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Mechanistic Study of Stereoselective Gas-Phase Reactions of Phosphenium Ions with *cis*- and *trans*-1,2-Diaminocyclohexanes

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The 1,3-dioxolane-2-phosphenium ion, 1,3-benzodioxole-2-phosphenium ion, and *o*-biphenylenephosphenium ion are reported to react in a stereoselective manner with *cis*- and *trans*-1,2-diaminocyclohexanes in the gas phase in a Fourier transform ion cyclotron resonance mass spectrometer. Elimination of NH_3 from an addition product was observed only for the *trans* isomer. Several reaction mechanisms were experimentally and computationally examined (B3LYP/6-31G(d)//HF/6-31G(d) + ZPVE level of theory). The most plausible mechanism is initiated by addition of one of the amino groups to the electrophilic phosphorus atom followed by proton transfer between the amino groups. A change to a diaxial conformation for the *trans* isomer facilitates anchimeric assistance by the now nucleophilic phosphorus atom as the C−N bond breaks to release NH_3. Intramolecular proton transfer competes with the conformational change and ultimately leads to ethylene glycol elimination. The transition states for the critical steps of these two reactions are calculated to be nearly equal in magnitude, which rationalizes the observation of both reactions for the *trans*-diamine. In contrast, the adduct of the *cis* isomer can eliminate NH_3 via a concerted 1,2-hydride shift without a need for a conformational change. However, the barrier associated with this reaction was found to be substantially greater than for proton transfer between the N- and O-atoms. The latter reaction dominates and ultimately leads to ethylene glycol elimination.

Introduction

Stereochemistry plays an important role in the pharmacological effects of many biologically active compounds.[1] For example, the *R* enantiomer of thalidomide is a sedative while the *S* enantiomer is highly teratogenic.[2] The *S* enantiomer of penicillamine is an antiarthrytic and the *R* enantiomer is extremely toxic.[3,4] Propanolol's *S* enantiomer, a β-adrenergic blocking agent that is used to treat hypertension and angina pectoris, is one hundred times more active than the *R* enantiomer.[4,5] Hence, in the pharmaceutical industry, it is imperative to be able to quickly determine the stereochemical structure of organic compounds. Methods commonly used for this task are competitive binding methods, NMR, and chromatography.[6−8] Although these methods have revolutionized enantiomer analysis, they have some shortcomings. A problem associated with competitive binding methods is the inability to measure the inactive enantiomer, which could be of toxicological importance.[6] Structural elucidation of mixtures of unknown compounds with overlapping NMR signals is difficult or impossible.[7] Finally, chromatographic analysis of stereoisomers requires standards and hence is not feasible for unknown compounds.

Mass spectrometry is fast, sensitive, and has modest requirements for the analyte's purity. Despite these attributes, mass spectrometry has not been generally used for stereoisomer analysis because the most common ionization method, electron-impact ionization, is insensitive to the stereochemical structure of molecules. An example is provided by the mass spectra of the diastereomeric *cis*- and *trans*-1,2-diaminocyclohexanes shown in Figure 1.[9] Chemical ionization has shown more promise by producing fewer but more informative product ions. Most chemical ionization methods employed for stereoisomer analysis are based on proton transfer or the formation of ionic adducts.[10] The reagent ions utilized for proton-transfer reactions include CH_5^+, H_3O^+, NH_4^+, and $C_4H_9^+$.[10,11] In these studies, the isomers were distin-

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(9) (a) Mass spectra measured in our laboratory. (b) While this work was being prepared for publication, Eberlin published a reaction that allows the diamines to be distinguished via a similar mechanism as discussed here: Moraes, L. A. B.; Eberlin, M. N. *J. Am. Soc. Mass Spectrom.* **2001**, *12*, 150−162.
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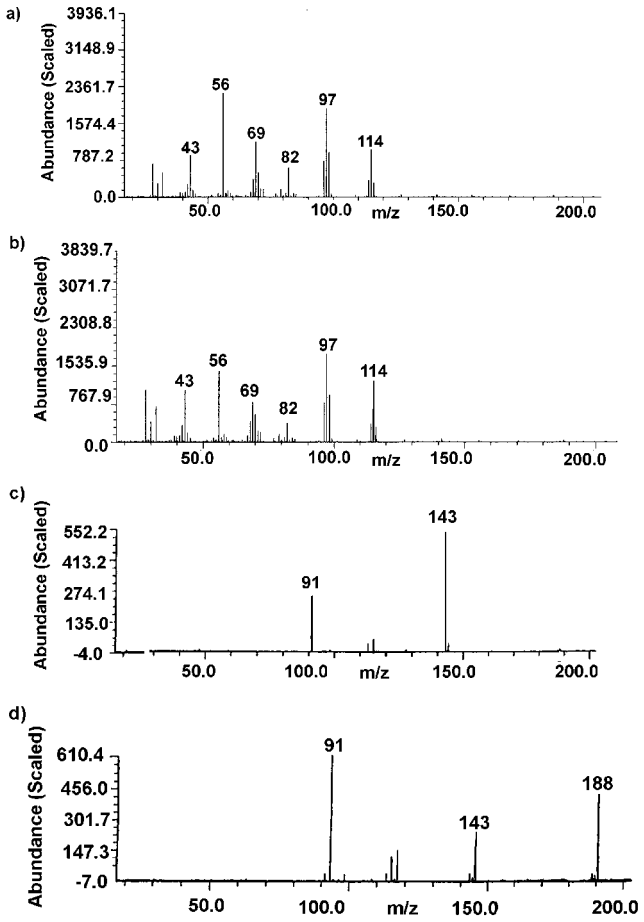

FIGURE 1. Electron-impact ionization mass spectra measured at 70 eV electron energy for (a) *cis*-1,2-diaminocyclohexane and (b) *trans*-1,2-diaminocyclohexane. (c) Reaction of the 1,3-dioxolane-2-phosphenium ion (*m*/*z* 91) for 750 ms with *cis*-1,2-diaminocyclohexane and (d) *trans*-1,2-diaminocyclohexane. The product ions arise from elimination of an ethylene glycol molecule from the adduct (*m*/*z* 143) and for the *trans* isomer from elimination of NH_3 from the adduct (*m*/*z* 188).

guished on the basis of differences in their relative basicities that led to observable differences in the abundances of the protonated molecules relative to fragment ions. The same principle applies for stereoisomer distinction based on adduct formation with reagents such as protonated pyridine and the trimethylsilyl cation.[12,13]

