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Stereospecific Ion–Molecule Reactions of Nucleophilic Gas-phase Reagents with Protonated Bifunctional Tetracyclic Terpene Epimers in the Triple Quadrupole Collision Cell

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Various nucleophilic reagents (methanol, acetone, ammonia and trimethylamine), characterized by different proton affinities, were introduced into the collision cell of the triple quadrupole as reactive gases for collisionally activated reaction (CAR) studies on stereoisomeric tetracyclic terpenes containing acetal and cyclobutanol functions. Under low-energy ($E_{lab} \sim 3$ eV) and multiple collision conditions, proton transfer from protonated terpenes (MH^+, selected by the first quadrupole) to the reagent gas was observed in each case, at varying efficiencies. At the same time, collision-induced decompositions (CIDs) were observed as competing processes in each tandem mass spectrum. For methanol, the reaction gas having the lowest proton affinity, CID processes were heavily favored, whereas CAR processes dominated only for trimethylamine (highest proton affinity) reacting with the *exo* terpene epimer. The latter reagent gas receives the proton in an exothermic transfer which is strikingly stereospecific. The underlying stereochemical effect is attributed not only to proton affinity differences which favor transfer from the *exo* epimer, but also to steric and kinetic factors which are evidently highly unfavorable for the *endo* configuration. © **1997 by John Wiley & Sons, Ltd.**

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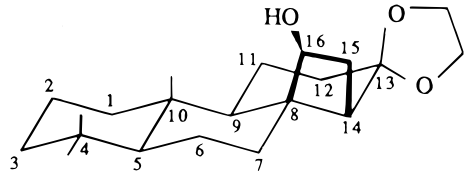
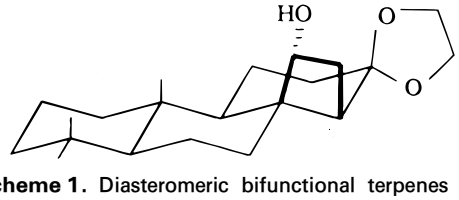
INTRODUCTION

The gas-phase reactivity of terpenes has been investigated from several different perspectives over the past few years.[1] In previous studies of tetracyclic bifunctional terpenes, we have shown that diastereomeric hydroxy-acetals (Scheme 1, *exo* **1** and *endo* **2** epimers) were protonated to different extents via ammonia chemical ionization (NH_3-CI) depending upon the hydroxyl stereochemistry.[2] Consecutive surface-induced dissociation–collision induced dissociation (SID–CID) mass spectrometric experiments were used to determine pathways of stereospecific decompositions (loss of the cyclobutanol ring as a neutral) for the two epimers. Those experiments demonstrated that the sites of attachment of ammonium ions leading to adduct formation were not strongly dependent upon hydroxyl stereochemistry. This contrasts sharply, however, with the highly stereochemistry-dependent forms of 'survivor' $[M + NH_4]^+$ adduct ions (i.e. those leaving the ion source), deduced from the highly differing fragmentation patterns (loss of C_2H_4O) of MH^+ ions formed from sequential decompositions of $[M + NH_4]^+$ which had left the ion source, as compared with MH^+ formed within the ion source. The selective formation of certain MH^+ species, either inside the ion source or upon CID of $[M + NH_4]^+$, which could decompose via stereospecific pathways for the two different epimers, served to explain the marked enhancement of relative peak intensities of diagnostic ions during these triple mass spectrometric (MS/MS/MS) experiments.[2]

Other high-pressure NH_3-CI experiments employing the same two stereoisomers established that they can



exo **1**



endo **2**

Scheme 1. Diasteromeric bifunctional terpenes which differ in the spatial orientation of the hydroxyl group.

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undergo ion–molecule reactions *via* competitive processes such as nucleophilic substitution (S_N2 or S_Ni)[3] and acetal aminolysis.[4,5] The stereospecific S_N2 pathway occurred in a regioselective manner at the C-16 hydroxyl group.[4,5] Nucleophilic substitution led to a protonated *exo* aminoacetal (regardless of initial hydroxyl configuration), whereas aminolysis produced ammonium-solvating hydroxyketone adducts.[6,7] The structures of these reaction products were deduced with the aid of low-energy collision-induced dissociation (CID) spectra obtained using a triple-quadrupole mass spectrometer (Nermag R30-10).[4,5] Furthermore, in favorable cases, assignment of the stereochemistry of the ammonium group introduced via nucleophilic substitution in the ion source can be provided by analysis of the CID spectrum. Alternatively, formation of $[M + NH_4 - H_2O]^+$ fragment ions from decompositions of $[M + NH_4]^+$ in the collision cell can be indicative of an S_Ni mechanism rather than the S_N2 pathway.[8]

