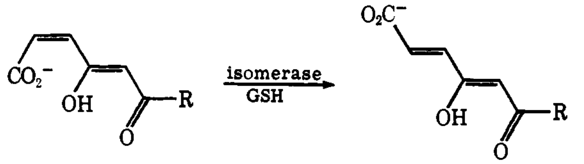
Mechanism of Cis–Trans Isomerization about Carbon–Carbon Double Bonds Catalyzed by Silver(I)[1]

Sir:

Several enzymes are now known to catalyze cis–trans isomerization about carbon–carbon double bonds.[2] One such system in which we have been interested is the enzyme-catalyzed isomerization of maleylacetone (Ia)[3,4] or maleylacetoacetate (Ib) to fumarylacetone (IIa) or fumarylacetoacetate (IIb) (eq 1), respectively.[2,4] Glutathione (GSH) is required as a coenzyme for enzymic reaction.



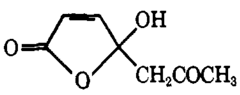
(1)

Ia, R = CH_3
b, R = $CH_2CO_2^-$

IIa, R = CH_3
b, R = $CH_2CO_2^-$

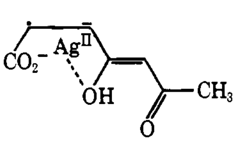
The possibility that this and other cis–trans isomerases derive their catalytic activity through the presence of an enzyme-bound metal increases with the discovery of the rapid catalyzed geometric isomerization of Ia and Ib by very dilute solutions of silver nitrate.[5] Silver ion is unique: it is the only one of 18 various metal ions studied that is capable of catalysis.[5] Because of our interest in catalyzed isomerization,[4,6] we have investigated the mechanism of this remarkable reaction.[7] Silver–enzyme coordination often leads to inactivation, but a metal which was heretofore considered inactive in model systems might exhibit substantially different chemistry when coordinated with enzyme and in the process might be rendered an active catalyst for isomerization.

The uniqueness of silver ion in this process suggests the involvement of a silver–π-olefin complex as the reactive species. Moreover, the presence of a hydroxy group α to the double bond, as in I, is known to enhance silver–olefin association.[8] That Cu(II) and Fe(III) are inactive suggests that a ketoenol-chelate complex of metal ion and substrate is unimportant. The early study[5] which we corroborate reports a pH–rate profile reminiscent of a monoprotic acid exhibiting increasing rate concomitant with increasing conjugate base formation. The kinetically determined apparent pK of maleylacetone (~3.5) fits well with the spectrophotometrically determined pK_1 of 3.95 (eq 2).[3] Silver-catalyzed isomerization apparently does not occur with III because of the ring-locked geometry. Several mechanisms involving π-olefin complexes can be proposed. The following experiments involving the Ag^+-catalyzed reaction were carried out to differentiate among mechanisms: (1) isomerization of Ia in solvent D_2O leads to no appreciable incorporation of maleylvinyl deuterium (nmr), (2) added thiocyanate does not enhance the rate, (3) sample degassing does not appreciably affect the rate,[9] (4) no esr signal can be observed during reaction, (5) reaction proceeds at the same rate in the dark, and (6) the reaction occurring in 7.5% acrylamide monomer leads to no polymerization. These results would appear to rule out radical ions IV or V as possible intermediates permitting facile rotation about the original maleyl C–C double bond. IV might be expected to undergo D exchange[10] and both IV and V might be expected to give an esr signal and catalyze polymerization. If the function of silver were to bring nucleophile and substrate together for nucleophile-catalyzed isomerization,[6] added thiocyanate might be expected to produce an observable rate enhancement.

