Stereoselective Chemical Ionization Mass Spectrometry: Reactions of $CH_3OPOCH_3^+$ with Cyclic Vicinal Diols

Kami K. Thoen,[†] Lan Gao,[†] Thilini D. Ranatunga,[†] Pirjo Vainiotalo,[‡] and
Hilkka I. Kenttämaa*,[†]

*Department of Chemistry, Purdue University, West Lafayette, Indiana 47907-1393, and Department of
Chemistry, University of Joensuu, P.O. Box 111, SF-80101 Joensuu, Finland*

The phosphenium ion $CH_3OPOCH_3^+$ readily attacks hydroxyl groups of neutral substrates in the gas phase in a Fourier-transform ion cyclotron resonance mass spectrometer. The electrophilic character of $CH_3OPOCH_3^+$ is in agreement with molecular orbital calculations (Becke3LYP/6-31G-(d) + ZPE) that predict a singlet electronic ground state for this species. The observed reactions provide a convenient synthetic route to various larger phosphenium ions in the gas phase. Most importantly, however, $CH_3OPOCH_3^+$ was found to be extremely sensitive to the stereochemical structure of the neutral substrate. The dramatically different reaction product distributions obtained for diastereomeric cyclic vicinal diols suggest that $CH_3OPOCH_3^+$ provides a powerful chemical ionization reagent for the mass spectrometric determination of the stereochemistry of diols.

Introduction

The biological action of a substance often greatly depends on its exact stereochemical structure. Obviously, access to fast and accurate methods for the determination of the stereochemistry of molecules is important to many areas of biomedical research, including drug development.[1,2] Mass spectrometry has not proven to be generally applicable for the identification of the stereochemical structure of molecules. However, this technique could offer several advantages, including speed, sensitivity, and direct analysis of mixture components. Hence, an extensive amount of research has been devoted to the development of mass spectrometric approaches for stereoisomer differentiation.[3]

Electron ionization mass spectrometry is usually insensitive to the stereochemistry of molecules. For example, the spectra measured for *cis*- and *trans*-1,2-cyclopentanediols are identical.[3] Chemical ionization, *e.g.*, via proton transfer or formation of an adduct with the ammonium ion, has shown more promise. This approach often produces fewer but more informative product ions. For example, *cis*- and *trans*-1,2-cyclopentanediols can be differentiated by using traditional chemical ionization methods[3] since intramolecular hydrogen-bond formation results in a more abundant ionized molecule for the *cis*-diol. However most stereoisomers yield only minor quantitative differences upon chemical ionization. Hence, the analysis requires calibration with pure standards, the composition of isomer mixtures cannot be determined, and the stereochemistry of unknown compounds cannot be readily identified. Finally, differentiation of flexible diastereomers is often not possible. For example, the chemical ionization mass spectra reported for the *cis*- and *trans*-1,2-cyclohexanediols are nearly identical.[3]

The chemical ionization reactions that have received most attention thus far involve protonation, proton abstraction, and formation of ionic adducts.[3] However, intriguing results have been reported for some unusual reagent ions. Specifically, protonated trimethyl borate has been reported[3] to react with *cis*-1,2-cyclopentanediol by addition followed by loss of two methanol molecules, while the *trans*-isomer mostly shows loss of one methanol. The differences observed for the flexible 1,2-cyclohexanediols were much less significant, however.

Inspired by the above studies, we recently examined the gas-phase reactions of the ion $CH_3OBOCH_3^+$ to probe its utility as a novel chemical ionization reagent. This ion is a very strong electrophile and readily attacks different types of nucleophiles, yielding simple but structurally diagnostic product distributions.[4−8] Encouraged by this result, we proceeded to examine the reactions of the ion with cyclic diastereomeric diols. Small amounts of a diagnostic methanol elimination product were obtained for the *cis*-diols only; hence, qualitatively different spectra were measured for diastereomers. However, all the reactions are dominated by OH abstraction, which leads to loss of the stereochemical integrity of the neutral diol.[6] Obviously, the ion $CH_3OBOCH_3^+$ is too electrophilic to provide a useful tool for stereoisomer analysis.

The above results suggest that a less aggressive electrophile with the key structural features of $CH_3OBOCH_3^+$, *i.e.*, two good leaving groups attached to a coordinatively unsaturated cationic center, might yield more abundant structurally informative products for stereo isomers. This could be accomplished by replacing the reactive boron center with a less electron deficient atom, such as phosphorus. We report here the results of the first systematic investigation of the chemical properties of the dimethoxyphosphenium ion

(1) Wainer, I. W., Ed. *Drug Stereochemistry. Analytical Methods and Pharmacology*; Marcel Dekker: New York, 1993.
(2) Stinson, S. S. *Chem. Eng. News* **1995**, *October 9*, 44−74.
(3) Plitter, J. S.; Turecek, F., Eds. *Applications of Mass Spectrometry to Organic Stereochemistry*; VCH Publishers: New York, 1994.