In the past, collisionally activated ion–molecule reactions in triple quadrupoles, hybrid (BEqQ) instruments and four-sector magnetic instruments have been used for purposes such as natural product analyses,[9] isomer distinction,[10,11] the determination of threshold reaction energies[12–14] and H–D exchange measurements.[15–20] This paper focuses on the use of collisionally activated reactions (CARs) to investigate the effects of hydroxyl stereochemistry upon the reactivity of protonated forms of isomeric bifunctional terpene derivatives (Scheme 1) towards nucleophilic reagents. In our experiments, mass-selected, near-thermolyzed ($E_{lab} \approx 3$ eV), protonated molecules ($\mathbf{1}H^+$ and $\mathbf{2}H^+$) formed via NH_3-CI were exposed to various nucleophilic reagent gases in the collision cell of the triple quadrupole under multiple collision conditions. Reagent gases such as methanol, acetone, ammonia and trimethylamine were used to compare the specific reactivities of protonated terpenes as a function of the proton affinity of the reagent gas and in view of structural influences (steric effects) of the diastereomeric terpenes themselves. Stereochemical effects are scrutinized by considering transition-state barriers to proton transfer for the respective protonated epimers.

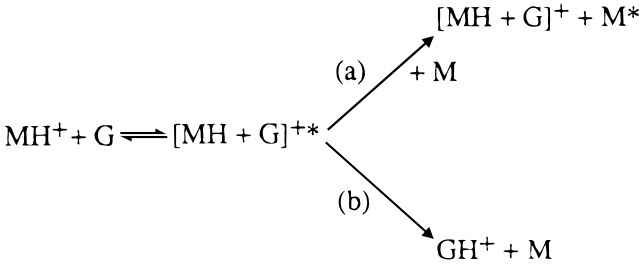
EXPERIMENTAL

All mass spectrometric experiments were performed on a Nermag (formerly of Rueil-Malmaison, France) R30-10 triple-quadrupole instrument. MH^+ ions were generated in the modified (small aperture) ion source under high-pressure CI conditions using either isobutane or ammonia as the reagent gas at source pressures of >0.1 Torr (1 Torr = 133.3 Pa), repeller voltage 0 V and electron energy 70 eV at a current of 0.035 mA. Reactive gases for CAR experiments were introduced into the second quadrupole until a pressure of 1 Torr was indicated on the collision cell housing pressure gauge. The collision energy was adjusted to ~3 eV (E_{lab}) using an independent polarization controller for the second quadrupole which was added as an instrumental modification to permit very low-energy collisions. The diastereomeric tetracyclic bifunctional terpenes utilized in this study were synthesized at the Ecole Polytechnique (Palaiseau, France).[21] Data acquisition for each pair of CAR spectra was accomplished within 4 min to maintain the instrumental conditions as constant as possible.

RESULTS AND DISCUSSION

CID spectra of $[M + NH_4]^+$ adducts can be used to deduce information pertaining to the relative proton affinities of M and NH_3.[22–24] By comparing the ratio of MH^+ to NH_4^+ obtained in fragment ion mass spectra of selected $[M + NH_4]^+$ for two similar compounds (e.g. with the same functional groups) having proton affinities close to that of ammonia, the relative proton affinities of the two compounds can be ranked. Moreover, in conventional NH_3-CI experiments, the efficiency of the proton transfer reaction from NH_4^+ to M can be directly dependent upon the exothermicity of the process.[20,24] This strategy can also be employed to assign the relative configuration of an epimer of unknown stereochemistry based on proton affinity (PA) differences. In considering the epimeric terpenes, the *endo* epimer may offer stabilization to a binding proton via chelation.[2] The proton affinities of both epimers are fairly close to that of ammonia and the MH^+/NH_4^+ ratio for the *endo* epimer in the fragment ion spectrum of $[M + NH_4]^+$ was observed to be larger than that for the *exo* epimer, in accordance with our ranking of the relative proton affinities.