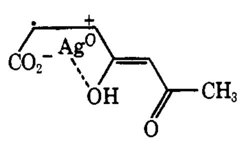


III

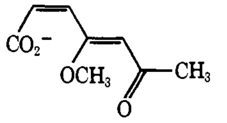
$+ H_2O \rightleftharpoons$ Ia $+ H_3O^+$ (2)



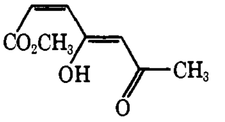
IV



V



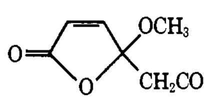
VI



VII

Two new derivatives of Ia, VI and VII, have been synthesized[11] and their Ag^+-catalyzed rate of cis–trans isomerization was measured. Under comparable reaction conditions the predominant course of reaction of VI at pH 4.0–7.4 is to undergo ring closure (eq 3) to form VIII as identified by uv and nmr. The rate of disappearance of VI in the presence and absence of 0.1 M Ag(I) is essentially the same. Ag(I)-catalyzed cis–trans isomerization of Ia is at least 35,000 times faster than the comparable (undetected) reaction for VI. VII, however, undergoes rapid Ag-catalyzed (k_{VII}/k_{Ia} ~ 10) isomerization (Figure 1), thereby ruling out a silver–carboxylate complex. That Ag(I) is inactive toward VI and the rate for VII approaches zero at low pH suggests that the

VI →



VIII

(3)

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[1] Research performed under the auspices of the U. S. Atomic Energy Commission.

[2] For a recent review, see: S. Seltzer, "The Enzymes," 3rd ed, Vol. VI, P. Boyer, Ed., Academic Press, New York, N. Y., 1972, p 381.

[3] J. Fowler and S. Seltzer, *J. Org. Chem.*, 35, 3529 (1970).

[4] S. Seltzer, manuscript submitted for publication.

[5] C. T. Kisker and D. I. Crandall, *Tetrahedron*, 19, 701 (1963).

[6] (a) K. D. Stevens and S. Seltzer, *J. Org. Chem.*, 33, 3922 (1968); (b) C. Santiago and S. Seltzer, *J. Amer. Chem. Soc.*, 93, 4546 (1971).

[7] This is the only system known to us that undergoes cis–trans isomerization catalyzed by Ag(I). For Ag^+-catalyzed rearrangements of carbocyclics, however, see: L. A. Paquette, *Accounts Chem. Res.*, 4, 280 (1971).

[8] (a) D. Gray, R. A. Weis, and W. D. Closson, *Tetrahedron Lett.*, 5639 (1968); (b) R. M. Keefer and L. J. Andrews, *J. Amer. Chem. Soc.*, 71, 3906 (1949); (c) C. F. Wilcox, Jr., and W. Gaal, *ibid.*, 93, 2453 (1971); (d) see, also, R. M. Keefer and L. J. Andrews, *ibid.*, 71, 1723 (1949); L. I. Andrews and R. M. Keefer, *ibid.*, 71, 2379 (1949); R. M. Keefer and L. J. Andrews, *ibid.*, 71, 2381 (1949), for similar complexes with Cu(I). In the light of these results it is somewhat surprising that Cu(I) is not also a catalyst in this isomerization.

[9] The rate increases by about 10% when the sample is degassed under standard high vacuum techniques.

[10] E. Vrachnou-Astra, P. Sakellaridis, and D. Katakis, *J. Amer. Chem. Soc.*, 92, 3936 (1970).

[11] Structures are in accord with nmr and uv spectra. *Anal.* Calcd for $C_8H_{10}O_4$: parent mass, 170.05789. Found: 170.05784 (for each).

