which time the adamantanol had precipitated. Evaporation of the mother liquor gives a clear semisolid, which is 80% desired olefin and 20% adamantylideneadamantane. The mixture of olefins was dissolved in 2 mL of methanol and cooled to −78 °C to afford crystals (20 mg) of isopropylideneadamantane-d_6, which was used without further purification.

3-Pentylideneadamantane (12). A solution of *tert*-butyllithium (2 mL, 1.9 M, 3.8 mmol) in pentane was added to 20 mL of diethyl ether at −43 °C. A solution of 2-iodoadamantane (460 mg, 1.75 mmol) in 9 mL of pentane was added, and the solution was stirred for 1 h. The solution was cooled to −78 °C, and 320 mg of 3-pentanone (3.8 mmol) was added dropwise via syringe. The solution was stirred 15 min at −78 °C and then slowly warmed to room temperature. The reaction mixture was washed with water and saturated bicarbonate solution and dried with $MgSO_4$. The solvents were removed by distillation under reduced pressure, and the crude alcohol was treated with 5 mL of 85% H_3PO_4 at room temperature for 18 h. The mixture was poured into ice and extracted with pentane. The pentane solution was washed with water and saturated bicarbonate and dried with $MgSO_4$. The solvents were removed under reduced pressure, and the crude olefin was Kugelrohr distilled to yield 200 mg (56%) of the desired 3-pentylideneadamantane: ^1H NMR ($CDCl_3$) δ 2.78 (br s, 2 H), 1.98 (q, 4 H), 1.9–1.6 (m, 12 H), 0.9 (t, 6 H).

3-Pentanone-*2,2,4,4-d*$_4$. The tetradeuterioketone was prepared by the method of Saunder et al.[20] A mixture of 3-pentanone (17.2 g, 0.1 mol), D_2O (6 mL, 0.3 mol), and K_2CO_3 (50 mg) was heated to reflux for 24 h. The mixture was cooled, and the aqueous layer was removed by pipet. A solution of K_2CO_3 in 6 mL of D_2O was added, and the mixture was heated to reflux for another 24 h. This cycle was repeated 5 times. The ketone was dried with anhydrous K_2CO_3 and distilled to yield approximately 4 g of 3-pentanone-*2,2,4,4-d*$_4$ which was free of H contamination by ^1H NMR.

3-Pentylideneadamantane-*2′,2′,4′,4′-d*$_4$ (12-*d*$_4$). A solution of 2-lithioadamantane was prepared by the method of Wynberg.[21] A solution of *tert*-butyllithium (1.9 M, 4 mL, 7.6 mmol) was added to 40 mL of anhydrous diethyl at −78 °C. A solution of 2-iodoadamantane (905 mg, 3.5 mmol) in 20 mL pentane was added, and the solution was warmed to −45 °C for 1 h. The solution was cooled to −78 °C, and 3-pentanone-*2,2,4,4-d*$_4$ (480 mg, 5.3 mmol) was slowly added via syringe. The solution was stirred 30 min at −78 °C and then slowly warmed to room temperature. The reaction mixture was washed with a saturated bicarbonate solution and dried with $MgSO_4$. The solvents were removed under vacuum, and the crude product was distilled (80 °C, 0.1 mmHg) to give 600 mg (76% yield) of the desired alcohol: ^1H NMR ($CDCl_3$) δ 2.14 (br d, 2 H), 2.08 (br s, 2 H), 1.9–1.5 (m, 10 H), 0.80 (s, 6 H).

A slurry of 200 mg (0.44 mmol) of alcohol in 10 mL of 85% H_3PO_4 was heated to 70 °C for 3 h. The solution was cooled to room temperature and poured onto ice. The aqueous mixture was washed with pentane, which was backwashed with water and saturated bicarbonate solution. The organic solution was dried with $MgSO_4$, and the solvents were removed to give an oil, which was distilled to give 80 mg (43%) of the desired olefin-d_4: ^1H NMR ($CDCl_3$) δ 2.78 (br s, 2 H), 1.9–1.6 (m, 12 H), 0.90 (s, 6 H). Mass spectral analysis shows 97% d_4, 3% d_3.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work and also to the Swiss National Science Foundation. D.L.K. thanks Amoco and Wisconsin Alumni Research Foundation for fellowships.

