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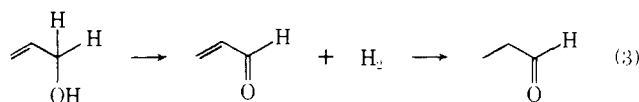
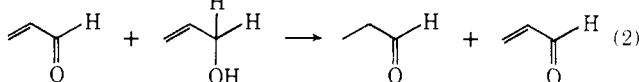
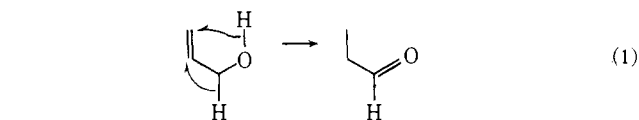
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Copper Catalyzed Rearrangement of Allylic Alcohols to Saturated Aldehydes and Ketones

Sir:

The rearrangement of allylic alcohols to saturated aldehydes or ketones in the presence of metal and metal oxide catalysts and in the vapor phase is a reaction of demonstrated synthetic utility.¹ Despite the long history of the reaction,² its mechanism remains controversial. Constable proposed that the transformation over metallic copper involved an intramolecular tautomerization reaction (eq 1).³ Weston and Adkins



suggested that the conversion of allyl alcohol to propionaldehyde over zinc oxide involved propenal as an intermediate (eq 2),⁴ although they favored an intramolecular mechanism for the transformation over aluminum oxide.⁵ On the basis of kinetic evidence, both groups of workers excluded the possibility of a dehydrogenation-hydrogenation mechanism (eq 3). More recently, however, Flid and Prostavok have proposed a mechanism (eq 4 through 6) involving the



formation of adsorbed H_2 on several metal and metal oxide catalysts, including metallic copper and zinc oxide.⁶ In light of these ambiguities an investigation into the mechanism of this unusual transformation was begun, using principally the technique of deuterium

(1) M. Kraus, *Collect. Czech. Chem. Commun.*, **37**, 460 (1972), and references cited therein.

(2) P. Sabatier and J. B. Senderens, *C. R. Acad. Sci.*, **136**, 983 (1902).

(3) F. H. Constable, *Proc. Roy. Soc., Ser. A*, **113**, 254 (1926).

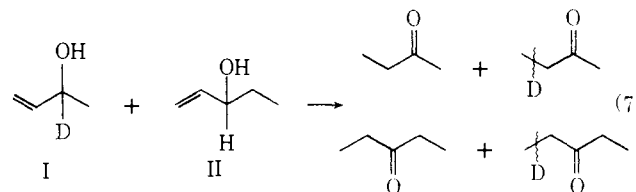
(4) P. E. Weston and H. Adkins, *J. Amer. Chem. Soc.*, **50**, 1930 (1928).

(5) P. E. Weston and H. Adkins, *J. Amer. Chem. Soc.*, **51**, 2430 (1929).

(6) R. M. Flid and N. S. Prostavok, *Tr. Mosk. Inst. Tekhnol. Khim. Tekhnol.*, No. 4, 19 (1953); M. Ya. Kagan, R. M. Flid, and N. S. Prostavok, *ibid.*, No. 5, 45 (1955).

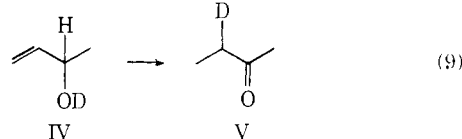
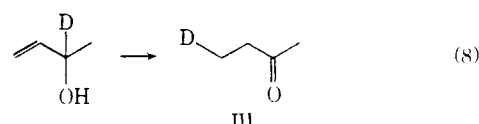
labeling. The catalysts chosen for study were metallic copper^{7a} and cupric oxide;^{7b} the experimental results reported here were obtained using metallic copper as catalyst, although qualitatively similar results were obtained over cupric oxide. The procedure and apparatus used for these studies has already been described;⁸ a 20- μl sample of the allylic alcohol was injected onto a 700-cm Teflon column packed with copper or cupric oxide and mounted in a gas chromatograph oven. Helium flow rate was maintained at 15 ml/min and oven temperatures utilized varied between 150 and 220°. The effluent (retention times were about 60 sec) was collected in a Dry Ice cooled trap and analyzed by reinjection onto a 7-m column packed with 10% UCW-98 on Chromosorb P (60/80). 1-Alken-3-ols of less than 11 carbons invariably gave 75–95% yields of saturated carbonyl compound, 5–20% α,β -unsaturated carbonyl compound (favored by higher reaction temperatures and lower alcohol concentrations), and traces of dehydration products. With these catalysts, increased alkyl substitution about the carbon-carbon double bond favors the dehydration and dehydrogenation reactions. The following observations are relevant to the mechanism of allylic alcohol-saturated ketone interconversion.