Collision-induced decomposition spectra (argon) of MH^+ ions of the bifunctional terpenes revealed decompositions of the cyclobutanol and acetal moieties under low-energy conditions ($E_{lab} = 20$ eV).[2] The presence of the fragment ion at *m/z* 291 (in low abundance) is strictly diagnostic of the presence of the *exo* hydroxyl group at the C-16 carbon atom.[2] Higher energy collisions ($E_{lab} = 60$ eV) permit the formation of ions wherein the polycyclic terpene backbone has been altered. Reaction of selected MH^+ ions, having low kinetic energies (e.g. $E_{lab} \sim 3$ eV), with nucleophilic reagent gas (G) introduced in the collision cell can result in (a) formation of the adduct ion which is stabilized by additional collisions or (b) protonation of the reagent under conditions where the proton transfer is exothermic (or only slightly endothermic):



In the situation where a proton transfer reaction is very close to thermoneutral, production of adduct ions of the form $[MH + G]^+$ is observed, rather than proton transfer or nucleophilic substitution.

Endothermic proton transfer to nucleophilic gas-phase reagent in the collision cell

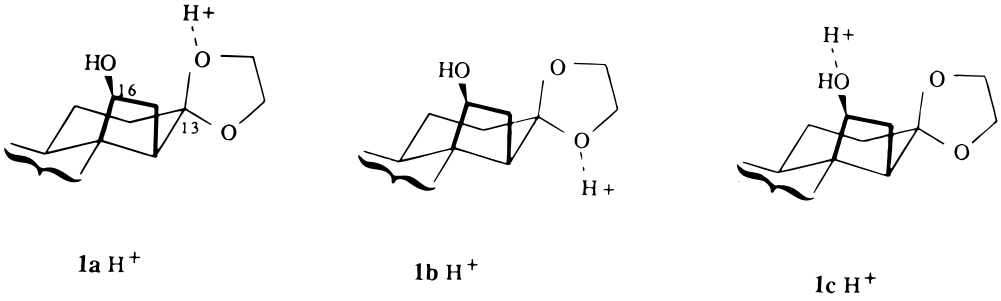
In a previous study,[2] it was shown that for the protonated bifunctional *exo* epimer (**1**, Scheme 1), owing to steric considerations the proton must be located on only one of the functions with no possibility of joint solvation. Upon NH_3-CI preparation, protonation took place mainly at the acetal sites [forms $\mathbf{1aH}^+$ and $\mathbf{1bH}^+$ (Scheme 2)] with a much lower level of protonation at the hydroxyl site (form $\mathbf{1cH}^+$). The latter tended to decompose *via* loss of C_2H_4O (forming *m/z* 291) or loss of H_2O (forming *m/z* 317), both from the cyclobutanol ring rather than the acetal ring.

A priori, under appropriate conditions, endothermic proton transfer can take place from both the hydroxyl and the acetal sites to reagents having proton affinities lower than those of cyclic alcohols. However, the proton affinity of the hydroxyl group [$PA_{ROH} = \sim 800$ kJ mol^{-1} (Ref. 25)] from minor form $\mathbf{1cH}^+$ is much lower than that of the acetal group from major forms $\mathbf{1aH}^+$ and $\mathbf{1bH}^+$,[2] making proton transfer from $\mathbf{1cH}^+$ much more efficient. Consequently, without the possibility of quantifying the distribution of ion structures present, it is very likely that the proton transferred in an endothermic reaction would originate from the $\mathbf{1cH}^+$ form rather than the $\mathbf{1aH}^+$ or $\mathbf{1bH}^+$ forms.

In the presence of methanol (PA = 761 kJ mol^{-1},[25] Fig. 1) or acetone (PA = 823 kJ mol^{-1},[25] Fig. 2), reagent gases possessing lower proton affinities than the hydroxy-acetal isomers, little propensity for endothermic proton transfer *via* CAR was noted. Instead, mainly collision-induced decompositions were observed producing certain fragment ions diagnostic of hydroxyl stereochemistry as noted previously.[2] Proton transfer to acetone and methanol forming the respective protonated monomers (and dimer, in the case of acetone) took place at very low efficiencies under our experimental conditions. Endothermic proton transfer reactions thus did not provide an obvious means of distinguishing stereoisomers, beyond what was already observed *via* CID using inert monoatomic gases.[2] Increasing the collision energy by 2–3 eV in the hope of favoring endothermic bimolecular processes actually led only to enhanced CID processes.

In comparing CID processes displayed in low-energy tandem mass spectra (E_{lab} = 3 eV, multiple collisions with nucleophilic gas) and MS/MS spectra at 20 eV (multiple collisions with inert Ar),[2] the following differences were noted:

1. For 3 eV collisions of MH^+ with nucleophilic gas, the relative abundances of fragment ions representative of higher energy skeletal fragments (i.e. those appearing between *m/z* 70 and 200) and those representative of lower energy substituent group decompositions (i.e. between *m/z* 230 and 280) are similar to the relative abundances of equivalent ions obtained from 20 eV collisions with Ar.