Registry No. 1, 30541-56-1; **1**-β,β'-d_2, 99810-90-9; **2**, 35544-39-9; **2**$^+$, 99829-61-5; **7**, 99810-87-4; **8**-d_1, 99810-88-5; **10**, 20441-18-3; **10**-d_1, 99810-93-2; **10**-d_6, 99810-94-3; **11**$^+$, 99810-84-1; **11**-$d_6{}^+$, 99810-97-6; **12**, 99810-86-3; **12**-d_4, 99810-95-4; **13**$^+$, 99810-85-2; **13**-$d_4{}^+$, 99810-98-7; 1-chloroadamantanone, 81315-72-2; 2,2-dibromoadamantane-*1-d*, 99810-89-6; adamantylideneadamantane-*1-d*, 99810-91-0; adamantanone-*1-d*, 99810-92-1; adamantanone, 700-58-3; acetone-d_6, 666-52-4; adamantylideneadamantane, 30541-56-1; 2-adamantanol, 700-57-2; 2-iodoadamantane, 18971-91-0; 3-pentanone, 96-22-0; 3-pentanone-*2,2,4,4-d*$_4$, 6400-97-1; 3-(adamant-2-yl)pentan-3-ol-*2,2,4,4-d*$_4$, 99810-96-5.

Supplementary Material Available: ESR spectra of **11**$^+$, **11**-$d_6{}^+$, **13**$^+$, and **13**-$d_4{}^+$ and their computer simulations (3 pages). See any current masthead for ordering information.

---

(20) Saunder, W. H., Jr.; Bonadies, S. D.; Braunstein, M.; Borchardt, J. K.; Hargreaves, R. T. *Tetrahedron* **1977**, *33*, 1577.

(21) Wieringa, J. H.; Wynberg, H. *Synth. Commun.* **1971**, *1*, 7.

(22) Nelson, S. F.; Teasley, M. F.; Kapp, D. L.; Wilson, R. M. *J. Org. Chem.* **1984**, *49*, 1843.

Protonated Hydronium Dication, H_4O^{2+}. Hydrogen–Deuterium Exchange of $D_2H^{17}O^+$ in HF:SbF_5 and $DH_2{}^{17}O^+$ in DF:SbF_5 and Theoretical Calculations[1a]

George A. Olah,*[1b] G. K. Surya Prakash,[1b] Mario Barzaghi,[1b] Koop Lammertsma,[1c] Paul von R. Schleyer,[1d] and John A. Pople[1e]

Contribution from the Donald P. and Katherine B. Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern Calfornia, Los Angeles, California 90089-1661, Department of Chemistry, University of Alabama, Birmingham, Alabama 35294, Institute of Organic Chemistry, University of Erlangen-Nurnberg, Erlagen, Germany, and Department of Chemistry, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213. *Received March 26, 1985*

Abstract: Isotopic hydronium ions $D_2H^{17}O^+$ and $DH_2{}^{17}O^+$ in 1:1 (molar) HF:SbF_5/SO_2 and DF:SbF_5SO_2 solutions, respectively, at −15 °C undergo slow hydrogen–deuterium exchange as monitered by ^{17}O NMR spectroscopy. The rate of such exchange increases with the increase in the acidity of the fluoroantimonic acid medium (1:2 molar composition). The previously observed lack of exchange of isotopic hydronium ions in the somewhat weaker Magic Acid, FSO_3H:SbF_5, medium ($H_0 \approx -21.5$) suggests that in the stronger HF:SbF_5 medium ($H_0 \approx -25$ to -28), the exchange occurs through the intermediacy of protonated hydronium dication. Consequently, the structure and stability of protonated hydronium dication has been probed by ab initio theory. The T_d symmetry structure, **2**, was found to be the minimum energy structure at the HF/6.31G* level. Although **2** at the HF/6.31G* level is thermodynamically unstable (dissociation preferred by 59.2 kcal/mol), it seems to have significant kinetic stability (deprotonation barrier 39.4 kcal/mol).

