STEREOCHEMISTRY OF ORGANIC IONS IN THE GAS PHASE: A REVIEW*

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The stereochemistry of organic ions in the gas phase can be regarded from two different points of view: (i) stereoselectivity in ion formation and (ii) stereospecificity of ion fragmentations. Fast ionization by electron or photon impact shows little stereoselection. Differences in the ionization energies and cross sections between stereoisomers are generally small, save for a few exceptions. Proton or larger ion transfer, as employed in chemical ionization mass spectrometry, gives more possibilities for stereoselection. Bi- or polyfunctional molecules can capture the proton in a hydrogen-bond stabilized $[M + H]^+$ ion, which is feasible only with a favourable spatial orientation of the chelating groups. Adduct ions $[M + R]^+$ can also be formed stereoselectively. The use of a chiral ionizing medium adds a new dimension, since enantiomers can be distinguished, or even independently identified. The stereochemistry of even-electron cations in the gas phase is most pronounced with polyfunctional species. The stereochemical behaviour is ruled by two reactivity principles, *i.e.* the geometry-dependent stabilization of $[M + H]^+$ ions by chelation, and the anchimeric assistance by neighbouring groups in elimination of small molecules (water, ammonia, alcohols, acetic acid, *etc.*). The stereochemistry of odd-electron cations seems to be governed by three principles, *i.e.* the thermochemistry of decompositions proceeding with simple-bond cleavage, stereoelectronic effects on bond dissociations in the presence of a control orbital, and long-range interactions resulting in transfer of a hydrogen atom or a larger group. All these three reaction classes have limited areas of application. The stereochemistry of even-electron anions has been developing rapidly. The reactivity of gas-phase anions finds numerous analogies in their

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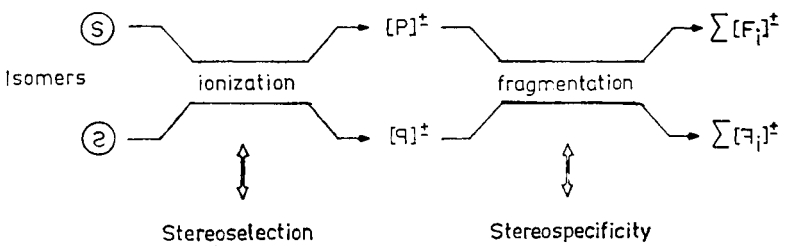
chemistry in solution, *e.g.* hydride transfer reactions and nucleophilic substitution. The applications of mass spectrometry to configurational assignment and structure elucidation remain restricted to selected classes of organic compounds.

1. INTRODUCTION

The chemistry of organic ions in the gas phase has evolved in the past two decades into a bushy, though little special branch of organic chemistry. Although the gas-phase and condensed-phase ionic reactions share some common features due to intrinsic electronic properties of the ions[1], the former reactions distinguish themselves by the absence of counterions, solvent molecules and intermolecular energy exchange, with unimolecular decompositions. A driving force for the exploration of otherwise exotic ionic reactions in the gas phase has been provided by analytical applications of mass spectrometry. With the advent of new instrumental techniques it has become possible to study reaction kinetics and energetics and to provide qualitative analysis of ionic and neutral products of unimolecular decompositions and ion–molecule reactions occurring in the gas phase.

The stereochemistry of organic ions in the gas phase has been a very active area of research, as documented by numerous reviews[1-6], and a recent comprehensive treatise[7]. The question of stereochemical behaviour of gaseous organic ions has been centered about the possibility of discerning two or more stereoisomers by their reactivity in unimolecular decompositions (as observed in mass spectra), or in ion–molecule reactions. In this paper we will follow a slightly different line. The whole process of stereodifferentiation may be divided into two more or less interconnected steps (Scheme 1). In the first step we start with a pair or an ensemble of stereoisomeric



SCHEME 1

molecules which are ionized. The interaction of the stereoisomer with the ionizing medium (an energetic electron, photon or a heavier charged species) may itself lead to stereodifferentiation. By analogy with organic chemistry this may be called stereoselective ionization. The chief advantage of ionization as a means of stereodifferentiation follows from the fact that one starts with fixed, non-interconverting structures, so that any isomerization following the ionization may be disregarded.

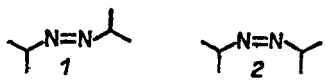
In the second step, the ions produced from stereoisomers may display different reactivity in unimolecular decompositions or ion–molecule reactions, leading to stereospecificity. One of the main obstacles to observing stereospecific fragmentations is the occurrence of non-specific isomerizations that can destroy the structural and stereochemical integrity of the isomers prior to a stereodifferentiating decomposition. The stereoselective ionization and stereospecific reactions will be treated separately.