Scheme 2. Proposed structures of protonated *exo* (**1**) bifunctional terpene.

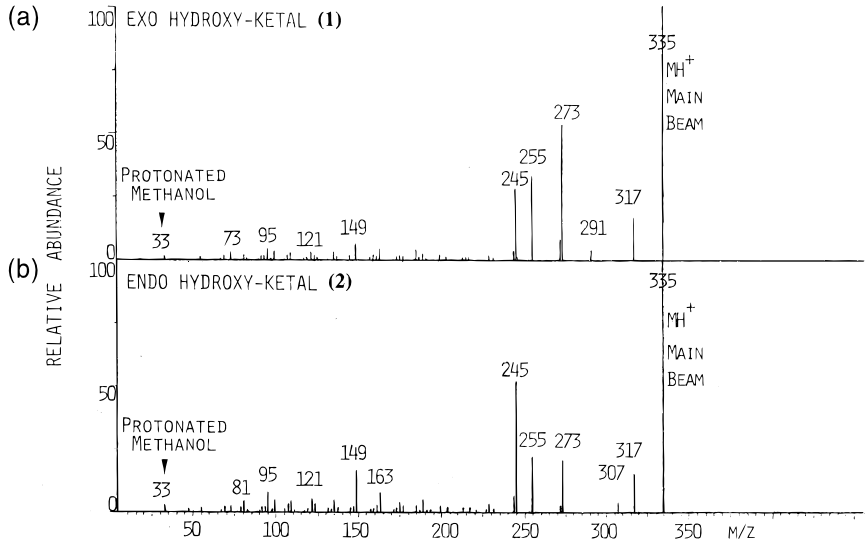


Figure 1. Collisionally activated reaction mass spectra of MH^+ (*m/z* 335) from (a) *exo* (**1**) and (b) *endo* (**2**) hydroxy-acetal terpene epimers with methanol as the reaction gas in the collision cell of the triple quadrupole.

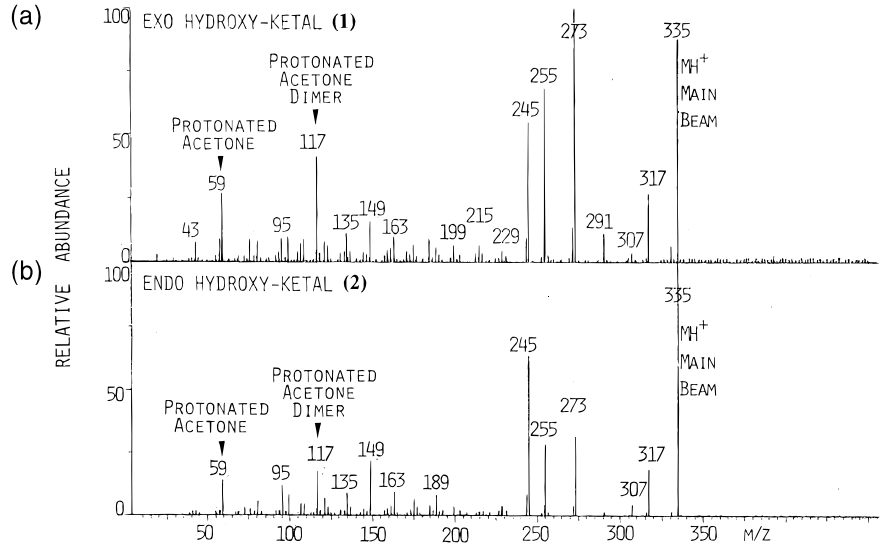


Figure 2. Collisionally activated reaction mass spectra of MH^+ (*m/z* 335) from (a) *exo* (**1**) and (b) *endo* (**2**) hydroxy-acetal terpene epimers with acetone as the reaction gas in the collision cell of the triple quadrupole.

2. The *m/z* 291 fragment ion, diagnostic of the *exo* epimer, appears in a higher relative abundance in the CAR spectra [Figs 1(a) and 2(a)] than in the 20 eV CID spectrum. For both epimers, the fragment ion at *m/z* 317 is significantly enhanced in CAR spectra relative to CID spectra.
3. The relative abundances of the parent ions (*m/z* 335) selected as the main beams in the MS/MS mode are lower in reactive collision experiments (Figs. 1 and 2) as compared with 20 eV collisions with Ar.