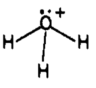
The existence of protonated water, H_3O^+ (**1**, hydronium ion), was first postulated in 1907.[2] Its preeminent role in acid-catalyzed reactions was first realized from the acid–base theory of Brønsted and Lowry.[3] The evidence for the presence of hydronium ion

0002-7863/86/1508-1032$01.50/0 © 1986 American Chemical Society

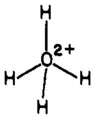
Table I. Energies (au) of OH_4^{2+} and OH_3^+ (Relative Energies in kcal/mol)

species	symmetry		3-21G// 3-21G	6-31G*// 6-31G*	on 6-31G* geometries			MP4SDTQ/ 6-31G**
					HF/6-31G**	MP2/6-31G**	MP3/6-31G**	
OH_4^{2+}	T_d	minimum	−75.80958	−76.19498	−76.22033	−76.42139	−76.42910	−76.43474
			(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
$H_3O^+\cdots H^+$		transition state for proton loss	−75.73475	−76.13220	−76.15110	−76.35243	−76.35841	−76.36474
		proton loss	(47.0)	(39.4)	(43.4)	(43.4)	(44.4)	(43.9)
OH_4^{2+}	D_{4h}	planar	−75.67607	−76.05481	−76.07569	−76.27164	−76.27911	−76.28400
			(83.8)	(88.0)	(90.8)	(93.7)	(94.1)	(94.6)
H_3O^+	C_{3v}	(at higher levels)	−75.89123	−76.28934	−76.31005	−76.50583	−76.51394	−76.51902
			(−51.2)	(−59.2)	(−56.3)	(−53.0)	(−53.2)	(−52.9)

in solutions and solid phase came mainly from IR,[4] Raman,[5] neutron diffraction.[6] The gaseous ion was observed in mass spectrometric studies.[7] In superacid solution the hydronium ion was found to be very stable as shown by ^1H and ^{17}O NMR spectroscopy.[8-10] In fact, Christe and co-workers have isolated[11] hydronium ion salts with a variety of counterions such as SbF_6^-, AsF_6^-, and BF_4^-.[9-11] All the available experimental and high-level ab initio theoretical data support the pyramidal nature of hydronium ion **1**.[10,12,13]



1



2

It has been shown by Gold and co-workers[8a] that long-lived isotopic hydronium ions such as H_3O^+, H_2DO^+, and HD_2O^+ ions could be prepared in $HSO_3F{:}SbF_5{-}D_2O/SO_2ClF$ or SO_2 solutions and studied by ^1H NMR spectroscopy without apparent exchange.

We would like now to report our observation that in the even stronger superacid HF:SbF_5 (or DF:SbF_5)[8b] the hydronium ion starts to undergo slow intermolecular proton–deuterium exchange. Addition of an excess of SbF_5 to the fluoroantimonic acid medium (from 1:1 to 1:2 molar HF:SbF_5 composition) enhances the rate of proton–deuterium exchange, indicating that at these high acidities the exchange occurs through the intermediacy of protonated hydronium dication **2**. The structure and stability of the proposed hydronium dication **2** has also been probed by ab initio theory at the HF/6.31G* level.

Scheme I

$$HD_2O^+ \xrightleftharpoons{-D^+} HDO \xrightleftharpoons{H^+} DH_2O^+ \xrightleftharpoons{-D^+} H_2O \xrightleftharpoons{H^+} \underset{\mathbf{1}}{H_3O^+}$$

Scheme II

$$HD_2O^+ \xrightleftharpoons{H^+} [H_2D_2O^{2+}] \xrightleftharpoons{-D^+} H_2DO^+ \xrightleftharpoons{H^+} [H_3DO^{2+}] \xrightleftharpoons{-D^+} H_3O^+$$