(4) Ranatunga, T. D.; H. I. Kenttämaa *J. Am. Chem. Soc.* **1992**, *114*, 860.
(5) Ranatunga, T.; H. I. Kenttämaa *Inorg. Chem.* **1995**, *34*, 18.
(6) Leeck, D. T. Ranatunga, T. D.; Smith, R. L.; Partanen, T.; Vainiotalo, P.; H. I. Kenttämaa *Int. J. Mass Spectrom. Ion Processes* **1996**, *141*, 229.
(7) Ranatunga, T.; Kenttämaa, H. I. *J. Am. Chem. Soc.* **1996**, *118*, 11893−11897.
(8) Thoen, K. K.; Tutko, D. T.; Ranatunga, T. D.; H. I. Kenttämaa *J. Am. Soc. Mass Spectrom.* **1996**, *7*, 1138.

$CH_3OPOCH_3^+$. This ion yields dramatically different and predictable product distributions for cyclic diastereomeric diols in the gas phase. Even *cis*- and *trans*-1,2-cyclohexanediols, compounds that are notoriously difficult to distinguish due to their flexible cyclohexane skeleton,[3] are readily distinguished on the basis of their reactions with $CH_3OPOCH_3^+$. These results suggest that phosphenium ion chemistry may allow the mass spectrometric determination of the stereochemical structure of unknown compounds without extensive *prior* purification and derivatization, possibly in mixtures of isomers.

Experimental Section

Trimethyl phosphite, dimethyl methylphosphonate, methanol-d_4, ethanol, 2-propanol, 1-butanol, 1,2-propanediol, 1,3-butanediol, and *cis*- and *trans*-1,2-cyclopentanediol were obtained commercially and used as received. Trimethyl phosphite-d_9, *cis*- and *trans*-1,2-cyclohexanediol, and *cis*- (*diendo*- and *diexo*-) and *trans*-2,3-trinorbornanediol were synthesized by standard literature procedures.[9] The purity of all reagents was verified by mass spectrometry and by gas chromatography.

The experiments were carried out in an Extrel FTMS 2001 Fourier-transform ion cyclotron resonance mass spectrometer. This instrument contains a dual cell that consists of two identical cubic 2-in. cells joined by a common wall (the conductance limit). The cell is aligned collinearly within the magnetic field produced by a 3.0 T superconducting magnet operated at approximately 2.5 T. The conductance limit and the two end trapping plates were held at +2.0 V unless otherwise specified. The cell was differentially pumped with two Balzers turbomolecular pumps (330 L/s), each of which was backed by an Alcatel 2012 mechanical pump. A nominal base pressure of <1 × 10⁻⁹ Torr was maintained within the cell, as read with two ion gauges.

Trimethyl phosphite, trimethyl phosphite-d_9, dimethyl methylphosphonate, and the alcohols were introduced into the instrument by using an Extrel single batch inlet system equipped with a variable leak valve. The diol samples were introduced with a heated solids probe (at a nominal pressure of about 1.0 × 10⁻⁷ Torr). The reactant ions were generated by electron ionization in one side of the dual cell. The ion signal was optimized by varying the electron beam time (30–70 ms), emission current (3–8 μA), and electron energy (20–70 eV). All ions were removed from the other cell region by changing its end trapping plate voltage from +2.0 V to −2.0 V for 10–15 ms. The ions generated in the first region were then transferred into the other region by grounding the conductance limit plate for approximately 100 μs. The ions were cooled by collisions with argon introduced into the cell at a peak pressure of 1 × 10⁻⁵ Torr through a pulsed valve system. All unwanted ions were ejected through the application of Stored Waveform Inverse Fourier Transform (SWIFT)[10] pulses to the excitation plates by using an Extrel SWIFT module. The isolated ions were then allowed to react with a neutral reagent for a variable period of time. Each reaction spectrum was background corrected by using a previously described procedure.[11]

The linear decay of $CH_3OPOCH_3^+$ shown in the plot of ln-(relative ion abundance) versus reaction time (Figure 1) suggests that the reactant ion was properly cooled *prior to* the reactions and that the reactions follow the expected pseudo-first-order kinetics. The second-order reaction rate constants ($k_{reaction}$) were derived from this type of data. The collision rate constants ($k_{collision}$) were calculated using the parameterized
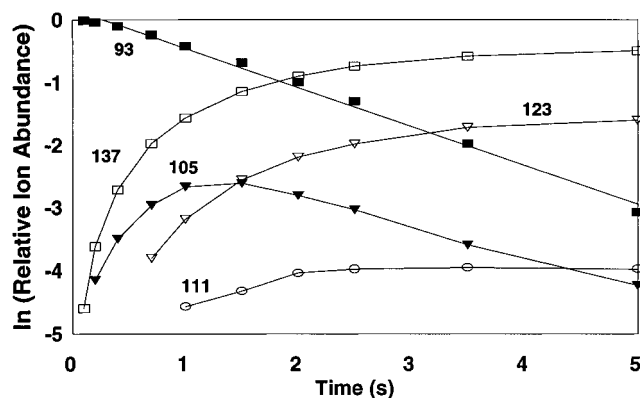

Figure 1. Temporal variation of the ion abundances for the reaction of $CH_3OPOCH_3^+$ (*m/z* 93) with 1,2-propanediol (MW 76). The primary reactions observed are elimination of CH_3OH (to produce the ion of *m/z* 137) and two CH_3OH molecules from the adduct (to yield the ion of *m/z* 105) and abstraction of water from the diol by $CH_3OPOCH_3^+$ (to generate the ion of *m/z* 111). Abstraction of water from another diol molecule by the primary product ion of *m/z* 105 occurs as a secondary reaction, producing the ion of *m/z* 123.

trajectory theory.[12a] The accuracy of the measured rate constants is estimated to be ±50% while the precision is better than ±20%. The pressure readings of the ion gauges were corrected for their sensitivity toward each neutral reagent[12b] and for the pressure gradient between the dual cell and the ion gauge. The latter correction factor was obtained by measuring the rates of reactions with known rate constants involving the neutral molecules of interest. Primary product ions were distinguished from secondary product ions on the basis of their appearance with fixed abundance ratios at short reaction times.