2. STEREOSELECTIVE IONIZATION

Ionization of organic molecules with energetic electrons or photons to yield cation-radicals provides two experimentally accessible parameters that can be employed for stereodifferentiation, that is, the ionization energy IE and the relative ionization cross section σ. A large number of ionization energies have been amassed from photoelectron spectra and electron impact measurements[8–50]. Tables I and II summarize the IE values for (*E*, *Z*) geometrical isomers of di-, tri-, and tetrasubstituted olefins. Vertical IE's are shown wherever the data come from photoelectron spectra.

With the exception of 1-trimethylsilyl-2-phenylethers[44], the relative geometry of the substituents on the carbon–carbon double bond does not give rise to major differences in the ionization energies of isomers. Typically, the differences are of the same order as the experimental errors (0·02–0·1 eV). Moreover, great caution should be taken when comparing data obtained with different techniques, or even on different instruments.

Significantly different IE's have been reported for (*E*)- and (*Z*)-2,5-dimethyl-3,4-diazahex-3-enes(*1*, *2*)[51]. In this case, the highest occupied molecular orbital (HOMO) is of an *n* type (b_2 for *2* and a_g for *1*)[51] because of the splitting of two interacting *n*-orbitals at the nitrogen atoms. The splitting has been shown to increase with the bond angle C—N=N, which in turn has been calculated to be larger in the (*Z*)-isomer, possibly because of steric interaction of the isopropyl groups.



IE_{vert} 8.47 eV 8.24 eV

Very little is known about the relative ionization cross sections of geometrical isomers[52,53]. A recent example[37] shows a significant difference in ionization cross sections for (*E*)- and (*Z*)-1-propen-1-ols (Fig. 1), which manifests itself as different slopes of the ΔI *vs* *E* curves near the threshold of ionization. The effect has been rationalized by different populations of rotamers in the (*E*)-isomer which prefers a *syn*-conformation in the neutral molecule whereas an *anti*-conformation in the

TABLE I

Ionization energies of (*E*)- and (*Z*)-olefins R^1—CH=CH—R^2

R^1	R^2	Ionization energy, eV		Reference
		(*E*)	(*Z*)	
CH_3	CH_3	9·116	9·124	8, 9
		9·12	9·12	8
		9·122	9·124	10
		9·37	9·36	10
		9·32	9·29	10
		9·13	9·13	11
CH_3	C_2H_5	9·23	9·22	10
		9·04	9·04	10
CH_3	n-C_3H_7	8·97	8·95	12
CH_3	i-C_3H_7	8·97	8·98	12
CH_3	$CH{=}CH_2$	8·67	8·64	13, 14
		8·61	8·60	15—17
CH_3	$C{\equiv}CH$	9·05	9·11	18
		9·11	9·17	19
CH_3	$CH_2CH{=}CH_2$	8·98	9·04	20
CH_3	(*E*)-CH=CH—CH_3	8·26	8·25	13, 20
		8·09	8·26	14, 15
CH_3	(*Z*)-CH=CH—CH_3	8·25	8·18	13
CH_3	i-C_4H_9	8·92	8·92	12
CH_3	t-C_4H_9	8·91	8·92	12
CH_3	n-C_6H_{13}	8·90	8·90	21
$HC{\equiv}C$	$C{\equiv}CH$	9·07	9·10	22
$HC{\equiv}C$	n-C_4H_9	8·87	8·91	18
$CH_2{=}CH$	$CH{=}CH_2$	8·27	8·30	23
		8·29	8·31	24
		8·30	8·32	15
$CH_2{=}CH$	C_6H_5	7·95	8·39	14, 25
C_2H_5	C_2H_5	8·97	8·95	12
C_2H_5	n-C_4H_9	9·03	9·05	26
C_2H_5	n-C_5H_{11}	8·84	8·84	21
C_2H_5	n-C_6H_{14}	9·00	9·01	26
		8·83	8·83	21
n-C_3H_7	n-C_3H_7	9·01	9·03	26
n-C_3H_7	n-C_4H_9	8·81	8·80	21
n-C_3H_7	n-C_5H_{11}	8·97	8·97	26
		8·78	8·78	21
i-C_3H_7	i-C_3H_7	8·84	8·85	12
$CH_3C{\equiv}C$	n-C_4H_9	8·46	8·46	18
cyclo-C_3H_5	cyclo-C_3H_5	7·70	7·72	27