Results and Discussion

The isotopic hydronium cations $D_2H^{17}O^+$ and $H_2{}^+DO$ were prepared by protonating D_2O (20% ^{17}O enriched) and H_2O (40% ^{17}O enriched) in 10-fold excess of 1:1 HF:SbF_5/SO_2 and 1:1 DF:SbF_5/SO_2 solutions, respectively, at −78 °C. The ^{17}O NMR spectra of the isotopic hydronium were recorded at −15 °C. In the proton-coupled ^{17}O NMR spectra[9,10] of ^{17}O enriched H_3O^+ (**1**) in HF:SbF_5/SO_2, the oxygen is observed as a quartet at δ ^{17}O 9 ± 0.2 (with reference to SO_2 at 505 ppm) with $J_{^{17}O-^1H} = 106 \pm 1.5$ Hz. When protonation of D_2O (20% ^{17}O enriched) was carried out in HF:SbF_5(1:1)/SO_2 solution at −78 °C and the proton-coupled ^{17}O NMR spectrum was obtained immediately after preparation (at −15 °C after 4 min), the spectrum shows a doublet centered at δ ^{17}O 9.0 ($J_{O-H} \approx 105$ Hz), indicating the formation of isotopic HD_2O^+ ion. After an hour at −15 °C, the broad doublet develops into a triplet, which subsequently changes into a quartet (total time ≈ 4 hs) indicating complete exchange of both deuterium atoms to form the triprotio hydronium ion, H_3O^+ (**1**). Similarly the DH_2O^+ ion generated from H_2O (40% ^{17}O enriched) in DF:SbF_5/SO_2 solution changes from broad triplet to a broad singlet (due to unresolved ^{17}O–D coupling) in a period of 4.25 to 4.5 h, indicating formation of D_3O^+ ion. In a preparation of DH_2O^+ ion in the increased acidity of 1:2 DF:SbF_5 the solution exchange to D_3O^+ ion occurred under 3.5 h, indicating faster exchange at higher acidity.[14]

Two possible mechanisms can be considered for the observed hydrogen–deuterium exchange in the isotopic hydronium ion in the highly acidic fluoroantimonic acid system ($H_0 \approx -25$ to -28). One involves the deprotonation/dedeuteration equilibrium of the hydronium ion with water protonation by excess acid accounting for the exchange (Scheme I). The other proceeds through protonation of the nonbonded electron pair of the hydronium ion in Scheme II. A similar mechanism can be written for the isotopic hydronium ions in the DF:SbF_5 medium.

The isotopic exchange results observed by NMR spectroscopy cannot per se differentiate between the two mechanisms although the increase in the exchange rate with increased SbF_5 concentration of DF:SbF_5/SO_2 solutions strongly supports the latter mechanism. Reversible deprotonation of the hydronium ion in

---

(1) (a) Considered as Onium Ions. Part 31, at USC. For past 30 see: Prakash, G. K. S.; Bruce, M. R.; Olah, G. A. *J. Org. Chem.* **1985**, *50*, 2405. (b) University of Southern California. (c) University of Alabama—Birmingham. (d) University of Erlangen-Nurnberg. (e) Carnegie-Mellon University.

(2) Hantzsch, A.; Caldwell, K. S. *Z. Phys. Chem.* **1907**, *58*, 575. Goldschmidt, H.; Udby, O. *Ibid.* **1907**, *60*, 728.

(3) (a) Brønsted, J. N. *Recl. Trav. Chim. Pays-Bas.* **1923**, *42*, 718. Brøsted, J. N. *J. Phys. Chem.* **1926**, *30*, 777. (b) Lowrey, T. M. *Trans. Faraday Soc.* **1924**, *20*, 13. Lowrey, T. M. *Chem. Ins.* (*London*) **1923**, 1048.

(4) Bethell, D. E.; Sheppard, N. *Chem. Phys.* **1953**, *21*, 1421. Ferisso, C. C.; Horning, D. F. *Ibid.* **1955**, *23*, 1464. Giguere, P. A. *Rev. Chim. Miner.* **1966**, 627. Fourmier, M.; Roziere, J. *C. R. Acad. Sci. Ser. C* **1970**, *270*, 729.

(5) (a) Taylor, R. C.; Vidale, G. L. *J. Am. Chem. Soc.* **1956**, *78*, 5999. (b) Giguere, P. A.; Madec, C. *Chem. Phys. Lett.* **1976**, *37*, 569 and references cited therein.

(6) Lundgren, J. O.; Williams, J. M. *J. Chem. Phys.* **1973**, *58*, 788. Lundgren, J. O.; Tellgren, R.; Olovsson, I. *Acta. Crystallogr. Sect. B* **1978**, *B34*, 2945.

(7) (a) Kebarle, P.; Haynes, R. M.; Colling, J. G. *J. Am. Chem. Soc.* **1967**, *89*, 5753. (b) Castelman, A. W., Jr.; Tang, N. I.; Munkelwitz, H. R. *Science* **1971**, 173.

(8) (a) Gold, V.; Grant, J. L.; Morris, K. P. *Chem. Commun.* **1976**, 397 and references cited therein. (b) Olah, G. A.; Prakash, S. G. K.; Sommer, J. "Superacids"; Wiley-Interscience: New York, 1985; and references therein. (c) For recent acidity measurements see: Gold, V.; Laali, K.; Morris, K. P.; Zdunek, L. Z. *J. Chem. Soc., Perkin Trans 2* **1985**, 859.