Ions were excited for detection by applying an excitation sweep of 124 V_{p-p} amplitude, 2.7 MHz bandwidth, and 3.2 kHz/μs sweep rate or by the SWIFT method (17–800 u, 0.5 cm radius for all ions). A minimum of 20 acquisitions were signal-averaged to improve the signal-to-noise ratio. The spectra were recorded as 32K or 64K data points, using one zero-fill *prior to* Fourier transformation.

Molecular orbital calculations were carried out using density functional theory and the Gaussian 92 Revision F suite of programs.[13] The geometries of the singlet and triplet states of the dimethoxy phosphenium ion were fully optimized at the Becke3LYP/6-31G(d) level of the density functional theory. The energies obtained in these calculations were corrected for the zero-point vibrational energy obtained from the harmonic vibrational frequencies (scaled by 0.9804) calculated at the same level of theory. The force constant matrixes of the stationary points were confirmed to have the correct number of negative eigenvalues (zero for equilibrium structures).

Results and Discussion

All the phosphenium ions studied thus far in solution carry strongly π-donating substituents.[14] Although gas-phase experiments allow the generation and study of highly reactive ionic species, the current knowledge on the reactivity of gaseous phosphenium ions is largely limited to HPH⁺ and FPF⁺ (both have a singlet electronic

(9) (a) Partanen, T.; Pykäläinen, M.; Hulkkonen, H.; Savolainen, O.; Vainiotalo, P. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1743. (b) Owen, L. N.; Smith, P. N. *J. Chem. Soc.* **1952**, 4026. (c) Roebuck, A.; Adkins, H. *Org. Synth. Colloid* **1955**, *3*, 217.

(10) Marshall, A. G.; Wang, T. C. L.; Ricca, T. L. *J. Am. Chem. Soc.* **1985**, *107*, 7893.

(11) Leeck, D. T.; Stirk, K. M.; Zeller, L. C.; Kiminkinen, L. K. M.; Castro, L. M.; Vainiotalo, P.; Kenttämaa, H. I. *J. Am. Chem. Soc.* **1994**, *115*, 3028.

(12) (a) Su, T.; Chesnavich, W. J. *J. Chem. Phys.* **1982**, *76*, 5183. (b) Bartmess, J. E.; Georgiadis, R. M. *Vacuum* **1982**, *33*, 149.

(13) Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, Gaussian, J. A. Inc., Pittsburgh, PA 1992.

(14) (a) Cowley, A. H.; Kemp, R. A. *Chem. Rev. (Washington, D.C.)* **1985**, *85*, 367. (b) Burford, N.; Losier, P.; Sereda, S. V.; Cameron, T. S.; Wu, G. *J. Am. Chem. Soc.* **1994**, *116*, 6474.

Table 1. Ionic Products Observed upon Reaction of Alcohols and Diols with $CH_3OPOCH_3^+$ and $CD_3OPOCD_3^+$

	$CH_3OPOCH_3^{+\,a}$		$CD_3OPOCD_3^{+\,a}$		
alcohol/diol	m/z	% rel intensity	m/z	% rel intensity	reaction
ethanol	107	100		c	adduct − CH_3OH
(MW 46)	121	b			[adduct − CH_3OH] + ethanol − CH_3OH: $(CH_3CH_2O)_2P^+$
2-propanol	75	26		c	2-propanol + CH_3^+
(MW 60)	111	≅45			H_2O abstraction: $(CH_3O)_2PHOH^+$
	121	22			adduct − CH_3OH
	139	b			[adduct − CH_3OH] + H_2O
	153	7			adduct
1-butanol	135	100		c	adduct − CH_3OH
	177				adduct − $2CH_3OH$
1,2-propanediol	105	42		c	adduct − $2CH_3OH$
(MW 76)	111	≅4			H_2O abstraction: $(CH_3O)_2PHOH^+$
	123	b			[adduct − $2CH_3OH$] + H_2O
	137	54			adduct − CH_3OH
cis-1,2-cyclopentanediol	111	4	131	90	H_2O abstraction: $(CH_3O)_2PHOH^+$
(MW 102)	131	89	149	b	adduct − $2CH_3OH$
	149	b	166	10	[adduct − $2CH_3OH$] + H_2O
	163	7			adduct − CH_3OH
trans-1,2-cyclopentanediol	111	≅23	117	≅26	H_2O abstraction: $(CH_3O)_2PHOH^+$
(MW 102)	131	19	131	15	adduct − $2CH_3OH$
	149	b	149	b	[adduct − $2CH_3OH$] + H_2O
	163	58	166	59	adduct − CH_3OH
	181	b	184	b	[adduct − CH_3OH] + H_2O
cis-1,2-cyclohexanediol	81	3		c	HO^- abstraction − H_2O
(MW 116)	99	7			HO^- abstraction
	111	≅3			H_2O abstraction: $(CH_3O)_2PHOH^+$
	145	57			adduct − $2CH_3OH$
	163	b			[adduct − $2CH_3OH$] + H_2O
	177	30			adduct − CH_3OH
trans-1,2-cyclohexanediol	81	6		c	HO^- abstraction − H_2O
(MW 116)	99	2			HO^- abstraction
	111	≅11			H_2O abstraction: $(CH_3O)_2PHOH^+$
	145	3			adduct − $2CH_3OH$
	177	78			adduct − CH_3OH
cis-2,3-(*diendo*)-trinorbornanediol	111	≅17	111	≅26	HO^- abstraction
(MW 128)	157	70	157	64	adduct − $2CH_3OH$
	175	b	175	b	[adduct − $2CH_3OH$] + H_2O
	189	13	192	10	adduct − CH_3OH
cis-2,3-(*diexo*)-trinorbornanediol	111	≅10	111	≅8	HO^- abstraction
(MW 128)	157	59	157	54	adduct − $2CH_3OH$
	175	b	175	b	[adduct − $2CH_3OH$] + H_2O
	189	31	192	38	adduct − CH_3OH
trans-2,3-trinorbornanediol	111	≅47	111	≅29	HO^- abstraction
(MW 128)	111	53	117	23	H_2O abstraction: $(CH_3O)_2PHOH^+$
	221		227	48	adduct