In addition to the above studies, others have examined a number of unusual reagent ions for their ability to differentiate diastereomeric compounds. The *cis*- and *trans*-1,2-cyclopentanediols have been extensively employed as a test case in these investigations. Suming et al. demonstrated that protonated trimethylborate can be used to distinguish the isomeric diols.[14] When protonated trimethylborate reacts with *cis*-1,2-cyclopentanediol, two CH_3OH molecules are eliminated from the addition product to yield an ion of *m*/*z* 143. Only one CH_3OH molecule is eliminated when the ion reacts with *trans*-1,2-cyclopentanediol. Unlike the *cis*-diol where both OH groups are located on the same side of the molecule, the *trans*-diol has an OH group on each side. The OH moiety that remains after the first elimination is too far away to form a bond with the boron, which is required for a second CH_3OH molecule to be eliminated. Mancel and Sellier used protonated acetonitrile to differentiate the diastereomeric diols.[15] When the acetonitrile ion reacts with the *trans* isomer, a facile elimination of a H_2O molecule occurs from the addition product. Fragmentation was not observed for the adduct ion of the *cis* isomer, which was rationalized by the greater stability of this adduct due to internal hydrogen bonding.

In contrast to the cyclopentanediol system, differentiation of the *cis*- and *trans*-1,2-cyclohexanediols has proven to be challenging due to the flexibility of the cyclohexane skeleton. Suming et al.[14] examined reactions of protonated trimethylborate and Mancel and Sellier[15] of protonated acetonitrile with the *cis*- and *trans*-1,2-cyclohexanediols, but only minor differences in the product abundances were reported.

The study by Suming et al.[14] based on protonated trimethylborate inspired us to examine the usefulness of dicoordinate boron cations, borenium ions ($R-B^+-R$), for differentiation of the well-studied *cis*- and *trans*-1,2-cyclopentanediols and the notoriously difficult-to-distinguish *cis*- and *trans*-1,2-cyclohexanediols. However, borenium ions are highly electrophilic and abstract HO^- when reacted with alcohols.[16,17] This reactivity destroys the stereochemical integrity of the molecule. Therefore, a less electrophilic reagent cation was needed. Dicoordinate phosphorus cations known as phosphenium ions[18] ($R-P^+-R$) were selected for subsequent studies because they are not as electrophilic as borenium ions. Our studies[19] on phosphenium ions have demonstrated that they can yield qualitatively different reaction products for the cyclic diastereomeric diols. For example, the dimethoxyphosphenium ion, $CH_3O-P^+-OCH_3$, yields distinctly different product ions upon reaction with the *cis*- and *trans*-1,2-cyclohexanediols (Scheme 1).[19] Two CH_3OH molecules are eliminated from the addition product of the *cis* isomer, but steric hindrance prevents this for the *trans* isomer.

The above results suggest that phosphenium ions may have an unprecedented ability to distinguish cyclic stereoisomeric compounds. Furthermore, it may be possible to predict product ions solely on the basis of the relative orientation of the functional groups in the analyte molecules. Therefore, this method may be applicable to unknown analytes.

The success of the diol study inspired us to examine the reactivity of phosphenium ions toward compounds with other functionalities. Differentiation of the diastereomeric *cis*- and *trans*-1,2-diaminocyclohexanes[9a,9b] (Figure 1) is as challenging as that of the *cis*- and *trans*-1,2-

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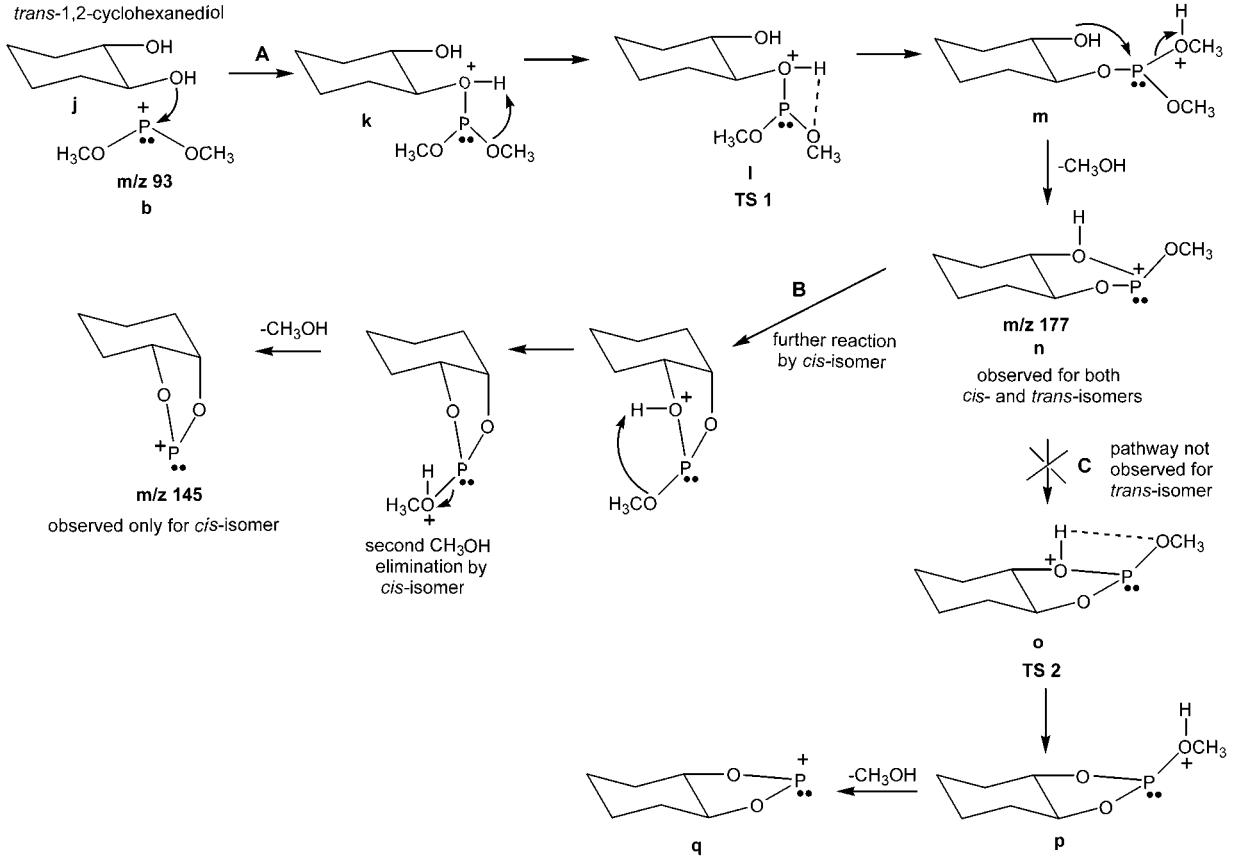
SCHEME 1



cyclohexanediols. The present study reports on the stereoselective reactivity of $CH_3O-P^+-OCH_3$ and two cyclic phosphenium ions, the 1,3-dioxolane-2-phosphenium ion and the 1,3-benzodioxole-2-phosphenium ion, toward *cis*- and *trans*-1,2-diaminocyclohexanes.