The reaction is intermolecular. Coinjection of 1-buten-3-ol-3-*d* (I) and 1-penten-3-ol (II) produced large amounts of labeled 3-pentanone and unlabeled 2-butanone (eq 7).⁹ Control experiments ascertained



that the unreacted allylic alcohols had not undergone H-D exchange and that 2-butanone-4-*d*, and 2-butanone-1,1,1,3,3-*d*₅ did not undergo extensive H-D exchange with 3-pentanone under these conditions. Thus, the observed exchange is intrinsic to the reaction and intramolecular mechanisms can be excluded as major pathways to product.

The hydroxyl hydrogen and the hydrogen atom at C-3 do not become equivalent during the rearrangement. Reaction of 1-buten-3-ol-3-*d*, produces 2-butanone-4-*d* (III) more than 80% specifically labeled (eq 8).¹⁰ To



(7) (a) Electrolytic dust obtained from Fischer Scientific Co. or wire obtained from Matheson Coleman and Bell. (b) Black powder obtained from Matheson Coleman and Bell or wire obtained from J. T. Baker Chemical Co.

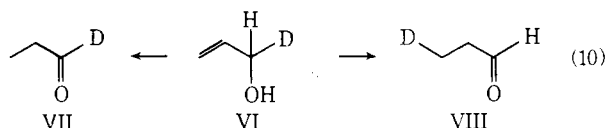
(8) M. Y. Shiekh and G. Eadon, *Tetrahedron Lett.*, 257 (1972).

(9) Determined by mass spectral analysis of the pure ketones.

(10) Determined by integration of the nmr spectrum of the pure ketone. The nmr spectrum (CCl_4) consists of a triplet of triplets ($J_{\text{vic}} = 7.6 \text{ Hz}$, $J_{\text{gem}} = 2 \text{ Hz}$) at 1.00, a singlet at 2.05, and a broadened triplet ($J_{\text{vic}} = 7.6 \text{ Hz}$) at 2.35 ppm.

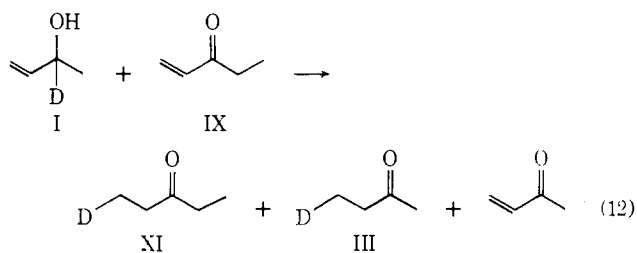
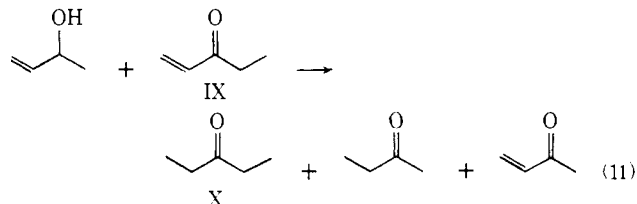
eliminate a hydrogen–deuterium isotope effect as the cause of the observed specificity, the reaction of 1-buten-3-ol-*O-d* (IV) was investigated; the product isolated was 2-butanone-3-*d* (V) about 80% specifically labeled (eq 9).¹¹ In light of these observations then, the reaction mechanism cannot involve the intermediacy of molecular hydrogen.

The rate determining step in the reaction involves cleavage of the C-3-H bond. This was suggested by the observation that 1-buten-3-ol-3-*d* was markedly less reactive than the unlabeled alcohol. To arrive at a quantitative value for the isotope effect, 1-propen-3-ol-3-*d* (VI) was prepared. Hydrogen migration produces propanol-1-*d* (VII) while deuterium migration produces propanal-3-*d* (VIII) (eq 10); nmr measurements



established that, at 180°, hydrogen migration predominates roughly four to one. No isotope effect was observed in the reaction of 1-buten-3-ol-*O-d*; the transfer of the hydroxy proton and the C-3 hydrogen must therefore occur in separate steps.