[a] Relative product ion abundances are given only for primary product ions. The values were calculated by assuming that the secondary products [adduct − CH_3OH] + H_2O and [adduct − $2CH_3OH$] + H_2O are formed from the primary products [adduct − CH_3OH] and [adduct − $2CH_3OH$], respectively, by abstraction of H_2O. [b] Secondary product. [c] Not examined.

ground state[15]).[16] These ions have been found to undergo insertion into heteroatom−hydrogen bonds, proton transfer, hydride abstraction, electron abstraction, and adduct formation. Similar observations have been reported for CH_3PF^+, $CH_3PCH_3^+$, CH_3PH^+, $HPOCH_3^+$, and $CH_3OPOCH_3^+$ upon reaction with their neutral precursors.[16]

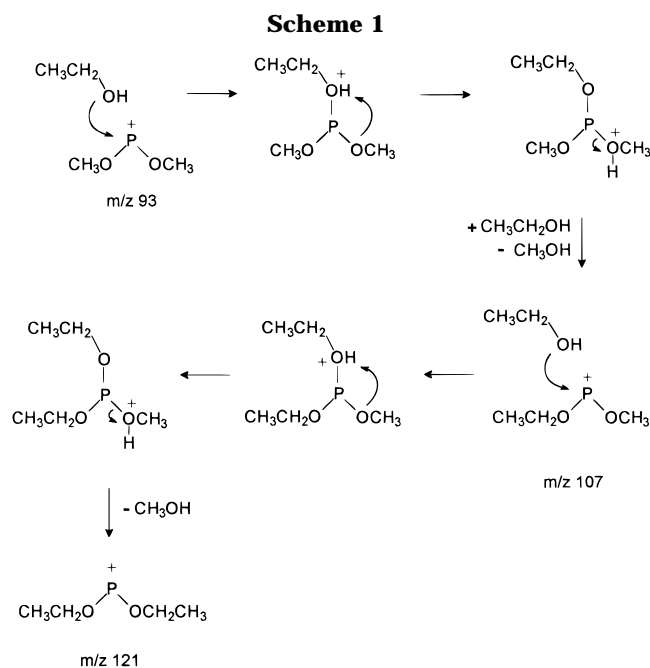In contrast to the above results, the ion $CH_3OPOCH_3^+$ (and $CD_3OPOCD_3^+$) reacts with gaseous alcohols and diols by predominant addition followed by elimination of one or both of the methoxy groups of the reactant ion as methanol. Water and OH^- abstractions are also common. No radical-type reactions (*e.g.*, H atom abstraction) were observed. These findings suggest a singlet electronic ground state for the ion $CH_3OPOCH_3^+$. The primary product ions and their relative abundances, together with the major secondary product ions, are given in Table 1. The observed reactivity is discussed in detail below.

Methanol, Ethanol, 2-Propanol, and 1-Butanol. Reaction of the ion $CH_3OPOCH_3^+$ (m/z 93) with methanol-d_4 occurs by replacement of the two methoxy groups of the ion with methoxy-d_3 (first forming $CD_3OPOCH_3^+$, m/z 96, and then $CD_3OPOCD_3^+$, m/z 99). Similarly, the reaction with ethanol leads to a fast ($k_{reaction}/k_{collision} = 0.9$; *i.e.*, nine collisions out of 10 lead to a reaction) stepwise replacement of the methoxy groups of $CH_3OPOCH_3^+$ with ethoxy groups, producing the longer chain phosphenium ions $CH_3OPOCH_2CH_3^+$ (m/z