Similarities in the relative abundances of fragment ions (point 1 above) suggest that the internal energy uptake by the protonated terpenes was approximately the same during 3 eV collisions with methanol or acetone, as compared with 20 eV collisions with Ar. This apparent contradiction, i.e. the lack of increased fragmentation at augmented collision energy, can be rationalized using the model developed by Orlando and co-workers[26–28] for peptides and long-chain compounds building upon assumptions proposed by Douglas,[29] which considered that at low collision energies long-lived collision complexes are produced. The opportunity for excitation energy exchange increases with the lifetime of this ion–molecule complex.[30] This means that a better collisional excitation efficiency takes place in a narrow energy window at lower energies than observed from direct CID (monoatomic target gas) or from impulse–spectator collision processes (occurring at higher collision energies to polyatomic ions). In the model modification proposed by Orlando and co-workers[26–28,30], the lifetime of the produced ion–molecule complex is considered to be increased during endothermic proton transfer processes; this reasoning can also apply to our experiments.

The increases in relative ion abundances of the *m/z* 291 and 317 fragment ions from the *exo* epimer in reactive collision experiments noted in point 2 above are unexpected if the $\mathbf{1c}H^+$ form is indeed present in only very minor abundance among 'survivor' $\mathbf{1}H^+$ ions leaving the ion source. Moreover, the relative abundances of these fragment ions could not be augmented by increasing the collision energy, which implies that the parent ion is predominately in the form of $\mathbf{1a}H^+$ or $\mathbf{1b}H^+$. Nevertheless, one possible rationalization for the increase in the relative abundances of these high-mass ions in CAR spectra relative to CID spectra is based upon the previous model describing the low-energy collision complex and also based upon the reversibility of the proton migration step (enthalpy dependent). In the ion–molecule complex, we consider first that endothermic proton transfer from the protonated hydroxy-acetal to the introduced nucleophilic neutral can occur rapidly compared with ion–molecule complex dissociation. Second, by exothermic proton transfer from GH^+ back to **1**, within the lifetime of the complex, it is possible to produce both protonated acetal (e.g. $\mathbf{1a}H^+$) and protonated hydroxyl ($\mathbf{1c}H^+$) forms in competition according to the following equation:

$$\mathbf{1}a\mathbf{H}^+ + \mathrm{G} \rightarrow \{\mathbf{1}a\mathbf{H}^+ + \mathrm{G}\}^* \leftrightharpoons \{\mathbf{1} + \mathrm{GH}^+\}^* \rightarrow \{\mathbf{1}c\mathbf{H}^+ + \mathrm{G}\}^* \rightarrow \mathbf{1}c\mathbf{H}^+ + \mathrm{G}$$

Third, competitive dissociations of the $\mathbf{1c}H^+$ ion lead to both the diagnostic $[\mathbf{1c}H - C_2H_4O]^+$ ion at *m/z* 291 and the $[\mathbf{1c}H - H_2O]^+$ ion at *m/z* 317.[2] These losses are likely to occur at faster rates than decompositions leading to fragments at *m/z* 273, 255 and 245 from either $\mathbf{1a}H^+$ or $\mathbf{1b}H^+$. A consequence of this assumed reversibility of the proton transfer is thus the ability to transfer indirectly the proton from the acetal to the hydroxyl site for the *exo* epimer, which is sterically not possible on a unimolecular basis.[2] Relocation of the proton on to the hydroxyl group could thus be responsible for subsequent decompositions leading to the observed enhancement of *m/z* 291 and 317 fragment ions for the *exo* epimer. This situation contrasts with that of the *endo* epimer where the proton is chelated by the two nucleophilic groups.

Finally, the decrease in the relative abundances of parent ions during reactive collision experiments (point 3) can be rationalized by considering that for ion–molecule reactions, higher collision cross-sections are

obtained when using polyatomic molecules with polarizable substituents (e.g. bearing lone-pair electrons) as compared with equimolar quantities of inert collision gas (e.g. noble gas atoms). Statistically, at a given pressure, the number of efficient collisions is thus increased for such polyatomic species.

