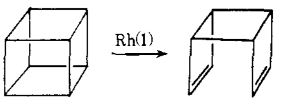

(3)

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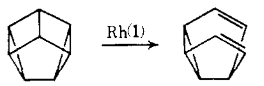

(4)

Our views on the mechanism of the Ag(I)- and Pd(II)-catalyzed rearrangements and on the origin of the difference between the catalytic activity of these metals and that of Rh(I) are still speculative. The fact that Pd(II) ($4d^8$) resembles Ag(I) ($4d^{10}$) rather than the isoelectronic Rh(I) ($4d^8$) in its catalytic properties rules out a simple explanation in terms of a difference of electronic configuration (*i.e.*, d^8 *vs.* d^{10}). A possibly significant distinction is the greater tendency of Rh(I), relative to Ag(I) or Pd(II), to undergo oxidation or oxidative addition. We are continuing to examine mechanistic aspects of these interesting and useful reactions, particularly with a view toward isolation or trapping of intermediates.

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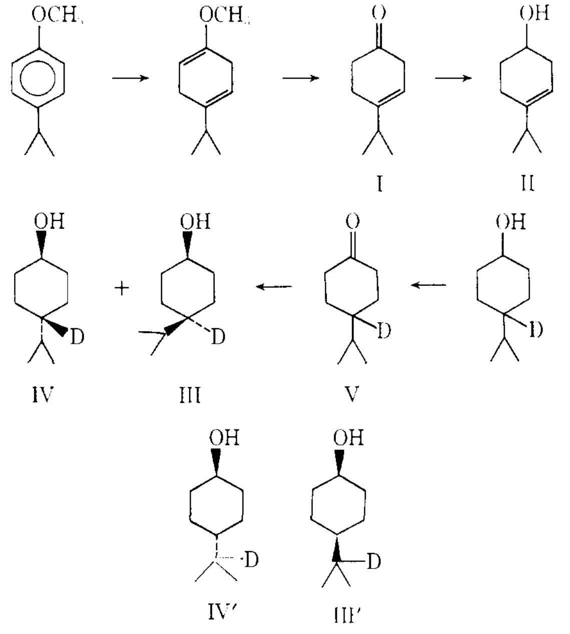
Hidden Stereochemistry in Mass Spectrometry[1,2]

Sir:

Although mass spectrometry has developed into an effective probe of molecular constitution,[3] it has appeared to be an inefficacious technique for stereochemical problems.[4] The fact that this inapplicability derives from the often found apparent whimsical correlation between three-dimensional structure and fragmentation[5] adds special interest to recent investigations of the mass spectrometry of isomeric cyclohexanols. These studies led to the suggestion[5] that stereospecific reactions were hidden in the mass spectra of these compounds even in the absence of apparent rational stereochemical dependence in their fragmentation patterns. We now wish to report that this suggestion is correct, since labeling studies on the loss of water from *cis*- and *trans*-4-isopropylcyclohexanol, molecules which show little stereochemical dependence[5] on their fragmentation, reveal high stereosensibility and specificity for this elimination reaction.

p-Isopropylanisole was converted to 4-isopropyl-3-cyclohexenone by Birch reduction with lithium wire in liquid ammonia.[6] The resulting ketone (I) was shown by gas chromatography to contain no conjugated isomer and was subject to reduction with lithium aluminum hydride to produce the derivative Δ-3 alcohol (II). This material (II) was treated with excess deuterioborane (from boron trifluoride etherate and sodium borodeuteride) followed by refluxing acetic acid. After normal work-up and treatment with lithium aluminum hydride, there resulted a colorless oil which was identical by gas chromatography with an authentic mixture of *cis*- and *trans*-4-isopropylcyclohexanol.[7] These diastereomeric alcohols were oxidized quantitatively by Jones reagent[8] to 4-deuterio-4-isopropylcyclohexanone (V).[9] Reduction of this ketone produced both (III and IV) diastereomeric alcohols in a ratio of 85:15 with *trans*-IV predominating.[10] Vapor-phase chromatog-

Scheme I



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(1) We are grateful to the National Institute of General Medical Sciences for support of this research.

(2) Reported in part at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, Abstract No. ORGN 64.

(3) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967.