(9) Mateescu, G. D.; Benedikt, G. M. *J. Am. Chem. Soc.* **1979**, *101*, 3959.

(10) Olah, G. A.; Berrier, A. L.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1982**, *104*, 2373.

(11) Christe, K. O.; Schack, C. J.; Wilson, R. D. *Inorg. Chem.* **1975**, *14*, 2224.

(12) Symons, M. C. R. *J. Am. Chem. Soc.* **1980**, *102*, 3982.

(13) (a) Rodwell, R. R.; Radom, L. *J. Am. Chem. Soc.* **1981**, *103*, 2865. (b) Whiteside, R. A.; Frisch, M. J.; Pople, J. A. The Carnegie-Mellon Quantum Chemistry Archive, 3rd ed., 1983.

(14) (a) Similar observations have been made by G. D. Mateescu and G. Benedikt of Case Western Reserve University. We thank Prof. G. D. Mateescu for communicating his results to us. Also see: Mateescu, G. S.; Benedikt, G. M.; Kelly, M. P. In "Synthesis and Applications of Isotopically Labelled Compounds"; Proceedings of an International Symposium, Kansas City Mo., 1982; Duncan, W. P., Susan, A. B., Eds.; Elsevier: Amsterdam, 1983, pp 483. (b) It was not feasible to carry out kinetic measurements on the exchange reaction due to the slowness of the reaction. However, the observed overall H–D exchanges were well reproducible in repeated runs. A 10–20% isotope effect is also observed in the case of the DF:SbF_5 system (relatively slower exchange compared to the HF:SbF_5 system). However, it is not possible at this time to interpret this effect in terms of either Scheme I or Scheme II.

Scheme I should be helped by lower and not higher acidities. The acidity of the used HF:SbF_5 or DF:SbF_5 systems ($H_0 \approx -25$ to -28 depending on molar ratio) is the strongest of any presently known superacids and exceeds even that of Magic Acid, HSO_3F:SbF_5 ($H_0 \approx -21.5$),[8b] used previously by Gold and co-workers[8a] to study isotopomers of H_3O^+ by ^1H NMR spectroscopy. They observed no exchange between the isotopomers in the Magic Acid medium, although the time frame of their experiments was not stated. Their observation is in accord with apparent absence of deprotonation equilibria in the superacid system. In our study in the higher acidity fluoroantimonic acid system we did observe intermolecular isotopic exchange. These observations seem to support Scheme II for the exchange mechanism involving protonated isotopomeric hydronium ions $H_2D_2O^{2+}$ and H_3DO^{2+}.

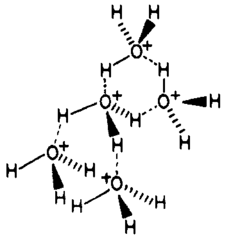
In order to evaluate the structure and stability of H_4O^{2+} (**2**) ab initio theoretical calculations were also carried out.[15]

The H_4O^{2+} dication is isoelectronic with H_4N^+, CH_4, and BH_4^-, all with known tetrahedral geometries. At the HF/6-31G*, the H_4O^{2+} T_d symmetry structure is a minimum energy structure; all the eigenvalues of the Hessian matrix are positive. Apparently the double positive charge can be adequately accommodated in the tetrahedral structure to prevent spontaneous fragmentation.

Thermodynamically H_4O^{2+} is, however, unstable toward dissociation by 59.2 kcal/mol (HF/6-31G*), although it has significant kinetic stability with a deprotonation barrier of 39.4 kcal/mol (same level). These energies remain nearly the same when valence electron correlation interactions are included: i.e., the deprotonation energy for H_4O^{2+} is -59.3 kcal/mol with a barrier of 43.9 kcal/mol (MP4SDTQ/6-31G**//HF/6-31G*). the planar H_4O^{2+} structure is less stable than **2** by 94.6 kcal/mol. The heat of formation of H_4O^{2+} is estimated to be 557 kcal/mol from $\Delta H_f^\circ(H_3O^+) = 139$ kcal/mol,[15] $\Delta H_f^\circ(H^+) = 365.2$ kcal/mol,[16] the calculated heat of deprotonation.