TABLE I
(*Continued*)

R^1	R^2	Ionization energy, eV (*E*)	Ionization energy, eV (*Z*)	Reference
n-C_4H_9	n-C_4H_9	8·76	8·77	26
n-C_4H_9	t-C_4H_9	8·89	8·95	28
		8·74	8·70	12
t-C_4H_9	t-C_4H_9	8·21	8·25	56
F	F	10·21	10·23	29
		10·38	10·44	30
Cl	Cl	9·80	9·80	31, 32
Br	Br	9·55, 9·47	9·63	33, 34
		9·30	9·32	35
		9·55	9·63	32
I	I	8·92	8·94	36
OH	CH_3	8·64	8·70	37
OH	$CH{=}CH_2$	8·51	8·47	38, 39
CN	CN	11·16, 11·15	11·15	40, 41
C_6H_5	C_6H_5	7·70	7·80	42
CH_3S	SCH_3	7·85	7·80	43
$(CH_3)_3Si$	C_6H_5	7·89	8·19	44
$(CH_3)_3SiCH_2$	C_6H_5	7·61	7·77	44
$-CH_2CH_2CH{=}CHCH_2CH_2-$		8·7	8·9	45, 46
$-(CH_2)_8-$		8·91	8·97	47
$-(CH_2)_9-$		8·73	8·65	47
$-(CH_2)_{10}-$		8·74	8·78	47
$-(CH_2)_{13}-$		8·83	8·80	47

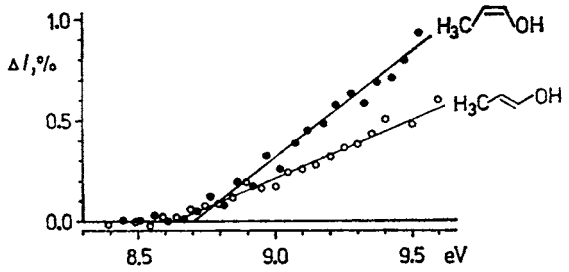


FIG. 1
Ionization efficiency curves of (*E*)- and (*Z*)-1-propen-1-ol

ion*. This makes vertical ionization in the (*E*)-isomer less probable than in the (*Z*)-isomer, in which the *syn*-conformations are disfavoured because of steric interaction of the hydroxyl group with the methyl[37]. It should be mentioned that the fonization energies of the isomeric 1-propen-1-ols are too close to permit stereodifierentiation.

Ionization energies of diastereoisomers can also depend on the relative configuration at chiral centers. This occurs especially if a strong electronic interaction in one isomer is removed or weakened upon ionization. For instance, through-space interaction of occupied π-orbitals in a non-conjugated diene possessing suitably positioned double bonds may result in orbital splitting[54], which increases the energy of the HOMO. Since the proximity of the interacting orbitals is forced by the molecular σ-bond framework, the relative configuration at the sp^3 centers can have an impact on the ease of ionization from the HOMO. This has been observed for stereoisomeric tetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-dienes (*3*, *4*)[55] and tricyclo[4.2.0.0^{2,5}]octa-3,7--dienes (*5*, *6*)[54,57]. A similar interaction of Walsh orbitals in the cyclopropane ring with a π-orbital leads to a higher HOMO and a decreased ionization energy in *trans*--isomers of tricyclo[3.2.1.0^{2,4}]oct-6-enes (*7*, *8*)[58], and tricyclo[6.1.0.0^{4,6}]non-2-enes (*9*, *10*)[59]. For interaction of two cyclopropane rings see ref.[60]. Interaction of lone-pair and aliphatic derivatives sometimes leads to observable conformational effects in photoelectron spectra[61–67] (for a review see ref.[95]). Also, steric interactions between σ-bonds in bridged systems can cause observable differences in the ionization energies of stereoisomers[68].

TABLE II

Ionization energies of (*E*)- and (*Z*)-tri- and tetrasubstituted olefins $R^1R^2C{=}CR^3R^4$

R^1	R^2	R^3	R^4	Ionization energy, eV		Reference
				(*E*)	(*Z*)	
i-C_3H_7	CH_3	CH_3	i-C_3H_7	8·24	8·27	48
C_2H_5	CH_3	C_2H_5	CH_3	8·16	8·17	12
$CH_2{=}CH$	CH_3	CH_3	H	8·47	8·39	13
$CH_3C{\equiv}C$	C_2H_5	CH_3	H	8·23	8·28	18
CF_3	F	F	CF_3	11·55	11·46	28, 49
$(CH_3)_2As$	CF_3	CF_3	H	8·71	8·61	50

* In a *syn*-conformation the dihedral angle between the $C_{(1)}$—$C_{(2)}$ and O—H bonds is 0°, in an *anti*-conformation this angle is 180°.