(15) (a) Harrison, J. F. *J. Am. Chem. Soc.* **1981**, *103*, 7406. (b) Redondo, P.; Largo, A.; Barrientos, C.; Ugalde, J. M. *J. Phys. Chem.* **1991**, *95*, 4318.
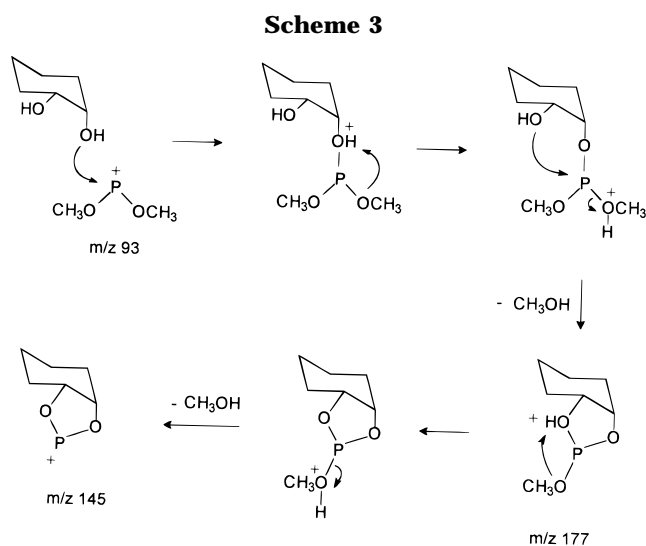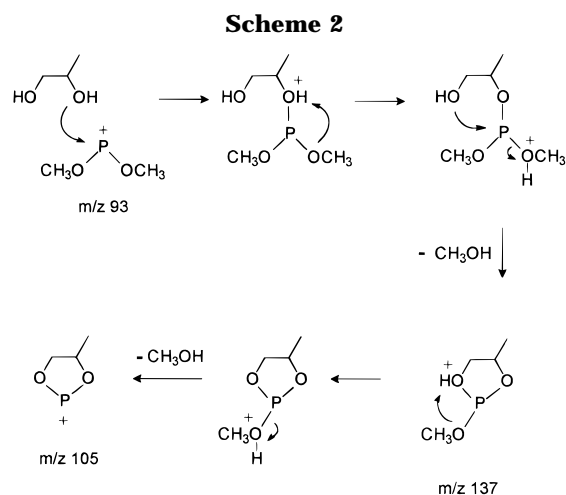
(16) (a) O'Hair, R. Gas-Phase Positive and Negative Ion Chemistry of Organophosphorus Compounds via Mass Spectrometric Techniques. In *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; Wiley & Sons Ltd.: New York, **1996**; Vol. 4. (b) Thorne, L. R.; Anicich, V. G.; Huntress, W. T. *Chem. Phys. Lett.* **1983**, *98*, 162. (c) Smith, D.; McIntosh, B. J.; Adams, N. G. *J. Chem. Phys.* **1989**, *90*, 6213. (d) Hodges, R. V.; McDonnell, T. J.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 1327. (e) Holtz, D.; Beauchamp, J. L.; Eyler, J. R. *J. Am. Chem. Soc.* **1970**, *92*, 7045. (f) Wanczek, K.-P.; Hartmann, H.; Roschenthaler, G.-V. *Adv. Mass Spectrom.* **1978**, *7B*, 1301. (g) Wanczek, K.-P. *Z. Naturforsch.* **1975**, *30a*, 329.

Scheme 1

m/z 93

$+ CH_3CH_2OH$
$- CH_3OH$

m/z 107

m/z 121

$- CH_3OH$

Scheme 2

m/z 93

$- CH_3OH$

m/z 105

$- CH_3OH$

m/z 137

Scheme 3

m/z 93

$- CH_3OH$

m/z 145

$- CH_3OH$

m/z 177

107) and $CH_3CH_2OPOCH_2CH_3^+$ (*m/z* 121; Table 1). In an analogous manner, 1-butanol yields first $CH_3OPOCH_2CH_2CH_2CH_3^+$ (*m/z* 135) and then $CH_3CH_2CH_2CH_2OPOCH_2CH_2CH_2CH_3^+$ (*m/z* 177; Table 1) via elimination of two methanol molecules upon collisions with 1-butanol. The consecutive nature of these reactions is verified by the observation of $CH_3CH_2CH_2CH_2OPOCH_2CH_2CH_2CH_3^+$ (together with some water abstraction product, *m/z* 153) upon reaction of the isolated ion $CH_3OPOCH_2CH_2CH_2CH_3^+$ with 1-butanol. A mechanism that rationalizes all these observations is illustrated in Scheme 1.

In contrast to the above results, the reaction of 2-propanol results in the replacement of only one methoxy group (to yield $CH_3OPOCH(CH_3)_2^+$, *m/z* 121; Table 1). Steric hindrance may prevent the replacement of the second methoxy group in the product ion. Indeed, the reaction of 2-pronanol occurs only at about one-third of the efficiency of that of ethanol ($k_{reaction}/k_{collision} = 0.3$ and 0.9 for 2-propanol and ethanol, respectively). The product ion of propanol, $CH_3OPOCH(CH_3)_2^+$ (*m/z* 121), abstracts water from another 2-propanol molecule (to yield the ion of *m/z* 139). In addition to the above reactivity, $CH_3OPOCH_3^+$ abstracts water from 2-propanol (to produce the ion of *m/z* 111), transfers a methyl group to 2-propanol (*m/z* 75), and produces a stable addition product (*m/z* 153).