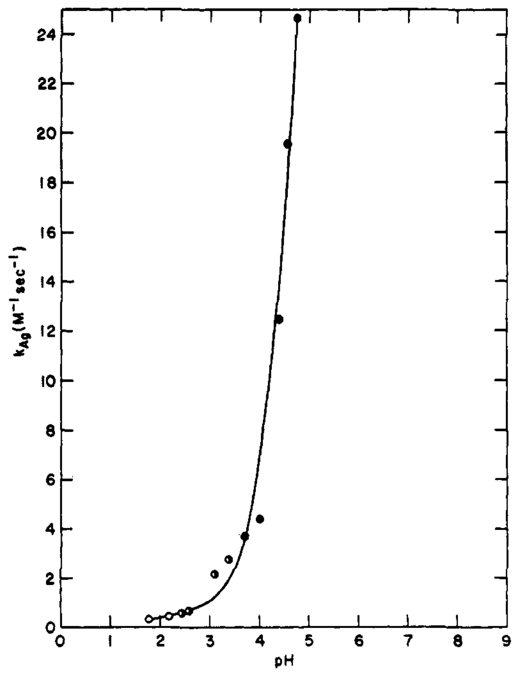
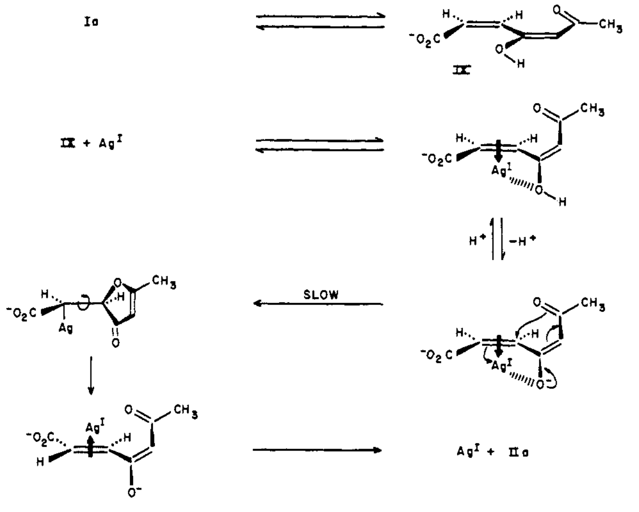


Figure 1. Second-order rate constants for silver(I)-catalyzed cis–trans isomerization of maleylacetone methyl ester (VII) *vs.* pH: closed circles refer to acetate buffers (0.02 *M*); open circles refer to malonate buffers (0.2 *M*); half circles refer to malonate buffers (0.01 *M*). Curve represents calculated values of $k_{obsd} = [k_{A^-}K + k_{HA}(H^+)]/[K + (H^+)]$, for $K = 10^{-5}$ *M*, as determined by least-squares fitting.

kinetically active species is a complex of silver and the enolate ion of VII.[12] We suggest the following mechanism (Scheme I) for the catalyzed isomerization of maleylacetone. Coordination of the enolate oxygen with tetrahedral silver facilitates twisting about the C-3–C-4 bond thereby to place the carbonyl oxygen below (or above) the C-1–C-2–C-3–C-4 plane and facilitate nucleophilic attack on the double bond. Isomerization of VI is prevented by the inability of its silver complex to form an enolate ion.

Scheme I



[12] There is no apparent general acid–base catalysis. Rates are essentially the same in 0.02, 0.25, and 0.50 *M* acetate buffers, pH 4.0.

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Angular Alkylation through Intramolecular Carbenoid Insertion. A New Stereocontrolled Route to Synthetic Intermediates to the Diterpene Alkaloids and C_{20}-Gibberellins[1]

Sir:

A crucial problem in the total synthesis of a large number of complex diterpenoids, for example, the *Garrya* and *Atisine* groups of diterpene alkaloids[2] and a few C_{20}-gibberellins,[3] is the introduction of the C-10 functionalized angular carbon residue in combination with the C-4 substituents with appropriate stereochemical control, in a hydrophenanthrene or a hydrofluorene moiety. In spite of the notable achievements in the total synthesis[4] of these compounds there are only a limited number of methods[4,5] for realizing this synthetic task. We present here a new simple synthetic approach which rests in utilizing the carboxyl at C-4 for introduction of the functionalized C-10 substituent in a stereospecific manner in providing some key intermediates toward complex diterpenoids. Our method of angular alkylation is based upon a regioselective intramolecular α-ketocarbenoid insertion across the C-10 benzylic C–H bond in the carbenoid thermal decomposition of the α-diazomethyl ketones **4** and **4a** from the easily accessible[6] 20-nor ring-C-aromatic resin acid analogs **3** and **3a**. We also studied a number of model compounds.[7] For example, the thermal decomposition of a dilute solution of the crude diazoketone **1b** derived from the bridged bicyclo-[3.3.1]nonene derivative **1a**,[8] in the presence of anhydrous copper sulfate in tetrahydrofuran, afforded the tetracyclic liquid ketone **2**[9] [$\nu_{max}^{CHCl_3}$ 1740 cm^{-1}; 2,4-dinitrophenylhydrazone, mp 171°] in 53% overall yield from **1a** as the only isolable product after column chromatography.