Experimental Section

All experiments were conducted in an Extrel FTMS 2001 and a Finnigan FTMS 2001 Fourier transform ion cyclotron resonance mass spectrometer. Both have been described previously.[20−24] Each instrument contains a differentially pumped dual cell that is placed within the magnetic field produced by a 3.0 T superconducting magnet.

The phosphenium ions were produced by electron-impact ionization of 2-chloro-1,3,2-dioxaphospholane, 2-chloro-1,3,2-benzodioxolephospholane, trimethyl phosphite, and triphenylphosphine. The reagents were introduced into one cell region by using a Varian leak valve or a Finnigan-built batch inlet system equipped with a variable leak valve. The ionization conditions were optimized for the maximum ion signal for each experiment (typically 20−40 eV electron energy, 40−70 ms beam time, 8 μA emission current). All ions were removed from the other cell region by changing the end trapping plate voltage from +2.0 to −2.0 V for 10−15 ms. Ions generated in the first region were then transferred into the other by grounding the conductance limit for about 100 μs. The reactant ions were cooled by multiple collisions with argon introduced through a pulsed valve system into the cell at a nominal peak pressure of 1×10^{-5} Torr. The one-second argon pulse also allows the ions ample time to dissipate excess internal energy by IR emission. Previous studies by Dunbar et al. have shown that trapped ions tend to achieve thermal equilibrium with their surroundings by the IR emission mechanism.[25] Rate changes attributable to ion cooling during the kinetic analysis were not observed (i.e., the measured pseudo-first-order reaction rate constants neither increase nor decrease during the observation time). Thus, it is likely that the ions have achieved near thermal equilibrium with their surroundings before the reactions. The phosphenium ions were isolated by ejection of all unwanted ions through the application of the stored waveform inverse Fourier transform (SWIFT)[26] excitation method. The isolated ions were 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.[27]

The ions were excited for detection by using a chirp pulse with a sweep rate of 3.2-kHz/μs and a bandwidth of 2.7 MHz. The spectra were recorded as 64k data points and subjected to one zero fill *prior* to Fourier transformation. All the spectra were recorded as the average of at least 25 acquisitions.

Since the reactions studied under the conditions described above follow pseudo-first-order kinetics, their second-order rate constants (k_{exp}) were obtained from a semilogarithmic plot of

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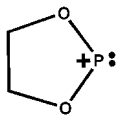
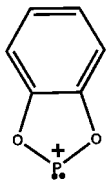
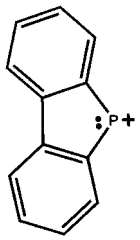
TABLE 1. Ionic Products and Their Relative Abundances Formed upon Reaction of Amines and Diamines with Various Phosphenium Ions

neutral reagent	$CH_3O-P^+-OCH_3$ *m/z* 93	 m/z 91	 m/z 139	 m/z 183
cis-1,2-diamino-cyclohexane (MW 114)	*m/z* 143 (adduct − $2CH_3OH$) 100%	*m/z* 205 (adduct) 6% *m/z* 143 (adduct − $HOCH_2CH_2OH$) 89% *m/z* 113 (H^- abstraction) 5%	*m/z* 253 (adduct) 3% *m/z* 143 (adduct − HOC_6H_4OH) 93% *m/z* 113 (H^- abstraction) 4%	*m/z* 297 (adduct) 100%
trans-1,2-diamino-cyclohexane (MW 114)	*m/z* 143 (adduct − 2CH3OH) 100%	*m/z* 205 (adduct) 18% *m/z* 188 (adduct − NH_3) 39% *m/z* 143 (adduct − $HOCH_2CH_2OH$) 30% *m/z* 113 (H^- abstraction) 13%	*m/z* 253 (adduct) 6% *m/z* 236 (adduct − NH_3) 43% *m/z* 143 (adduct − HOC_6H_4OH) 38% *m/z* 113 (H^- abstraction) 13%	*m/z* 297 (adduct) 28% *m/z* 280 (adduct − NH_3) 72%
isopropylamine (MW 59)		*m/z* 58 (H^- abstraction) 100%	*m/z* 58 (H^- abstraction) 100%	
cyclohexylamine (MW 99)		*m/z* 98 (H^- abstraction) 100%	*m/z* 98 (H^- abstraction) 100%	
triethylamine (MW 101)		*m/z* 100 (H^- abstraction) 100%	*m/z* 100 (H^- abstraction) 100%	
ethylenediamine (MW 60)		*m/z* 151 (adduct) 10% *m/z* 134 (adduct − NH_3) 22% *m/z* 89 (adduct − $HOCH_2CH_2OH$) 68%	*m/z* 199 (adduct) 15% *m/z* 182 (adduct − NH_3) 53% *m/z* 89 (adduct − HOC_6H_4OH) 32%	
ethylene-d_4-diamine (MW 64)		*m/z* 155 (adduct) 15% *m/z* 138 (adduct − NH_3) 25% *m/z* 89 (adduct − $HOCH_2CH_2OH$) 60%	*m/z* 203 (adduct) 12% *m/z* 186 (adduct − NH_3) 50% *m/z* 141 (adduct − HOC_6H_4OH) 38%	
1,2-diamino-2-methyl-propane (MW 88)		*m/z* 179 (adduct) 15% *m/z* 162 (adduct − NH_3) 62% *m/z* 117 (adduct − $HOCH_2CH_2OH$) 23%	*m/z* 227 (adduct) 19% *m/z* 210 (adduct − NH_3) 48% *m/z* 117 (adduct − HOC_6H_4OH) 33%	

the relative abundance of the reactant ion as a function of time. The collision rate constants (k_{coll}) were calculated by using a parameterized trajectory theory. [28] The reaction efficiencies are given by k_{exp}/k_{coll}.

All reagents were purchased from commercial sources and used without purification. The identities and purities of all reagents were verified by mass spectrometry.