1,2-Propanediol and 1,3-Butanediol. The reactivity of $CH_3OPOCH_3^+$ toward 1,2-propanediol resembles that observed for the alcohols. Water abstraction occurs as a minor pathway. The major reaction pathway involves elimination of methanol from the collision complex of $CH_3OPOCH_3^+$ with the diol (yielding an ion of *m/z* 137; Figure 1, Table 1). However, instead of undergoing elimination of the remaining methoxy group as methanol upon collision with another diol molecule (as was observed for methanol-d_4, ethanol, and 1-butanol), some of the product ions undergo an *intramolecular* methanol elimination to generate an ion that is likely to have a cyclic phosphenium ion structure (*m/z* 105, Table 1; Scheme 2; either of the hydroxyl groups may undergo the initial attack at the ion). The latter ion reacts further with another 1,2-propanediol molecule by water abstrac-

tion (*m/z* 123; Scheme 2). The same reactivity patterns were observed for 1,3-butanediol.

***cis-* and *trans-*1,2-Cyclopentanediols and -1,2-Cyclohexanediols.** As observed for 1,2-propanediol, elimination of one and two methanol molecules takes place for the adducts of $CH_3OPOCH_3^+$ with *cis-*1,2-cyclopentanediol and *cis-*1,2-cyclohexanediol (Scheme 3; Table 1). The origin of the eliminated methoxy groups was verified to be $CH_3OPOCH_3^+$ by examining the reaction of the deuterium-labeled ion $CD_3OPOCD_3^+$ with *cis-*1,2-cyclopentanediol. This reaction leads to elimination of one or two molecules of CD_3OH (Table 1). A secondary reaction involving abstraction of water from another diol molecule takes place for the product ions resulting from the elimination of two methanol molecules.

In sharp contrast to the *cis-*diols, reactions of the isomeric *trans-*diols are dominated by abstraction of water and/or HO^- by $CH_3OPOCH_3^+$ and by the loss of methanol from the addition product (Table 1; Figure 2). The observation of CD_3OH elimination upon reaction of $CD_3OPOCD_3^+$ with *trans-*1,2-cyclopentanediol verified the origin of the eliminated methoxy group to be the reactant ion. The methanol elimination products of the *trans-*diols abstract water from another diol molecule.

Products arising from elimination of two methanol molecules are minor for the *trans-*diols. The finding of dramatically different product distributions for the *cis-* and *trans-*1,2-cyclohexanediols is remarkable since the mass spectrometric distinction of these compounds is
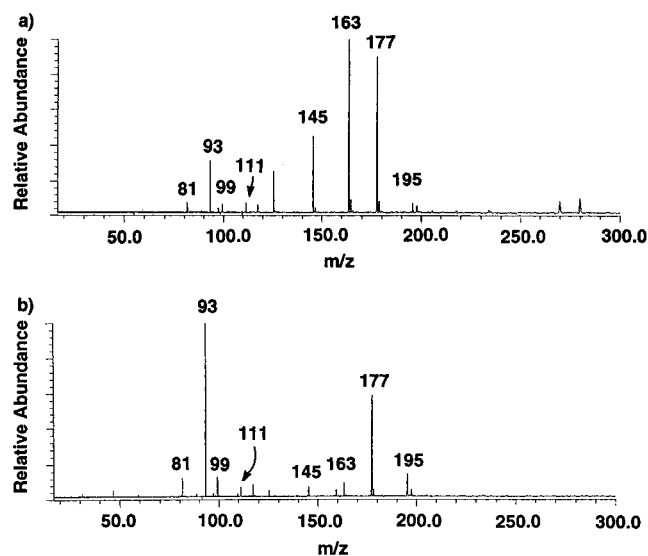
Scheme 4

Figure 2. Reactions of $CH_3OPOCH_3^+$ (*m/z* 93) for 3.0 s with (a) *cis*-1,2-cyclohexanediol and (b) *trans*-1,2-cyclohexanediol. The products of *m/z* 145 and 163, resulting from the loss of two CH_3OH molecules from the adduct (*m/z* 145) and subsequent abstraction of a water molecule from a second diol molecule (*m/z* 163), are abundant only for the *cis*-isomer.
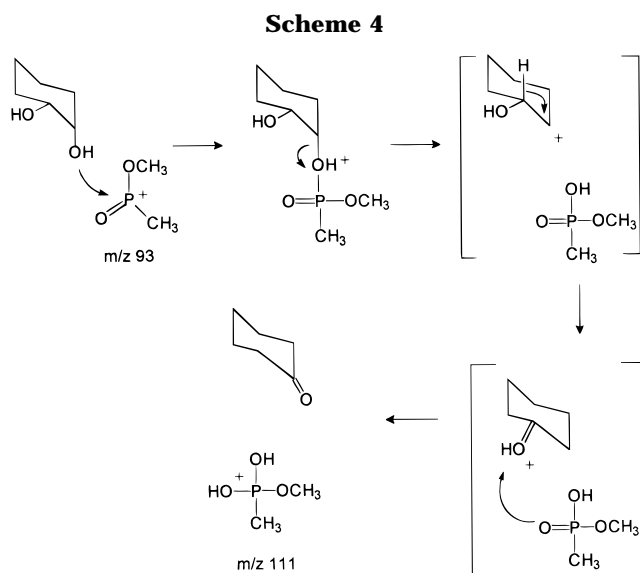
notoriously difficult due to the high degree of fluctional freedom inherent to the cyclohexane skeleton.[3]

2,3-Trinorbornanediols. The *cis*-(*diendo* and *diexo*)-2,3-trinorbornanediols exhibit reactivity that is different from that of the *trans*-2,3-trinorbornanediol and analogous to that of *cis*-1,2-cyclopentanediol and *cis*-1,2-cyclohexanediol. The *cis*-2,3-trinorbornanediols react with $CH_3OPOCH_3^+$ by addition followed by loss of one and two methanol molecules (to give a product ion of *m/z* 157; Table 1). The reaction of these diols with $CD_3OPOCD_3^+$ results in loss of CD_3OH molecules (Table 1), as was observed for the other *cis*-diols.