Although the kinetic stability of H_4O^{2+} is substantial, it may be affected by tunneling. Taking the maximum deprotonation barrier of H_4O^{2+} (the "bare" barrier + zero-point energy for the transition structure[17]) we found, however, a sharp reduction in reaction rate below the classical barrier, i.e., from 10^9 to 10^3 within 5 kcal/mol. Similarly, the calculated H/D isotope effect (to $H^+/D^+ + H_3O^+$) only becomes substantial directly below the classical threshold. Since the tunneling for the deprotonation is small, we conclude that the kinetic stability of H_4O^{2+} is significant.

Concerning the quite unfavorable thermodynamics for the protonation of H_3O^+, despite the kinetic stability of H_4O^{2+}, it must be remembered that the calculational data refer to extremely diluted gas conditions and thus do not relate fully to the experimental solution work. Solvation effects may have a major influence. In particular in dications, solvation tends to diminish charge–charge repulsion effects and thus could bring H_4O^{2+} in a thermodynamically more accessible region. Superacid solutions of H_3O^+ could be highly structured. Thus, the H_4O^{2+} protons might be shared by more than one H_3O^+, ultimately four, in a dynamic fashion.



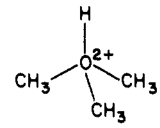
The theoretical data indicate H_4O^{2+} (T_d) to be a minimum energy structure which may not be generated, without substantial solvent stabilization, via protonation of H_3O^+ by H^+. Gas-phase reaction of H_3O^+ with a dication may be, however, a possible pathway for obtaining static H_4O^{2+}. We illustrate this for CH_4^{2+}, which was recently observed by charge stripping mass spectrometry[18] and has a calculated kinetic stability of ca. 17 kcal/mol and a exothermicity toward deprotonation of ca. 106 kcal/mol.[19] The calculated proton exchange reaction between CH_4^+ and H_3O^+ is favorable by 54.7 kcal/mol.

$$H_3O^+ + CH_4^{2+} \rightleftharpoons H_4O^{2+} + CH_3^+ \qquad \Delta H^\circ = 54.7 \text{ kcal/mol}$$

Our studies of the observed exchange of the hydronium ion, H_3O^+, in superacids of increasing strength strongly support a mechanism where the nonbonded electron pair of oxygen is involved in a second protolytic interaction and not via deprotonation–reprotonation equilibria (involving free H_2O) which would be facilitated by decreasing but not increasing acidity of the system. Whether OH_4^{2+} is only a high lying energetic intermediate on the reaction path, or solvation and association may stabilize it, cannot be answered from present studies. The transition state of the exchange reaction could also lie earlier on the reaction path, thus not resembling a symmetrical intermediate. Regardless, the protolytic exchange reaction of H_3O^+ focuses interest on OH_4^{2+} which was also studied by state of the art ab initio theory.

Conclusion

In conclusion the oxygen atom of the hydronium ion **1** possesses a nonbonded pair of electrons which is capable of interacting with an additional proton forming H_4O^{2+} (**2**). There is indication[20] of similar protonation or proto solvation of the lone pair on oxygen in tertiary oxonium ions such as **3**. The electrophilic reactivity of tertiary oxonium ions toward hydrocarbons is markedly increased in the presence of superacid solvents implying interaction of the proton with the remaining lone pair on the oxygen. Whereas trimethyl(triethyl)oxonium ions (Meerwein salts) generally do not alkylate aromatics, in the presence of superacids they do.[20]



3

The H_4O^{2+} dication as the parent of protonated oxonium ions is thus of particular interest.

Experimental Section

^{17}O-enriched H_2O (40% enriched) and D_2O (20% enriched) were purchased from MSD Isotopes Inc. The superacids used were freshly prepared from distilled HF/DF and SbF_5. SO_2 was purchased from Air-Products Co. and used as such.

Preparation of Hydronium Ions. The isotopic hydronium ions were prepared by adding 0.02 mL of ^{17}O-enriched water (H_2O or D_2O) to a tenfold excess of the appropriate fluoroantimonic acid in 1.5 mL of SO_2 at -78 °C in a 10 mm Quartz NMR tube with continuous stirring.

The ^{17}O NMR spectra were obtained on a Varian Associates Model FT-80 NMR spectrometer equipped with a broad-band variable-temperature probe.