Exothermic proton transfer to nucleophilic gas-phase reagent in the collision cell

Diastereomeric protonated hydroxy-acetals exhibited a much greater tendency towards proton transfer to trimethylamine whose high proton affinity [PA = 942 kJ mol^{-1} (Ref. 25)] makes this an exothermic transfer. For this process, a spectacular stereochemical effect (Fig. 3) favoring proton transfer from the protonated *exo*-hydroxy-acetal epimer ($\mathbf{1}H^+$) to trimethylamine (forming the protonated monomer at *m/z* 60) was observed. Relative to the parent MH^+ main beam, the abundance of this ion was more than 100 times greater for the *exo* than for the *endo* epimer under comparable conditions. Only the *endo* epimer can offer chelation of the ionizing proton by the *endo*-hydroxyl group and the axial oxygen of the acetal moiety, hence the added stability obtained by this chelated form of MH^+ is believed to be largely responsible for the decreased ability to transfer the proton to trimethylamine. In addition, chelation fixes the C-ring in a quasi-chair conformation, which may also severely restrict easy nucleophilic approach to the chelated proton. For the *exo* epimer, if the ionizing proton is attached to the acetal group in the preferred configuration ($\mathbf{1a}H^+$ or $\mathbf{1b}H^+$), this proton is less tightly bound and any steric constraints hindering the approach of nearby neutrals are less severe as compared with the *endo* epimer because the rate constants for transformations of boat and chair conformations are relatively rapid. If attached to the *exo*-hydroxyl group ($\mathbf{1c}H^+$), transfer of the proton is even more exothermic and facile, owing to the lower PA of this site.

Compared with the respective protonated monomers, the protonated dimer of trimethylamine (*m/z* 119, Fig. 3) was present in far lower abundance than that of acetone (*m/z* 117, Fig. 2). This may be attributed to the relatively large internal energy of the trimethylamine dimer due to the larger exothermicity of the proton transfer reaction giving rise to its formation. If the excess energy of proton transfer was indeed carried by the ionizing proton, a higher level of vibrational excitation of the trimethylamine dimer would result, causing the breakage of hydrogen bonds which could otherwise hold the dimer together, as happens more efficiently for acetone. Parenthetically, no nucleophilic substitution of trimethylamine at the hydroxylic group site (to form *m/z* 376) was detected, thus corroborating the exothermicity of the proton transfer reaction.

It should be noted that the intermediate adduct ion $[M\cdots H\cdots(CH_3)_3N]^+$ does not appear in the CAR spectrum of either epimer. The analogous ions $[M\cdots H\cdots CH_3OH]^+$ and $[M\cdots H\cdots(CH_3)_2CO]^+$ were also absent from the endothermic proton transfer reactions (see the previous section). Kinetic considerations must be responsible for the absence of these $[M\cdots H\cdots G]^+$ ions. Relatively fast decompositions of ions of this form will yield either MH^+ or GH^+ according to the respective PA values. If the PA differences between M and G are rather large for each of these systems, then the energy level for the formation of one of the products (either $GH^+ + M$ (exothermic transfer case) or $MH^+ + G$ (endothermic transfer case)) is likely to be not far above the energy level for formation of the $[M\cdots H\cdots G]^+$ adduct, hence, dissociation of the complex is likely to occur.