The unsaturated carbonyl compound is apparently an intermediate in the reaction. Coreaction of 1-buten-3-ol and 1-penten-3-one (IX) produces 3-pentanone (X) as well as 2-butanone and a large amount of 1-buten-3-one (eq 11). Further, reaction of 1-buten-3-ol-3-*d* (I) and



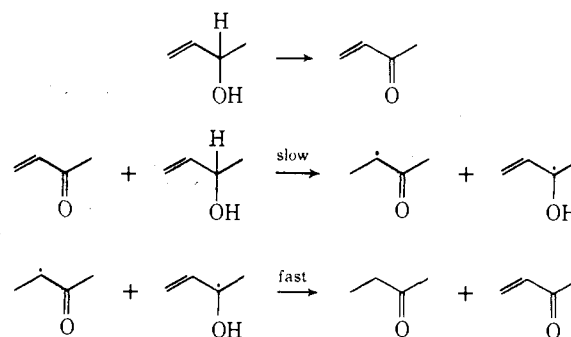
1-penten-3-one (IX) produces 3-pentanone-1-*d* (XI) in high isotopic purity (eq 12). Reaction of 1-buten-3-ol, 1-buten-3-ol-3-*d* (I), and 1-penten-3-one (IX) produces 2-butanone and 3-pentanone with virtually identical deuterium content. Since control experiments demonstrated that the unreacted allylic alcohols had not undergone extensive hydrogen–deuterium exchange, this observation suggests that both products are formed *via* a mechanism with the same rate-limiting step, *i.e.*, one involving the unsaturated carbonyl compound as an intermediate. The report of Satake and Akabori¹²

(11) Mass spectral analysis indicated that the ketone was 36% *do*, apparently, as a result of incomplete deuteration of the starting alcohol and the presence of adventitious water. After correcting for the undeuterated material, the nmr (CCl₄) consists of a pair of triplets ($J_{\text{vic}} = 1.1$ and 7.5 Hz) at 1.00, a singlet at 2.05, and a very broad quartet ($J \cong 8$ Hz) at 2.35 ppm. After integration and correction for unlabeled material, the ketone was calculated to be about 80% specifically labeled at C-3.

(12) K. Satake and S. Akabori, *Nippon Kagaku Zasshi*, 70, 84 (1949).

that an α,β -unsaturated aldehyde can be converted to the saturated aldehyde in the gas phase over metallic copper using saturated alcohols as reducing agents lends credence to this proposal.

A mechanism consistent with these observations is depicted below. Initially, dehydrogenation of the allylic alcohol generates a small amount of α,β -unsaturated ketone. In the rate limiting step, the C-3 hydrogen of the alcohol is transferred to the terminus of the ketone carbon–carbon double bond.¹³ A rapid abstraction of the hydroxyl hydrogen generates a new molecule of α,β -unsaturated ketone and a molecule of saturated ketone.



Efforts are underway to ascertain the generality of these mechanistic observations over other metal and metal oxide surfaces.

Acknowledgment. Support of this work by Research Corporation is gratefully acknowledged.

(13) W. R. Patterson and R. L. Burwell, Jr., *J. Amer. Chem. Soc.*, 93, 833 (1971), have suggested an analogous rate limiting step for the reduction of saturated ketones with alcohols over impure silica. "Hydride" transfer from the alcohol to the carbonyl group is catalyzed by a surface aluminum atom.

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Conformational Flexibility of the Neurohypophyseal Hormones Oxytocin and Lysine-vasopressin. A Carbon-13 Spin-Lattice Relaxation Study of Backbone and Side Chains

Sir:

Spin-lattice relaxation times (T_1) of carbon-13 nuclei are proving useful in determining rates of overall molecular reorientation as well as in monitoring segmental motion of amino acid side chains in peptides.¹⁻⁵ We

(1) P. Keim, R. A. Vigna, R. C. Marshall, and F. R. N. Gurd, *J. Biol. Chem.*, 248, 6104 (1973).

(2) R. Deslauriers, R. Walter, and I. C. P. Smith, *Fed. Eur. Biochem. Soc., Lett.*, 37, 27 (1973).

(3) R. Deslauriers, R. Walter, and I. C. P. Smith, *Biochem. Biophys. Res. Commun.*, 53, 244 (1973).

(4) A. Allerhand, D. Doddrell, V. Glushko, D. W. Cochran, E. Wenkert, P. J. Lawson, and F. R. N. Gurd, *J. Amer. Chem. Soc.*, 93, 544 (1971).

(5) (a) H. Saitō and I. C. P. Smith, *Arch. Biochem. Biophys.*, 158, 154 (1973); (b) I. C. P. Smith, R. Deslauriers, H. Saitō, R. Walter, C. Garrigou-Lagrange, H. McGregor, and D. Sarantakis, *Ann. N. Y. Acad. Sci.*, 222, 597 (1974); (c) H. Saitō and I. C. P. Smith, *Arch. Biochem. Biophys.*, in press.