Exchange Experiments. The exchange studies were carried out in the NMR spectrometer probe at -15 °C. The proton-coupled ^{17}O NMR spectra were monitered at half an hour intervals. About 2000 transients

---

(15) (a) The GAUSSIAN 82 package of programs was employed. Binkley, J. S.; Frische, M.; Raghavachari, K.; DeFrees, D.; Schlegel, B.; Whiteside, R. A.; Fluder, E.; Seeger, R.; Pople, J. A., Release Carnegie-Mellon University. (b) Similar calculations recently have been carried out; Koch, W.; Heinrich, N.; Schwarz, H.; Francis, M.; Stahl, D. *Int. J. Mass. Spectrom. Ion Proc.* **1985**, *67*, 305.

(16) Rosenstock, H. M.; Draxl, K.; Steiner, B. W.; Herron, J. T. *J. Phys. Chem. Ref. Date* **1977**, *6*, Suppl. 1.

(17) The algorithm for the tunneling correction to the RRKM theory was used. Miller, W. H. *J. Am. Chem. Soc.* **1979**, *101*, 6810.

(18) Rabrenovic, M.; Proctor, C. J.; Ast, T.; Herbert, C. G.; Brenton, A. G.; Beynon, J. H. *J. Phys. Chem.* **1983**, *87*, 3305. Ast, T.; Porter, C. J.; Proctor, C. J.; Beynon, J. H. *Chem. Phys. Lett.* **1981**, *78*, 439.

(19) Pople, J. A.; Tidor, B.; Schleyer, P. v. R. *Chem. Phys. Lett.* **1982**, *88*, 533.

(20) Olah, G. A.; DeMember, J. R.; Mo, Y. K.; Svoboda, J. J.; Schilling, P.; Olah, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 884.

were recorded for each spectrum which took approximately a minute (acquisition time 0.02 s).

Theoretical Calculations

Calculations were carried out with the GAUSSIAN 82 package of programs developed by Pople et al.[15a]

Acknowledgment. Support of the work at USC by the National Science Foundation is gratefully acknowledged.

Registry No. D_2HO^+, 12517-69-0; DH_2O^+, 12517-68-9; $HSbF_6$, 16950-06-4; $DSbF_6$, 54764-32-8; H_4O^{2+}, 12344-06-8; H_2, 1333-74-0; D_2, 7782-39-0.

Total Synthesis of (+)-Desepoxyasperdiol

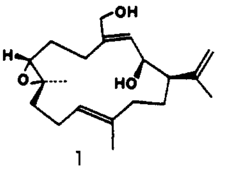
Marcus A. Tius* and Abdul H. Fauq

Contribution from the Department of Chemistry, University of Hawaii, 2545 The Mall, Honolulu, Hawaii 96822. *Received August 9, 1985*

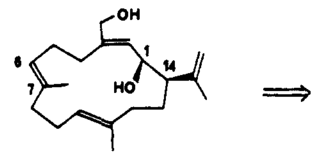
Abstract: A convergent enantioselective synthesis of desepoxyasperdiol is described. Key steps in the synthesis are the introduction of asymmetry by the regioselective ring opening of an optically active epoxy alcohol by isopropenylmagnesium bromide and the cyclization to the 14-membered ring using the conditions for the Horner–Emmons reaction which were developed by Masamune and Roush. The present work expands the scope of this reaction by demonstrating that it will simultaneously tolerate both a tertiary carbon nucleophile and an aldehyde with α-branching. During the course of this synthesis unusual behavior was noted for the reactions of (phenylthio)acetic acid dianion.

In recent years a plethora of cembrane natural products have been isolated and characterized, most of them from marine soft corals.[1] Although most of these are structurally unique and many show marked cytotoxic, antiinflammatory, carcinostatic, or other potentially useful physiological activity, relatively few have been prepared through total synthesis.

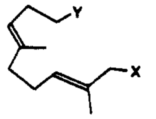
Asperdiol (**1**), a marine cembranoid isolated by Weinheimer in 1977 from a Caribbean gorgonian, is cytotoxic in vivo against several cancer cell lines.[2] Asperdiol is the only cembranoid in which antitumor activity occurs in the absence of an α-methylenebutyrolactone. Two total syntheses of the racemate of **1**, both using remote asymmetric induction, were reported in 1983.[3,4] In Still's synthesis[3] asymmetry at C-1 and C-14 was induced during the cyclization of the 14-membered ring, whereas Kato[4] used the C-1 alcohol to introduce the C-6, C-7 epoxide in (±)-desepoxyasperdiol (**2**). In this paper we describe an alternative convergent, asymmetric synthesis of (+)-desepoxyasperdiol. As a result of Kato's work,[4] this constitutes a formal total synthesis of **1**.