The crude diazo ketone **4**, prepared from **3**, on treatment with anhydrous copper sulfate in boiling

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[1] Presented at the 8th International Symposium on the Chemistry of Natural Products, New Delhi, India, Feb 6–12, 1972.

[2] For a review see: S. W. Pelletier, *Quart. Rev., Chem. Soc.*, **21**, 525 (1967).

[3] See: J. R. Hanson, "The Tetracyclic Diterpenes," Pergamon Press, Oxford, 1968, pp 54–56.

[4] (a) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Amer. Chem. Soc.*, **85**, 2342 (1963); **89**, 1483 (1967); (b) W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, *ibid.*, **86**, 929 (1964); **89**, 1499 (1967); (c) S. Masamune, *ibid.*, **86**, 290, 291 (1964); (d) R. W. Guthrie, W. A. Henry, H. Immer, C. M. Wong, Z. Valenta, and K. Wiesner, *Collect. Czech. Chem. Commun.*, **31**, 602 (1966); (e) W. Nagata, T. Wakabayashi, M. Narisada, Y. Hayase, and S. Kamata, *J. Amer. Chem. Soc.*, **93**, 5740 (1971).

[5] See for examples: (a) J. W. ApSimon and O. E. Edwards, *Can. J. Chem.*, **40**, 896 (1962); (b) W. L. Meyer and A. S. Levinson, *J. Org. Chem.*, **28**, 2859 (1963); (c) I. Iwai and A. Ogiso, *Chem. Ind. (London)*, 1084 (1963); (d) D. H. R. Barton and J. R. Hanson, *Chem. Commun.*, 117 (1965); (e) A. Tahara and K. Hirao, *Tetrahedron Lett.*, 1453 (1966); (f) T. Matsumoto, M. Yanagiya, E. Kawakami, T. Okuno, M. Kakizawa, S. Yasuda, Y. Gama, J. Omi, and M. Matsunaga, *ibid.*, 1127 (1968); (g) P. Grafen, H. J. Kabbe, O. Roos, G. D. Diana, T. Li, and R. B. Turner, *J. Amer. Chem. Soc.*, **90**, 6131 (1968).

[6] (a) U. R. Ghatak, N. R. Chatterjee, A. K. Banerjee, J. Chakravarty, and R. E. Moore, *J. Org. Chem.*, **34**, 3739 (1969); (b) U. R. Ghatak and N. R. Chatterjee, *Indian J. Chem.*, **9**, 804 (1971).

[7] See for other examples: (a) E. Wenkert, B. L. Mylari, and L. L. Davis, *J. Amer. Chem. Soc.*, **90**, 3870 (1968); (b) J. K. Chakrabarti, S. S. Szinai, and A. Todd, *J. Chem. Soc. C*, 1303 (1970); (c) R. C. Cambie and R. A. Franich, *Aust. J. Chem.*, **24**, 117 (1971).

[8] L. F. Johnson, J. Chakravarty, R. Dasgupta, and U. R. Ghatak, *Tetrahedron Lett.*, 1703 (1971).

[9] The synthetic compounds described are all racemates. Correct analytical figures have been obtained for all compounds for which physical and spectral data are given.