Calculations were carried out by Gaussian 98 Revision A.9.[29] An initial search for minimum energy structures was carried out using AM1 calculations. The reaction exothermicities and the energies of the proposed reaction intermediates and the transition states were estimated at the B3LYP/6-31G(d)//HF/6-31G(d) + ZPVE level of theory. The corresponding frequencies and zero point vibrational energies (ZPVE) were calculated from the HF/6-31G(d) harmonic frequencies and scaled by a factor of 0.9135 to account for the systematic overestimation of the vibrational frequencies by this method.[30]

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Results and Discussion

Reactions of several phosphenium ions were studied with the *cis*- and *trans*-1,2-diaminocyclohexanes. The reaction products are summarized in Table 1. The cyclic phosphenium ions were found to undergo a stereoselective addition/NH_3 elimination reaction with the diamines. Reaction exothermicities and relevant transition state energies were calculated for several reaction mechanisms in an attempt to identify the most plausible one. The proposed mechanism is supported by studies of the *o*-biphenylenephosphenium ion and several acyclic mono- and diamines.

Reactivity of $CH_3O-P^+-OCH_3$ toward the *cis*- and *trans*-1,2-Diaminocyclohexanes. Reactions of $CH_3O-P^+-OCH_3$ with the *cis*- and *trans*-1,2-diaminocyclohexanes were examined first because this ion successfully distinguishes the *cis*- and *trans*-1,2-cyclohexanediols.[18] When $CH_3O-P^+-OCH_3$ reacts with *cis*-1,2-cyclohexanediol, two CH_3OH molecules are eliminated. This observation was explained by a mechanism involving bond formation between the electrophilic phosphorus atom and a nucleophilic oxygen atom of one of the hydroxy groups of the diol (Scheme 1, step A). A rapid proton transfer occurs from the oxygen atom to one of the neighboring methoxy groups (possibly via the other hydroxyl group), followed by elimination of a CH_3OH molecule. The *cis* isomer is able to react further by a subsequent elimination of a second CH_3OH molecule (Scheme 1, pathway B), but this reaction is endothermic

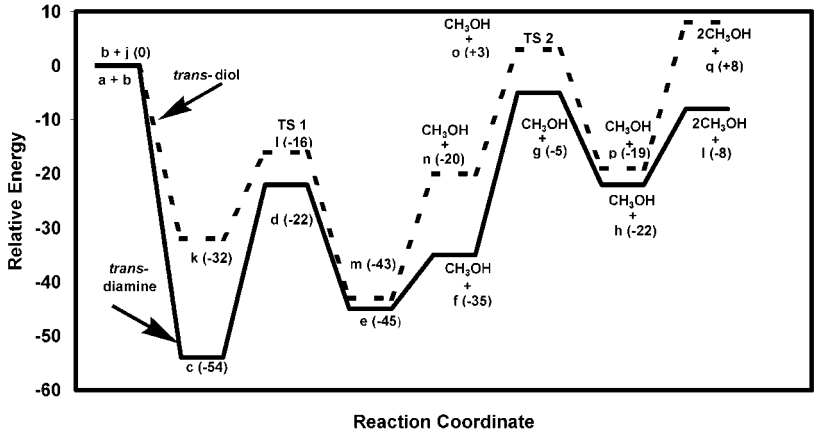
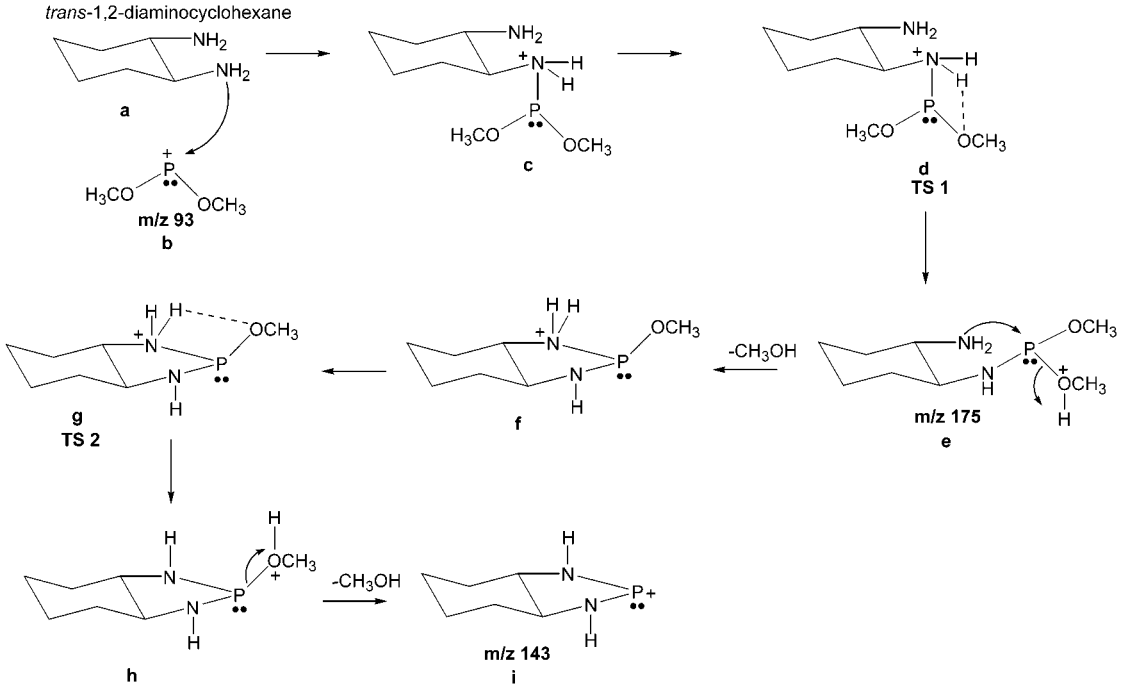


FIGURE 2. Potential energy surfaces calculated for reactions of $CH_3O-P^+-OCH_3$ with *trans*-1,2-cyclohexanediol (dashed line) and *trans*-1,2-diaminocyclohexane (solid line). The energy values are in kcal/mol and are given relative to the isolated reactants. The energy required for the loss of two CH_3OH molecules from the addition product of the *trans*-diol is above the total energy of the system (for the reaction mechanism, see Scheme 1). However, elimination of two CH_3OH molecules is energetically feasible for the adduct of the *trans*-diamine (for the reaction mechanism, see Scheme 2), thus making distinction of the diastereomeric diamines impossible.