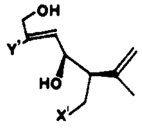
1



2



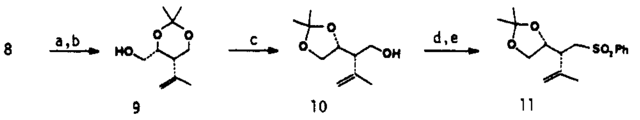
3



4

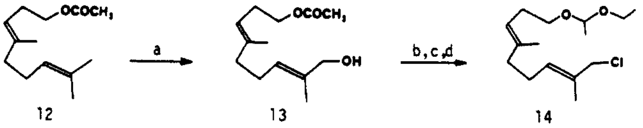
Retrosynthetic disconnection of the C-12, C-13 and the C-3, C-4 bonds generates fragments **3** and **4**. Fragment **3** is easily derived from geraniol whereas fragment **4** appeared to be a candidate for an aldol process.[5] All attempts to use the aldol condensation of aldehydes with the extended enolates derived from **5**[6] or **6**[7] led mainly to products derived from γ-alkylation. Therefore an alternative approach for controlling the stereochemistry at C-1 and C-14 was developed. Both enantiomers of epoxy alcohol **7**, are

Scheme I. Synthesis of Right-Hand Fragment[a]



[a] (a) 2,2-Dimethoxypropane, TsOH catalyst, 25 °C, 95%; (b) Li, liquid NH_3, −78 °C, 85%; (c) acetone, TsOH catalyst, 25 °C, 85%; (d) 3 equiv of NBS, 2.8 equiv of PPh_3, CH_2Cl_2, 25 °C; (e) 2 equiv of $PhSO_2Na$, HMPA, 25 °C, 65% overall.

Scheme II. Synthesis of Left-Hand Fragment[a]



[a] (a) 4 equiv of t-BuOOH, 0.05 equiv of SeO_2, CH_2Cl_2, 25 °C, 40%; 60% after a single recycle of **12**; (b) 2 equiv of MsCl, 2.3 equiv of pyridine, pentane, 0–25 °C, 70%; (c) CH_3OH, K_2CO_3, 25 °C; (d) 1.2 equiv of ethyl vinyl ether, PPTS catalyst, CH_2Cl_2, 25 °C, 70% overall.

---

(1) (a) Faulkner, D. J. *Tetrahedron* **1977**, *33*, 1421–1443. (b) Weinheimer, A. J.; Chang, W. C.; Matson, J. A. *Fortschr. Chem. Org. Naturst.* **1978**, *36*, 285–386. (c) Tursch, B.; Brackman, J. C.; Daloze, D.; Kaisin, M. In "Marine Natural Products"; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. II; pp 247–296.

(2) Weinheimer, A. J.; Matson, J. A.; van der Helm, D.; Poling, M. *Tetrahedron Lett.* **1977**, 1295–1298.

(3) Still, W. C.; Mobilio, D. *J. Org. Chem.* **1983**, *48*, 4785–4786. We thank Professor Still for a preprint of this paper.

(4) Aoki, M.; Tooyama, Y.; Uyehara, T.; Kato, T. *Tetrahedron Lett.* **1983**, 2267–2270.

(5) For reviews of the aldol reaction, see: (a) Heathcock, C. H. In "Comprehensive Carbanion Chemistry"; Durst, T., Buncel, E., Eds. Elsevier: Amsterdam, 1984; Part B, pp 177–237. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1–115. (c) Masamune, S. In "Organic Synthesis Today and Tomorrow"; Trost, B. M., Hutchinson, C. R., Eds.; Pergamon: Oxford, 1980; pp 197–215.

(6) (a) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290–2300. (b) Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557–558. (c) Heathcock, C. H.; White, C. T. *J. Am. Chem. Soc.* **1979**, *101*, 7076–7077. (d) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 7077–7079.

(7) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23–32.

0002-7863/86/1508-1035$01.50/0