The *cis*-(*diendo*)- and *cis*-(*diexo*)-isomers yield quantitatively different product distributions. For example, the major product ion observed for the *diendo*-diol is the ion resulting from the loss of two methanol molecules from the adduct (likely due to steric crowding, which provides a greater driving force for elimination of the bulky methoxy groups) while the *diexo*-isomer shows predominant loss of only one methanol (Table 1). Further, the *diendo*-isomer shows a much more pronounced HO^- abstraction product than the *diexo*-ion.

The *trans*-2,3-trinorbornanediol fails to react with $CH_3OPOCH_3^+$ by elimination of methanol molecules. Instead, formation of a stable adduct (*m/z* 221) and abstraction of water or HO^- from the diol were observed. The water and HO^- abstraction reactions yield product ions with the same mass value (*m/z* 111). The occurrence of both of these reactions was verified by using $CD_3OPOCD_3^+$. The reaction of $CD_3OPOCD_3^+$ with *trans*-2,3-trinorbornanediol yields a product ion of *m/z* 117 from water abstraction, together with an ion of *m/z* 111 from HO^- abstraction (Table 1).

Comparison of the Reactivity of $CH_3OPOCH_3^+$ and $CH_3P(O)OCH_3^+$. The factors that determine the stabilities of phosphenium ions toward isomerization are almost entirely unexplored. For example, the barrier separating the ion $CH_3OPOCH_3^+$ from the isomeric ion $CH_3P(O)OCH_3^+$ is unknown. To verfiy that the ion $CH_3OPOCH_3^+$ is indeed the reacting species in the experiments discussed above, the reactivity of the iso-

meric ion $CH_3P(O)OCH_3^+$ was briefly examined. The ion $CH_3P(O)OCH_3^+$ was generated by electron ionization of dimethyl methylphosphonate and reacted with *cis*-1,2-cyclohexanediol. In sharp contrast to $CH_3OPOCH_3^+$, $CH_3P(O)OCH_3^+$ reacts with the diol by exclusive water abstraction (to yield an ion of *m/z* 111). A likely mechanism for the reaction is shown in Scheme 4. The different reactivity observed for the isomeric ions demonstrates that they are distinct, stable species.

Molecular Orbital Calculations. Phosphenium ions are electron deficient due to a phosphorus center with only six valence electrons. Molecular orbital calculations suggest that many phosphenium ions are likely to be ground-state singlets.[14,15] Singlet phosphenium ions possess a lone pair of electrons (σ^2) and a formally vacant orbital ($3p^2$) on a phosphorus atom (approximately sp^2 hybridized) and hence can be considered as electrophilic carbenoids.[14] The observed reactivity, *i.e.*, the absence of radical-type reactions (*e.g.*, H atom abstraction) and the facile occurrence of addition/elimination reactions, strongly suggests a singlet ground state for $CH_3OPOCH_3^+$. This finding is supported by predictions obtained from molecular orbital calculations. At the Becke3LYP/6-31G-(d) + ZPE level of density functional theory, the singlet state of $CH_3OPOCH_3^+$ ($^1A'$) is calculated to lie 66.7 kcal mol^{-1} lower in energy than the triplet state ($^3A'$). In agreement with the expectation of an increase in the singlet−triplet separation with ligand electronegativity,[14,15] this energy difference is significantly greater than the singlet−triplet splitting calculated earlier for H_2P^+ (−16 kcal mol^{-1}), $HPOH^+$ (−18 kcal mol^{-1}), and HPF^+ (−43 kcal mol^{-1}) but smaller than that calculated for F_2P^+ (−84 kcal mol^{-1}).[15]

According to the calculations, the triplet $CH_3OPOCH_3^+$ possesses C_s symmetry and the singlet C_{2v} symmetry (Figure 3). The latter ion has a nearly planar C−O−P−O−C skeleton, a conformation which maximizes dative π-bonding between the oxygen lone pairs and the formally vacant P(3p) orbital. The geometrical parameters calculated for this ion are very similar to those calculated earlier by others for the singlet $HPOH^+$.[15] Both ions are characterized by a nearly planar structure, short P−O bonds (1.564 Å for $CH_3OPOCH_3^+$; 1.538 Å for $HPOH^+$) and small O−P−O bond angles (100.1° for $CH_3OPOCH_3^+$; 96.2° for $HPOH^+$). In contrast to the singlet $CH_3OPOCH_3^+$, the triplet ion has a nonplanar

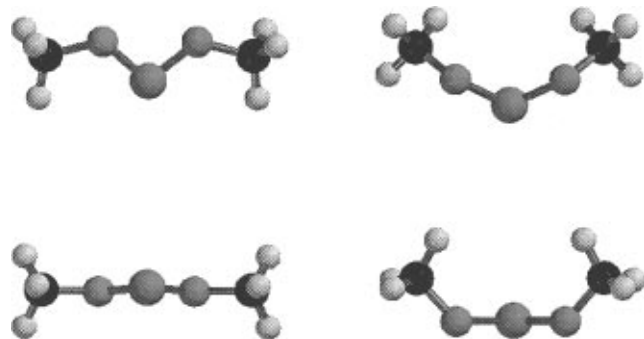**Figure 3.** The optimized structures of the singlet (two structures on the left) and triplet $CH_3OPOCH_3^+$ (right) (Becke3LYP/6-31G(d) level of theory).