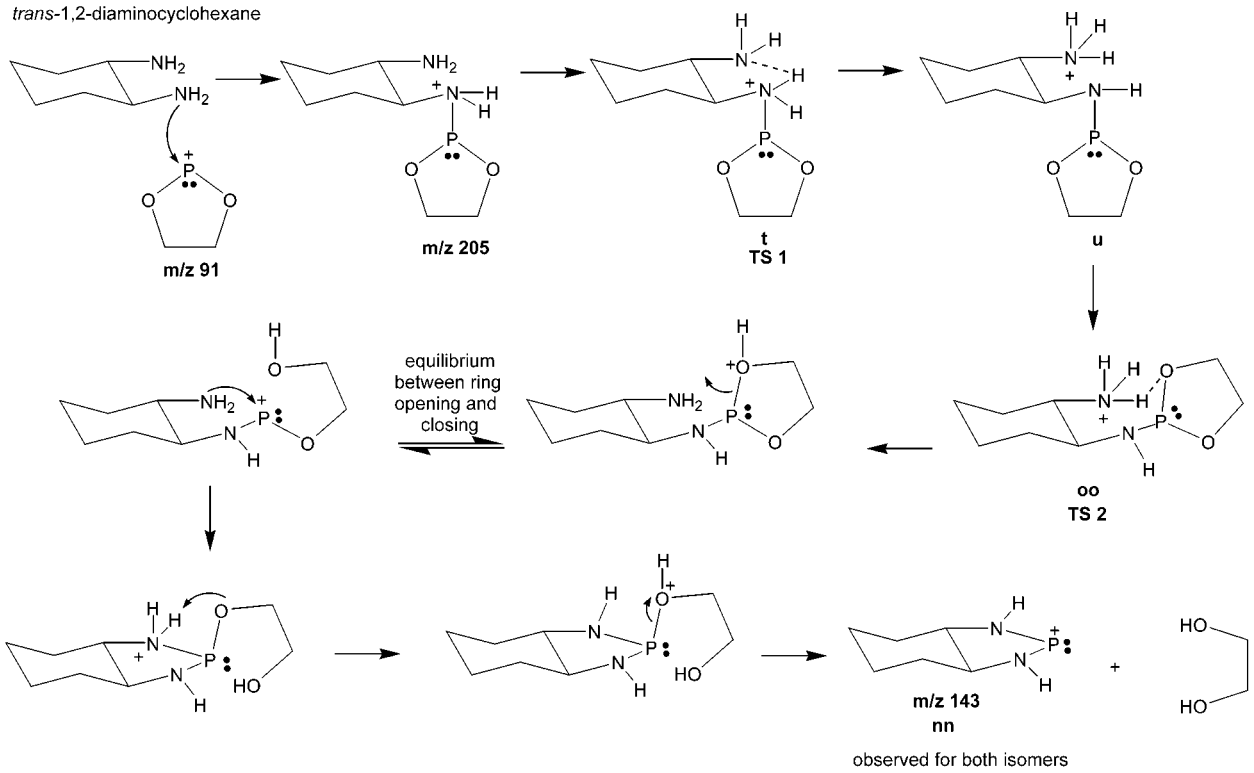
SCHEME 2



for the trans isomer (Figure 2, Scheme 1, pathway C). Analogous reactivity was expected for the interaction of $CH_3O-P^+-OCH_3$ with the diastereomeric diamines. However, both diamine isomers were found to eliminate two CH_3OH molecules from the addition product (Scheme 2). Unlike the *trans*-diol,[19] the *trans*-diamine is not inhibited from the double CH_3OH elimination. To understand the difference in reactivity of $CH_3O-P^+-OCH_3$ toward the *trans*-diol and the *trans*-diamine, the key features of the potential energy surface were calculated (Figure 2). The initial adduct formation is more energetic for the *trans*-diamine than for the corresponding diol. This difference is attributed to the fact that the diamine is more nucleophilic than the diol. In relation to the isolated reactants, the transition state for the first methanol elimination is within the energy of the system for the diol as well as the diamine. However, the transition state for the elimination of the second methanol molecule, as well as the final products, lie above the energy of the isolated reactants for the *trans*-diol (Scheme 1, pathway C), thus making the second methanol elimination unfeasible. In contrast, the transition state and final products are energetically accessible for the *trans*-diamine. These results explain why $CH_3O-P^+-OCH_3$ can distinguish the *cis*- and *trans*-1,2-cyclohexanediols but not the *cis*- and *trans*-1,2-diaminocyclohexanes.

Cyclic Phosphenium Ions. The cyclic phosphenium ions, 1,3-dioxolane-2-phosphenium and 1,3-benzodioxole-2-phosphenium ions, were selected for this study since they cannot undergo irreversible alcohol elimination as easily as $CH_3O-P^+-OCH_3$. When a cyclic ion reacts with the diastereomeric diamines, the first C–O cleavage

SCHEME 3



process is reversible (Scheme 3). An equilibrium involving ring opening and closing is established that results in a longer-lived complex. Only the 1,3-dioxolane-2-phosphenium ion is discussed in detail below because identical reactivity was observed for both cyclic ions. This ion yields qualitatively different products for the diastereomeric diamines but not by the expected reaction. The predicted reactivity, elimination of an ethylene glycol molecule via the mechanism shown in Scheme 3, was observed for both isomers. Therefore, the attempt to increase the stereoselectivity of the alcohol elimination reaction by using cyclic rather than acyclic phosphenium ions failed. However, a new reaction pathway was observed for the cyclic phosphenium ions that differentiates the isomers. An NH_3 molecule is eliminated from the addition product of only the *trans*-diamine to form an ion of *m*/*z* 188 (Table 1). The mechanism of this interesting reaction was examined experimentally and computationally, as described below.

Studies of Simple Amines and Diamines. To determine whether one or two amino groups are required for the addition/ammonia loss reaction, the 1,3-dioxolane-2-phosphenium ion was allowed to react with simple amines and diamines. The only reactivity that was observed for cyclohexylamine, isopropylamine, and triethylamine is H^- abstraction (Table 1). This reaction was also observed for the diastereomeric diamines, but it corresponds to only a minor reaction pathway. These results suggest that the presence of only one amino group does not lead to the loss of an NH_3 molecule. The same applies to elimination of an ethylene glycol molecule. However, elimination of NH_3 and elimination of an ethylene glycol molecule from the collision complex (as well as H^- abstraction, Table 1) were observed when the ion reacts with ethylenediamine or 1,2-diamino-2-methylpropane. Therefore, the presence of two amino groups is necessary for both reactions.