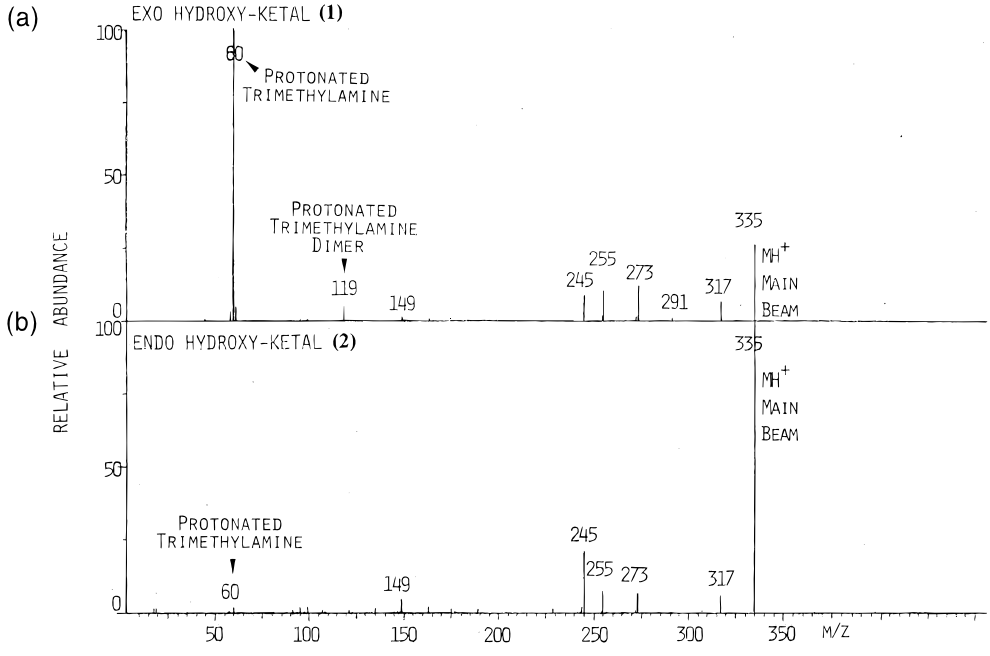


Figure 3. Collisionally activated reaction mass spectra of MH^+ (*m/z* 335) from (a) *exo* (**1**) and (b) *endo* (**2**) hydroxy-acetal terpene epimers with trimethylamine as the reaction gas in the collision cell of the triple quadrupole.

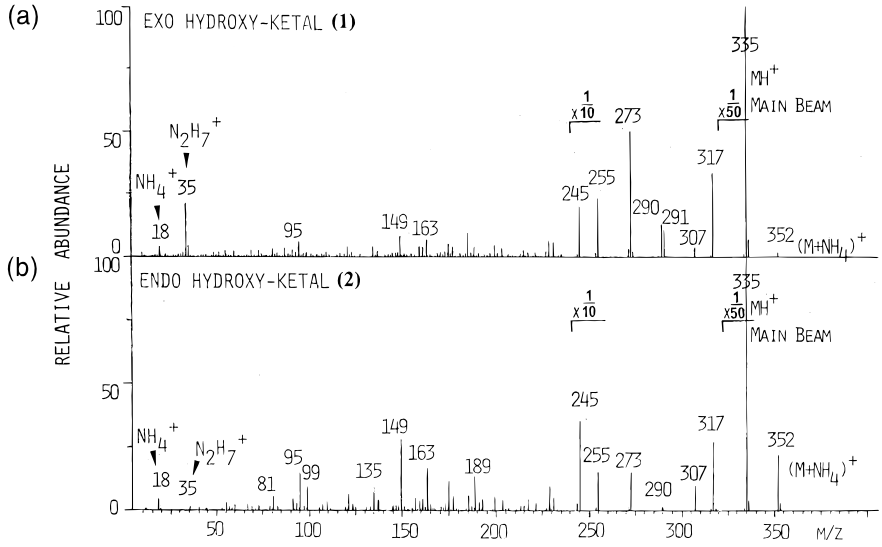


Figure 4. Collisionally activated reaction mass spectra of MH^+ (*m/z* 335) from (a) *exo* (**1**) and (b) *endo* (**2**) hydroxy-acetal terpene epimers with ammonia as the reaction gas in the collision cell of the triple quadrupole.

Thermoneutral (approximately) proton transfer to nucleophilic gas-phase reagent in the collision cell

(Use of ammonia [PA = 846 kJ mol^{-1} (Ref. 25)] as the collision gas presents the intermediate situation where the proton affinity of the hydroxy-acetal molecule is only slightly different from that of the reactive gas. In this situation, where proton transfer from MH^+ to NH_3 is close to thermoneutral, the adduct species $[M\cdots H\cdots NH_3]^+$ (*m/z* 352) is indeed observed in the CAR spectrum (Fig. 4). Relative to the two previous cases (highly endothermic or highly exothermic proton transfers), the depth of the potential well is larger for the thermoneutral transfer (i.e. a greater potential energy difference exists between the stablilized adduct ion and the lowest energy protonated species plus neutral).[31] The exact thermochemistry, however, depends upon the slightly varying proton affinities of the specific nucleophilic site holding the proton on the epimer substrate (M) and the possibility for the low-energy collision complex to convert, for example, the $1aH^+$ form to the $\mathbf{1c}H^+$ form, as noted previously. These phenomena can explain the variation in the abundances of the produced NH_4^+ and $N_2H_7^+$ species as a function of hydroxyl group stereochemistry. Notably, $N_2H_7^+$ is markedly enhanced for the exo epimer having the lower proton affinity. The observation of a very prominent $(\mathbf{2}\cdots H\cdots NH_3]^+$ peak suggests a particularly large potential well, implying that PA_{NH_3} is very close to $PA_{\mathbf{2}}$. This conclusion, when combined with the above information, is consistent with a PA_{NH_3} just slightly larger than $PA_{\mathbf{1}}$.