The presence of a hydrogen bond in one stereoisomer and its absence in the other can lead to significant and predictable differences in the corresponding ionization energies. The factors that stabilize the hydrogen bond in molecules, *i.e.* the electro-

IE, eV	8.08	8.46	8.90	9.08

IE, eV	8.90	9.05	9.0	8.5

static and exchange interactions[69], are dependent on the donating ability of the donor orbital, which often represents the HOMO. Upon electron removal, the donor properties of the HOMO are diminished which leads to a loss of hydrogen-bond stabilization in the cation-radical. The neat result is a higher ionization energy of the stereoisomer that can develop a hydrogen bond in the neutral molecule, compared with that of a stereoisomer in which the hydrogen bond is precluded on geometrical grounds. Hydrogen bonding effects on ionization energies have been studied systematically by Brown[70–73] and a few other groups[64,74,75]. Differences in ionization energies have been found for stereoisomeric 2-amino- and 2-dimethylaminocyclopentanols[70], 2-bromocyclopentanols[64], 2-amino- and 2-dimethylaminocyclohexanols[71], 2-methoxycyclopentanols[71], 2-hydroxy-3-dimethylaminobicyclo[2.2.1]heptanes[75], 7-hydroxybicyclo[2.2.1]hept-2-enes[72,74], 2-hydroxybicyclo[2.2.2]oct-5-enes[73], 9-hydroxybicyclo[4.2.1]non-3-enes[73], 9-hydroxybicyclo[4.2.1]nona-2,4-dienes[73] and 9-hydroxy-1,2,3,4-tetrahydro-1,4-methanonaphtalenes[73]. The interaction of an allylic heteroatom with the double bond has also been found to be geometry-dependent[76,77].

In the absence of strong through-space orbital interactions or hydrogen bonds the ionization energies exert little sensitivity to molecular geometry in diastereoisomers. Nearly indiscernible ionization energies have been reported for a number of molecular systems, *e.g.* 1,2-dimethylcyclopropanes[78], 1,2-dimethylcyclopentanes[79], dimethylcyclohexanes[79–81], substituted cycloheptanes[79], di-, tri-, and tetramethyl-1,3-oxathianes[82], bicyclo[4.3.0]nonanes[83,84], 1,2-dimethylcyclopentanes[79], dimethylcyclohexanes[79–81], substituted cycloheptabicyclo[4.4.0]decanes[8,84,85] and their methyl derivatives[86], bicyclo[4.3.0]nona-3,7-dienes[87] and their 8-(N-

-pyrrolidyl) derivatives[88], 7-oxabicyclo[4.3.0]nonanes[89], 3-methoxy-2,5-dioxabicyclo[4.4.0]decanes[90], vicinal bis(ethynyl)cyclopropanes, oxiranes and thiiranes[22], and other systems[91-96].

In summarizing this section, it is obvious that the ionization energy measurements, by virtue of their limited accuracy, sample and time consumption and relative insensitivity to molecular geometry, are not very suitable for differentiation of stereoisomers.

3. STEREOSELECTIVE ION–MOLECULE REACTIONS

In contrast to interactions of molecules with energetic electrons or photons, the reactions with thermal ions in the gas phase have limited rate constants[97], enabling thus step-wise or time-resolved bond reorganization when passing from the reactants to products. This is shown schematically in a hypothetical energy-profile diagram depicting a proton transfer between a Brønsted acid AH^+ and the substrate molecule B (Fig. 2). The reaction can be characterized by two parameters; (i) the exothermicity given by the difference in the proton affinities $\Delta H_r = PA(B) - PA(A)$ or gas-phase basicities* and (ii) the rate constant of the overall process, k_{exp}.**

Although both these quantities are interrelated, that is, the rate constant k_{exp} increases monotonously with the reaction exothermicity up to the collision rate limit[100], k_{exp} is a function of both ΔH_r^0 and ΔS_r^0, so entropy-related effects may be, and also have been observed. From a stereochemical point of view, the proton transfer from an acid AH^+ to diastereoisomeric molecules B_1 and B_2 can be stereoselective, if the corresponding rate constants differ to some extent. This is depicted schematically in Fig. 3 which shows the dependence of the logarithm of the reaction efficiencies*** for B_1 and B_2 on the strength of the acid AH^+. With sufficiently strong acids, $PA(A) \ll PA(B_1), PA(B_2)$, protonation of both stereoisomers would occur with an equally high probability, so there would be little or no stereoselection. In contrast, if the PA(A) is chosen so that $PA(B_1) < PA(A) < PA(B_2)$, the more basic stereoisomer B_2 will be protonated preferentially.