Reaction Mechanism. Several mechanistic pathways were considered for the ammonia loss reaction. All the mechanisms share the first two steps. The reactions are likely initiated by formation of a bond between a nucleophilic nitrogen of one of the amino groups and the electrophilic phosphorus of the phosphenium ion (Scheme 4). Subsequently, a proton transfer occurs between the neighboring nitrogens of the adduct. Support for the hypothesis that the extra hydrogen that is lost in NH_3 elimination comes from the neighboring nitrogen was obtained by examination of the reaction between the 1,3-dioxolane-2-phosphenium ion and ethylene-d_4-diamine, where the hydrogens on the carbon skeleton have been replaced with deuteriums (Table 1). The major reaction involved elimination of NH_3 with no deuteriums incorporated, thus demonstrating that the hydrogen that is abstracted does not come from the carbons.

The final steps of the mechanisms differ. Elimination of the NH_3 molecule could conceivably occur by a stepwise direct-bond cleavage followed by a 1,2-hydride shift to form the resonance stabilized "hydride-shift" product (Scheme 4, pathway A). However, calculations indicate that this reaction is not energetically feasible (Figure 3).

Other possible reaction pathways involve anchimeric assistance for the ammonia loss by the nitrogen, phosphorus, or oxygen atom.[9b] These pathways require the cyclohexane skeleton (in u; Scheme 4) to undergo a ring flip that orients the amino groups in a diaxial conformation (the ring-flip intermediates are referred to as ff, gg, and hh in Scheme 4 and Figure 3; their structures are provided as Supporting Information upon request). This orientation facilitates anchimeric assistance by any of the aforementioned atoms. However, the final product of

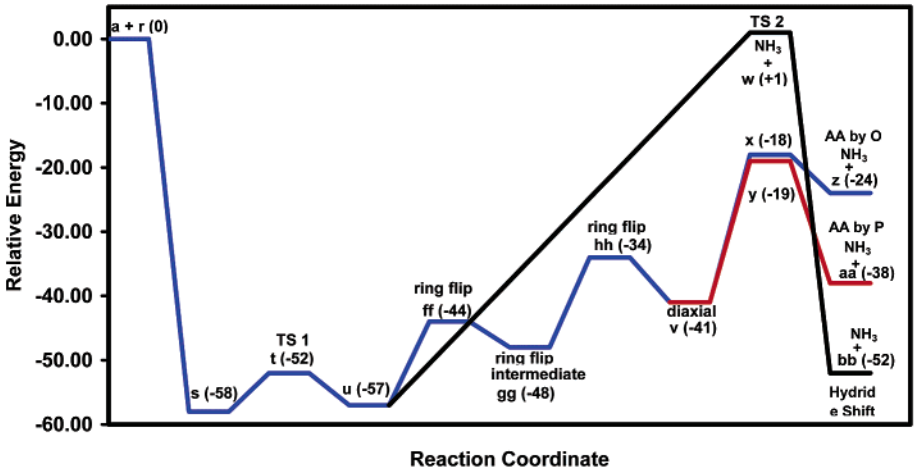
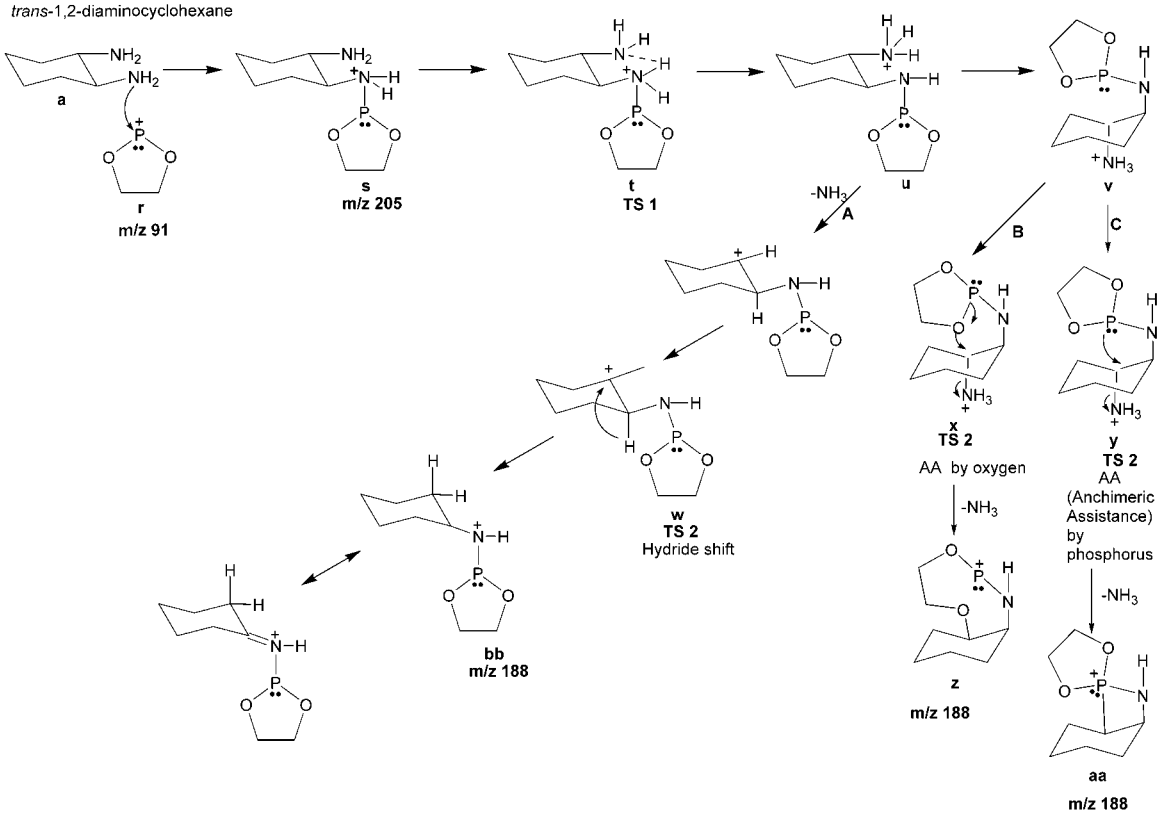


FIGURE 3. Potential energy surfaces calculated for NH_3 loss from the adduct of the *trans*-diamine with 1,3-dioxolane-2-phosphenium ion via a mechanism involving hydride shift (black line; for the reaction mechanism, see Scheme 4, pathway A), and involving anchimeric assistance by the oxygen atom (blue line; for the reaction mechanism, see Scheme 4, pathway B), and by the phosphorus atom (red line; for the reaction mechanism, see Scheme 4, pathway C). Energy values are given in kcal/mol relative to isolated reactants.