geometry, longer P—O bonds (1.618 Å) and greater O—P—O bond angles (115.3°). Similar structural differences were reported earlier for the lowest-energy singlet and triplet states of $HPOH^+$ (^3A: P—O bond lengths 1.549 Å; O—P—O bond angle 117.5°).[15] The spin density on the phosphorus atom in the triplet $CH_3OPOCH_3^+$ is 1.27e, with a spin of only 0.31e on the adjacent oxygen atoms ($\langle S^2 \rangle = 2.006$).

The calculated natural charge distributions suggest that the positive charge is highly localized on the phosphorus atom in the singlet $CH_3OPOCH_3^+$ (+1.65; triplet, +1.42). This finding, together with a calculated large LUMO coefficient on the phosphorus atom, explains why nucleophiles readily attack the phosphorus atom in the singlet $CH_3OPOCH_3^+$.

Finally, the origins of the dramatically different product distributions obtained for the *cis-* and *trans-*1,2-cyclohexanediols upon reaction with $CH_3OPOCH_3^+$ were explored computationally. The structures and relative stabilities of the product ions of m/z 145 formed upon elimination of two methanol molecules from the adducts of *cis-* and *trans-*1,2-cyclohexanediols with $CH_3OPOCH_3^+$ were examined at the Becke3LYP/6-31G(d) + ZPE level of theory. The product formed from the *cis-*diol is calculated to be more stable than that of the *trans-*diol by 2.8 kcal/mol at 0 K (see Figure 4 for the optimized structures). The product of the *cis-*diol is also entropically (vibrational entropy 16.6 cal/mol K) favored over that of the *trans-*isomer (16.0 cal/mol K). Hence, the observation of a more abundant ion of m/z 145 for the *cis-*diol is not surprising.

Conclusions

$CH_3OPOCH_3^+$ is a strong electrophile and readily attacks hydroxyl groups in neutral substrates. All the alcohols and diols studied (except *trans-*2,3-norbornanediol) induce elimination of one or both of the methoxy groups of the ion as methanol molecules, as verified by deuterium labeling experiments. These reactions provide a convenient synthetic route for the generation of various larger phosphenium ions in the gas phase. The observed reactivity is in agreement with the indication given by molecular orbital calculations that $CH_3OPOCH_3^+$
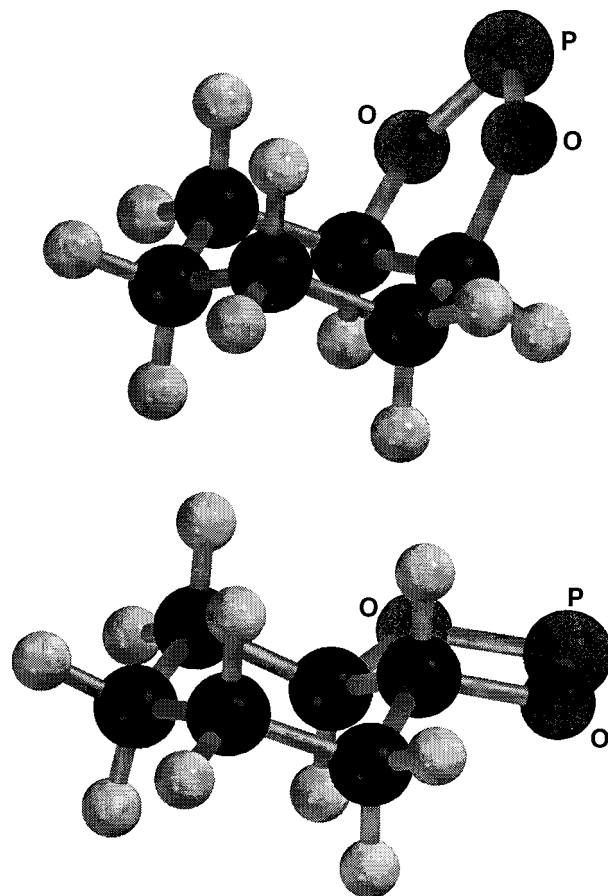

Figure 4. The optimized structures of the products formed upon elimination of two methanol molecules from the adduct of (a) *cis-* and (b) *trans-*1,2-cyclohexanediols with $CH_3OPOCH_3^+$ (Becke3LYP/6-31G(d) level of theory).

has a singlet electronic ground state and that nucleophiles should readily attack the phosphorus atom of this ion.

The most remarkable result obtained in this work is the discovery that the phosphenium ion $CH_3OPOCH_3^+$ yields dramatically different product distributions for diastereomeric vicinal diols. Different products were obtained even for *cis-* and *trans-*1,2-cyclohexanediols, compounds that yield essentially identical mass spectra in all the experiments reported thus far.[3] Furthermore, the reaction products are *predictable* on the basis of the relative orientation of the hydroxyl groups. Hence, phosphenium ion chemistry may allow the determination of the stereochemical structure of *unknown* compounds *without extensive prior purification* and derivatization, possibly even in mixtures of isomers.