York, N.Y., 1974.
(8) The actual species isolated was the neutral form of I. NMR (CCl_4) δ 1.80 (s, 3, CH_3), 1.6–2.4 (m, 6), 5.58 (q, 2, CH_2CF_3, J = 16 Hz), 5.75 (s, 1, vinyl H). Other possible structures which were rejected on the basis of the NMR data are (1) the Schiff base of the β,γ-unsaturated ketone (the vinyl hydrogen would not be a singlet), (2) the corresponding endo dienamine (two vinyl hydrogens are predicted, one singlet and one multiplet), and (3) the exo dienamine (there should be no methyl singlet). The NMR of the intermediate in D_2O–DCl showed substantial downfield shifts of all protons, consistent with the formation of I. Both the singlets corresponding to the methyl group and the α hydrogen were split into two peaks in the protonated form. We attribute this result to syn–anti isomerization around the carbon–nitrogen double bond. An analogous result has been found in a similar system.[9] NMR (D_2O–DCl) δ 2.09 and 2.17 (s, 3, CH_3), 1.7–2.9 (m, 6), 4.39 (q, 2, CH_2CF_3), 6.25 and 6.47 (s, 1, vinyl H).
(9) G. S. Hammond and R. C. Neuman, *J. Phys. Chem.*, **67**, 1655 (1963).
(10) A. R. Fersht and W. P. Jencks, *J. Am. Chem. Soc.*, **92**, 5432 (1970).
(11) All reactions were followed at 25.0° and ionic strength of 1.0 (NaCl). The pH range investigated was 4.7–6.9.
(12) A term dependent on concentration of amine *and* protonated amine has been found in the elimination of acetic acid from 9-acetoxy-10-methyl-*cis*-decalone. This reaction also involves enolization of a ketone via iminium ion formation.[13]
(13) D. J. Hupe, M. C. R. Kendall, and T. A. Spencer, *J. Am. Chem. Soc.*, **94**, 1254 (1972).
(14) R. M. Pollack and D. L. Whalen, unpublished results.
(15) D. S. Noyce and M. Evett, *J. Org. Chem.*, **37**, 394 (1972).

Robert H. Kayser, Ralph M. Pollack*
Laboratory for Chemical Dynamics, Department of Chemistry
University of Maryland Baltimore County
Baltimore, Maryland 21228
Received November 14, 1974