SCHEME 4



backside attack by the nitrogen atom is not thermodynamically accessible, being 6 kcal above the isolated reactants. Anchimeric assistance by the phosphorus atom is kinetically as well as thermodynamically feasible, as all the transition states and the final products are lower in energy than the isolated reactants (Scheme 4, pathway C). The oxygen atom can also attack from the backside (Scheme 4, pathway B). On the basis of calculations, this transition state lies 1 kcal/mol higher in energy (Figure 3) than the corresponding transition state for the phosphorus atom, and the ring-opened final product of the oxygen-attack pathway is 14 kcal higher in energy than the final product arising from phosphorus attack.

Collision-Activated Dissociation (CAD) and Ion/Molecule Reaction Studies. CAD was conducted to examine the structure of the ammonia loss-product (*m*/*z* 188) formed in the reaction between the 1,3-dioxolane-2-phosphenium ion and *trans*-1,2-diaminocyclohexane. The observed fragment ions correspond to an adduct of 1,3-dioxolane-2-phosphenium ion and NH_3 (from loss of cyclohexadiene; *m*/*z* 108), loss of neutral 1,3-dioxolane-2-phosphenium (*m*/*z* 97), loss of 1,3-dioxolane-2-phosphe-

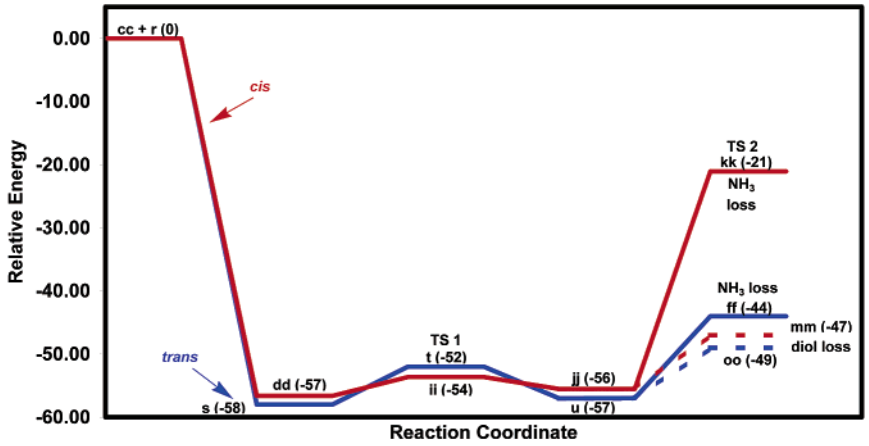


FIGURE 4. Potential energy surfaces calculated for the product-determining steps for the reactions of 1,3-dioxolane-2-phosphenium ion with *cis*- (red trace) and *trans*-1,2-diaminocyclohexanes (blue trace). For the *cis* isomer, these steps correspond to concerted hydride-shift/NH_3 elimination and nitrogen-to-oxygen proton transfer leading to ethylene glycol elimination (Scheme 5). For the *trans* isomer, the critical steps involve conformational change required for NH_3 elimination (Scheme 4) and nitrogen-to-oxygen proton-transfer preceding ethylene glycol elimination (Scheme 3). The energy values are in kcal/mol and given relative to isolated reactants.

nium bonded to NH (to form cyclohexene radical cation of *m*/*z* 82), and 1,3-dioxolane-2-phosphenium ion (*m*/*z* 91). The structure of the last ion was verified by isolating it and allowing it to react with *trans*-1,2-diaminocyclohexane. The products were identical to those reported earlier in this paper for the reaction of 1,3-dioxolane-2-phosphenium ion with *trans*-1,2-diaminocyclohexane. The CAD results therefore indicate that the ammonia loss-product (*m*/*z* 188) contains an intact phosphenium ion moiety. Hence, these results are in a better agreement with the product formed by phosphorus assistance than with that formed upon anchimeric assistance by oxygen.

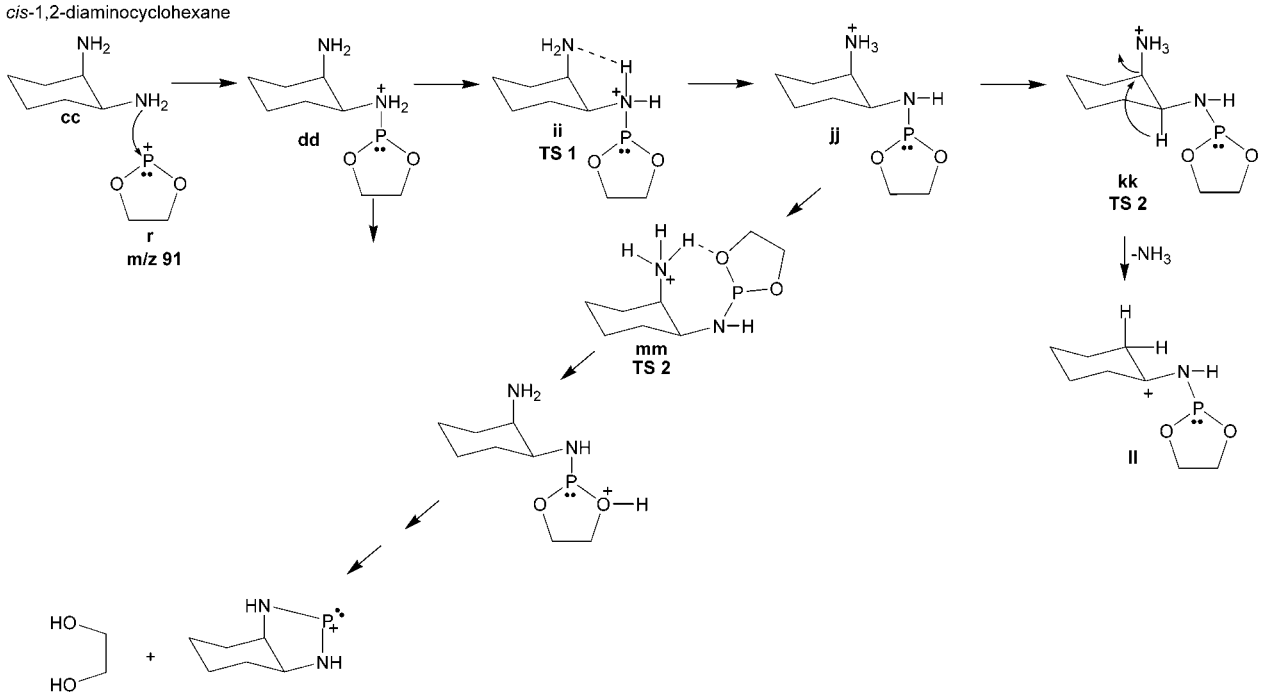
Further support for the phosphorus anchimeric assistance pathway was gained by studies of the *o*-biphenylenephosphenium ion generated by electron ionization of triphenylphosphine (Table 1).[31,32] Unlike the 1,3-dioxolane-2-phosphenium ion, the *o*-biphenylenephosphenium ion does not have other nucleophilic atoms besides phosphorus. When the ion reacts with the *trans*-diamine, an NH_3 molecule is eliminated from the adduct to yield the ion of *m*/*z* 280. Only adduct formation was observed for the *cis*-diamine. These results demonstrate that the presence of an oxygen atom is not a necessary requirement for the NH_3 elimination to take place, and hence, that anchimeric assistance by the phosphorus atom is the likely mechanism for the NH_3 loss. The *o*-biphenylenephosphenium ion yields a clearer distinction between the diastereomeric diamines than the 1,3-dioxolane-2-phosphenium ion because this ion does not have leaving groups whose loss can compete with the ammonia loss.