(4) The stereochemical potential of mass spectrometry is of high interest, and considerable work on stereoisomers has been reported. See the references in: M. M. Green, *J. Amer. Chem. Soc.*, 90, 3872 (1968). See also a review by S. Meyerson and A. W. Weitkamp, *Org. Mass Spectrom.*, 1, 659 (1968). The following recent papers also contain leading references and further stereochemical studies: M. M. Green, R. J. Cook, J. M. Schwab, and R. B. Roy, *J. Amer. Chem. Soc.*, **92**, 3076 (1970); M. L. Gross and C. L. Wilkins, *Tetrahedron Lett.*, 3875 (1969); M. K. Hoffman, M. M. Bursey, and R. E. K. Winter, *J. Amer. Chem. Soc.*, **92**, 727 (1970); S. Meyerson and A. W. Weitkamp, *Org. Mass Spectrom.*, 2, 603 (1969); V. L. Sadovskaya, V. I. Zaretskii, N. S. Wulfson, and V. F. Sizoy, *ibid.*, 2, 347 (1969); M. S. Baird and C. B. Reese, *Tetrahedron Lett.*, 2117 (1969); R. Shapiro and S. Nesnow, *J. Org. Chem.*, **34**, 1695 (1969); W. Benz and H. Dürr, *Tetrahedron*, **24**, 6503 (1968); R. M. Dodson, P. J. Cahill, and V. C. Nelson, *Chem. Commun.*, 620 (1968); J. Deutsch and A. Mandelbaum, *J. Amer. Chem. Soc.*, **92**, 4288 (1970).

(5) M. M. Green, R. J. Cook, W. Rayle, E. Walton, and M. F. Grostic, *Chem. Commun.*, 81 (1969).

(6) A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.*, **75**, 5360 (1953).

(7) Prepared from 4-isopropylphenol by hydrogenation followed by conversion to standard ketone derivatives in agreement with literature melting points: H. Erdtman and J. Gripinberg, *Nature (London)*, **161**, 719 (1945).

(8) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 142.

(9) This oxidation and the subsequent reduction served to assure that the isomeric alcohols III and IV were identical with respect to incorporation and position for deuterium. Following heavy precedent we assign the deuterium to C-4. See: D. J. Pasto and F. M. Klein, *J. Org. Chem.*, **33**, 1468 (1968), and references therein.

(10) Stereochemical assignments were based on relative retention times on gas chromatography. See: E. L. Eliel, N. L. Allinger,

raphy on a diglycerol column served to preparatively separate the deuterated isomers.

In addition, deuterium was incorporated at the isopropyl group by treatment of α-methyl-*p*-methoxystyrene with deuterioborane followed by refluxing acetic acid.[11] This procedure was followed by the synthesis outlined above substituting hydroborane for deuterioborane. The overall procedure is exhibited in Scheme I.

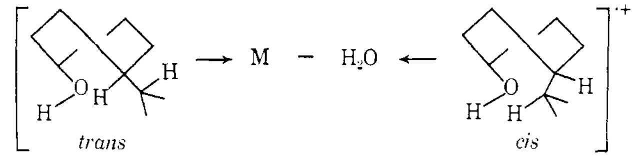
Table I shows the analysis for the loss of DOH and HOH from the molecular ions of the various deuterated alcohols and clearly demonstrates that there are hidden in the apparent nonspecific loss of water[5] processes which are highly stereospecific. In detail, the isomers with deuterium accessible through either a 1,4 or 1,5 elimination show appreciable (>80%) loss of DOH (IV and III′), thereby requiring that the cis and trans isomers of 4-isopropylcyclohexanol eliminate water in the highly stereospecific manner exhibited in Scheme II.

Table I[a]

Compd	% M − DOH	% M − HOH
III	13	87
IV	81	19
III′	82	18
IV′	17	83

[a] The deuterium incorporation was determined by mass spectral analysis of the derived ketones. It was d_0/d_1 = 43/57 (III and IV) and 9/91 (III′ and IV′). Rigorous exclusion of oxygen produced the incorporation shown for III and IV. Less exacting conditions allowed only trace deuterium incorporation. The conditions for III′ and IV′ were far less critical. All figures shown here are corrected to 100% from these deuterium incorporation data. The method of preparation requires identical position and amount of deuterium within each isomer pair. All the data were taken on a CEC-103 mass spectrometer at 70 eV and *ca.* 130°. Corresponding runs on an MS-902 mass spectrometer gave closely similar results.

Scheme II[a]



[a] This is one of various transition states which may be adduced to fit the determined stereospecificity.