This same experiment was subsequently repeated, but this time starting with a different bifunctional terpene derivative, the hydroxy-*ketone* analog, where the acetal group at C-13 (Scheme 1) has been replaced with a

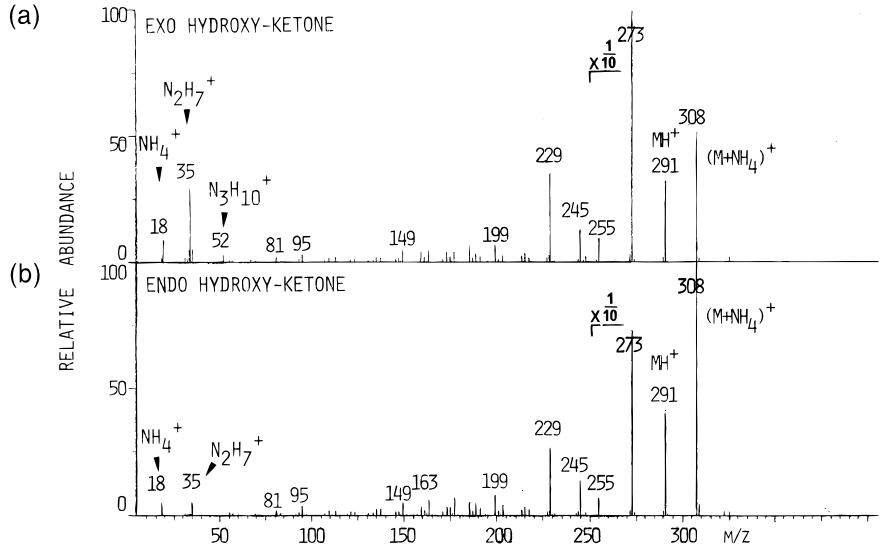


Figure 5. Employing the hydroxy-*ketone* analogs of the terpene epimers (ketone group at C-13 in place of the acetal group shown in Scheme 1), collisionally activated reaction mass spectra of MH^+ (*m/z* 291) from (a) *exo*- and (b) *endo*-hydroxyl configurations with ammonia as the reaction gas in the collision cell of the triple quadrupole.

ketone function. As shown in (Fig. 5), the relative abundances of $[M\cdots H\cdots NH_3]^+$ adduct species were significantly higher for these analogs relative to the hydroxy-acetal molecules, indicating that their proton affinities are even closer to that of ammonia than the hydroxy-acetal analog. In addition, $[M\cdots H\cdots NH_3]^+$ was significantly more stable towards decomposition for the *endo* hydroxy-ketone epimer than for the *exo* epimer, as evidenced by the larger $[M\cdots H\cdots NH_3]^+/[MH^+]$ ratio. The ratio of peaks $[MH^+]/[NH_4^+ + N_2H_7^+]$ for the *endo* epimer was also larger than the comparable ratio observed for the *exo* epimer, indicating that the PA of the *endo* hydroxy-ketone epimer is larger than that of the *exo* variety, corroborating what was observed for the hydroxy-acetal molecules

CONCLUSION

Collisionally activated reactions in the triple-quadrupole collision cell have been used to probe stereochemical effects with regard to the ease of proton transfer reactions in the gas phase. The reticence of the *endo*-hydroxy-acetal epimer towards proton transfer is attributed to an enhanced stabilization of $2H^+$ due to solvation of the ionizing proton by both the *endo*-hydroxyl group and the axial oxygen of the acetal group. Chelation of the ionizing proton by the *endo*-hydroxyl group and the axial oxygen of the acetal group fixes the C-ring in a quasi-chair conformation, which may severely restrict easy approach to the solvated proton by nucleophilic gas-phase reagents. The almost total absence of proton transfer from this *endo* form is considered to be due to a kinetic effect involving the presence of a large intrinsic barrier for such proton transfer. This barrier is proposed to correspond to the transition state for isomerization of the constrained quasi-chair conformation of the C-ring, to the boat conformation considered to be more amenable to proton transfer. It appears that a change of geometry of this type, which involves breakage of a hydrogen bond to the ionizing proton, is necessary to permit access of the nucleophilic reagent to the proton. The pathway from the constrained quasi-chair conformation to the boat conformation involves passage through an unfavorable transition state wherein degrees of freedom are lost. This results in a high intrinsic barrier for this isomerization and, consequently, the possibilities for proton transfer for the protonated *endo* epimer are minimal. In contrast, for the *exo* epimer, the ionizing proton is less tightly bound, and any steric constraints limiting accessibility of nucleophilic reagent gases to this proton are much less severe. Moreover, the rate constants for transformations of boat and chair conformations are relatively rapid, further facilitating proton transfer from this epimer.

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