Reactivity of *cis*-1,2-Diaminocyclohexane. Unlike in the reaction of 1,3-dioxalane-2-phosphenium ion with *trans*-1,2-diaminocyclohexane, the elimination of the NH_3 molecule was not observed in reaction with *cis*-1,2-diaminocyclohexane. Anchimeric assistance cannot occur for this isomer because it cannot adopt the diaxial conformation needed for the backside attack by the nucleophilic phosphorus atom. However, NH_3 elimination could still be feasible via assistance from a concerted 1,2-hydride shift (Scheme 5). This reaction is associated with a barrier (Figure 4) that is about 2 kcal/mol *lower* than that associated with NH_3 loss for the *trans*-diamine adduct (Figure 3). Therefore, it is somewhat surprising that elimination of NH_3 does not take place for the *cis* isomer.

A likely explanation for the different behavior of the isomeric diamines toward NH_3 loss from the adduct has to do with a competing reaction channel, elimination of an ethylene glycol molecule. This pathway dominates the reaction of *cis*-diamine with 1,3-dioxalane-2-phosphenium ion and is also significant for the *trans*-diamine (Table 1). Figure 4 shows a slice of the superimposed potential energy surfaces for the first few steps of the NH_3 and ethylene glycol loss pathways for both diamines. Addition of each amine to the ion (to form s and dd for *trans*- and *cis*-diamine, respectively; Figure 4) is followed by intramolecular proton transfer, which leads to formation of an ion with an acidic NH_3^+ group (u and jj; Figure 4; Schemes 4 and 5). From this point on, the pathways differ. The relative transition state energies for the first step of the two reaction channels appear to control the competition. Proton transfer from the NH_3^+ group to one of the oxygens attached to the phosphorus (*cis:* TS mm; Scheme 5; *trans*: TS oo, Scheme 3) leads to the pathway that ends with diol elimination. For the *cis* isomer, the transition state for this proton transfer (mm, Figure 4) is calculated to lie 26 kcal/mol *lower* in energy than the transition state that directly leads to NH_3-elimination (kk, Figure 4; Scheme 5). Therefore, the proton-transfer pathway is favored, and diol-elimination takes place predominantly. However, for the *trans* isomer, both reaction channels are kinetically favorable. The transition state involving proton transfer from the NH_3^+ group to an oxygen (oo; Scheme 3; on the way to ethylene glycol elimination), and the transition state corresponding to the first step of equatorial-to-axial conformation change (ff; Figure 3; Figure 4; eventually leading to NH_3 elimination), only differ by 5 kcal/mol in energy. Therefore,

(31) Miller, J. M. *J. Chem. Soc. A* **1967**, 828−834.
(32) Williams, D. H.; Ward, R. S.; Cooks, R. G. *J. Am. Chem. Soc.* **1968**, *90*, 966−972.

SCHEME 5



entrance to each reaction channel is nearly equally favorable, and both reactions are observed to occur.

Conclusions

A mass spectrometric method utilizing phosphenium ions as chemical ionization reagents has been developed for the analysis of diastereomeric cyclic diamines. The cyclic phosphenium ions, 1,3-dioxolane-2-phosphenium ion, 1,3-benzodioxole-2-phosphenium ion, and *o*-biphenylenephosphenium ion, are demonstrated to yield qualitatively different products for *cis*- and *trans*-1,2-diaminocyclohexanes. Elimination of an NH_3 molecule from the addition product of only the *trans* isomer is the distinguishing reactivity. Additional experimental studies were carried out to explore the mechanism of this interesting reaction, including examination of the reactions of mono- and diamines. A computational study involving transition-state calculations was conducted to explore the feasibility of different mechanistic pathways for the ammonia loss. The most feasible mechanism involves formation of a bond between the electrophilic phosphorus atom and an amino group of the trans isomer. A proton transfer between the nitrogens is followed by a ring flip to form the diaxial conformation. This orientation facilitates the backside attack from the now nucleophilic phosphorus atom to the electron-deficient carbon bonded to ammonia. This reactivity was not observed for the adduct of *cis*-1,2-diaminocyclohexane that undergoes exclusively a kinetically and thermodynamically more favorable ethylene glycol elimination.

All the cyclic phosphenium ions studied differentiate the *cis*- and *trans*-1,2-diaminocyclohexanes, but the *o*-biphenylenephosphenium ion offers the best differentiation. The latter ion does not have leaving groups (i.e., an ethylene glycol molecule) to compete with the NH_3 elimination.

This study, in addition to the previous work where $CH_3O-P^+-OCH_3$ was used to distinguish the *cis*- and *trans*-1,2-cyclohexanediols via a different reaction mechanism, demonstrates the utility of phosphenium ions as chemical ionization reagents for stereoisomer analysis by mass spectrometry. Earlier studies of chemical ionization reagents with diastereomeric substrates are mostly based on the relative basicities of the isomers which generally lead to only minor differences in ion abundances. However, phosphenium ions yield qualitatively different reaction products[9b] even with the difficult-to-distinguish *cis*- and *trans*-1,2-cyclohexanediols and *cis*- and *trans*-1,2-diaminocyclohexanes.[9b]

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Supporting Information Available: Cartesian coordinates and total computed energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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