Even more important than this finding of a highly stereospecific elimination of water in these molecules is the implication that deuterium labeling studies of electron impact induced elimination reactions (M − HX) are the likely road to gain the so-far unrealized but expected[12] potential for mass spectrometry in stereochemical studies. Thus, while there is no question of the stereochemical assignments in these well-studied cyclohexanols, there is little doubt that the present tools for determining stereochemistry in related compounds are weak. Indeed, in substituted cyclooctanols, only unequivocal synthesis made available the configurations of the 5-substituted isomers,[13] while the application of nmr to assign configuration to these flexible ring systems has been challenged.[14] Other methods including the often used relative retention times on chromatography are equivocal and may be subject to unexpected breakdowns. The combination of deuterium labeling in conjunction with mass spectrometry may therefore serve a useful function in this regard and our present work is directed to accomplishing this goal in systems less well defined than the model studied herein.

S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 115–116 and 177–178, and references therein.

(11) The *p*-methoxy as well as the α-methyl group assure deuterium incorporation at the resultant tertiary position. See: H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962, pp 115 and 118. The *p*-methoxy-α-methylstyrene was prepared according to R. L. Huang and F. Morsingh, *J. Chem. Soc.*, 160 (1953). It gave an nmr spectrum in accord with its structure.

(12) See ref 10, pp 187–188.

(13) See for example: A. C. Cope and R. B. Kinnel, *J. Amer. Chem. Soc.*, **88**, 752 (1966); A. C. Cope and D. L. Nealy, *ibid.*, **87**, 3122 (1965).

(14) F. A. L. Anet and M. St. Jacques, *ibid.*, **88**, 2586 (1966).

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Aromatic Substitution. XXVII.[1a,b] Friedel–Crafts Benzylation of Toluene and Benzene with Substituted Benzyl Chlorides. Substituent Effects in the Electrophilic Substituting Agent Affecting the Nature of the Transition State as Reflected by Substrate and Positional Selectivity

Sir:

Electrophilic aromatic substitution is one of the most thoroughly studied types of organic reactions.[2] Still many of the mechanistic aspects remain undecided and controversial. In our previous studies[3] we reported a series of electrophilic aromatic substitutions involving strongly electrophilic reagents which showed low substrate selectivity as reflected by $k_{\text{toluene}}/k_{\text{benzene}}$ rate ratios, but at the same time high positional selectivity (generally high ortho:para ratios with only a small amount of meta isomer formed). We expressed our view that in these systems the rate-determining transition state that lies early on the reaction coordinate thus has substantial π character. Our conceptions gained interest[4] but were also repeatedly criticized[5] and it was suggested that the low substrate selectivity observed was

(1) (a) Part XXVI: G. A. Olah, J. Lukas, and E. Lukas, *J. Amer. Chem. Soc.*, 91, 5319 (1969). (b) Presented in part at the joint Meeting of the American Chemical Society and the Chemical Institute of Canada, Toronto, Ontario, May 1970, Abstract ORGN 21.

(2) For recent reviews see: (a) R. Breslow, "Organic Reaction Mechanisms," W. A. Benjamin, New York, N. Y., 1969; (b) L. Stock, "Aromatic Substitution Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1968; (c) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, 1, 35 (1963); (d) G. A. Olah, "Friedel-Crafts and Related Reactions," Vol. I–IV, Wiley-Interscience, New York, N. Y., 1963–1964.

(3) G. A. Olah, S. J. Kuhn, and S. Flood, *J. Amer. Chem. Soc.*, **83**, 4571 (1961); G. A. Olah, S. J. Kuhn, S. Flood, and J. C. Evans, *ibid.*, **84**, 3687 (1962); G. A. Olah, S. J. Kuhn, and S. Flood, *ibid.*, **84**, 1688 (1962); G. A. Olah and N. Overchuk, *ibid.*, 87, 5786 (1965).

(4) For example, R. Breslow "Organic Reaction Mechanism," W. A. Benjamin, New York, N. Y., 1969, Chapter 5.

(5) C. D. Ritchie and H. Win, *J. Org. Chem.*, **29**, 3093 (1964); W. S. Tolgyesi, *Can. J. Chem.*, 43, 343 (1965) (for a rebuttal, see G. A. Olah and N. Overchuk, *ibid.*, **43**, 3279 (1965)); P. Kreienbühl and H. C. Zollinger, *Tetrahedron Lett.*, 1739 (1965); J. H. Ridd in "Studies on Chemical Structure and Reactivity," Methuen, London, 1965, p 152; H. Cerfontain and A. Telder, *Recl. Trav. Chim. Pays-Bas.*, **86**, 37 (1967); S. W. Caille and J. P. Corriu, *Chem. Commun.*, 1251 (1967); *Tetrahedron*, **25**, 2005 (1969); and most notably C. K. Ingold in "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, p 290.