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* The proton affinity is defined as the enthalpy change in the reaction $B + H^+ \rightarrow BH^+$. The gas-phase basicity (GB) is derived from the Gibbs energy change in the reaction $AH^+ + B \rightleftarrows BH^+ + A$, $GB(B) = GB(A) + \Delta G_r^0$ (refs[98,99]).

** For the reaction:

$$AH^+ + B \underset{k_3}{\overset{k_1}{\rightleftharpoons}} (A\cdot\cdot H\cdot\cdot B)^+ \underset{k_4}{\overset{k_2}{\rightleftharpoons}} A + BH^+$$

the experimental rate constant k_{exp} is determined from the rate of disappearance of AH^+, $-d[AH]^+/dt = k_1[AH]^+[B] - k_3[A..H..B]^+ = k_1k_2/(k_2 + k_3)[AH]^+[B]$, assuming steady-state conditions, $d[A..H..B]^+/dt = 0$, and $k_2 \gg k_4$.

*** The reaction efficiency is defined as a ratio k_{exp}/k_{coll}, where k_{coll} is the collision rate constant defining the rate of ion–molecule encounters at given pressure[100].

Winkler and Stahl [101] reported on the stereoselective protonation of diastereoisomeric cyclohexane- and cyclopentanediols in isobutane and ammonia plasma[98] (Scheme 2). With t-$C_4H_9^+$ as an acid, PA(2-methylpropene) = 810 kJ mol^{-1} (ref.[99]), the proton transfer is exothermic and protonation takes place in all stereoisomers. Nevertheless, while the *cis*-isomers give predominantly $[M + H]^+$ species, the *trans*-isomers also form $[M + C_4H_9]^+$ adduct ions. This suggets that the protonation of the *cis*-diols is slightly more facile than that of their *trans*-isomers. The effect is much more pronounced when using NH_4^+, which is a weaker acid (PA(NH_3) =

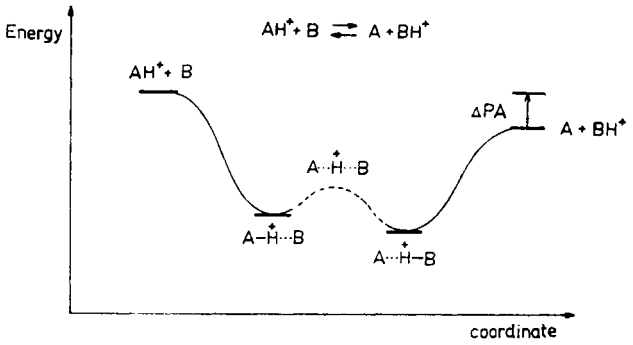


FIG. 2

Hypothetical energy profile for the proton transfer $AH^+ + B \rightleftarrows A + BH^+$

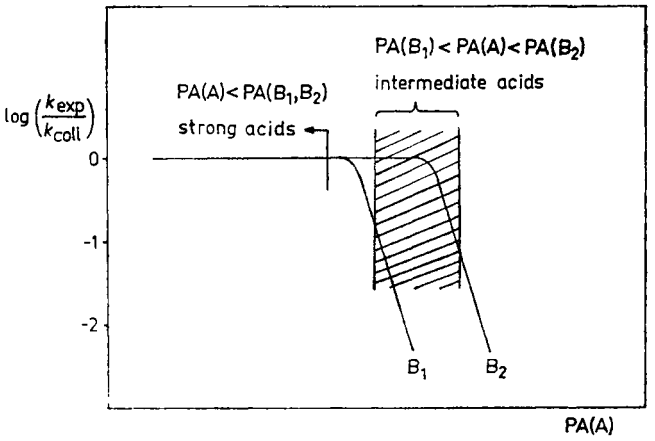
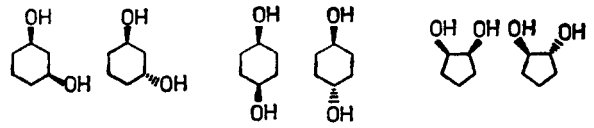


FIG. 3

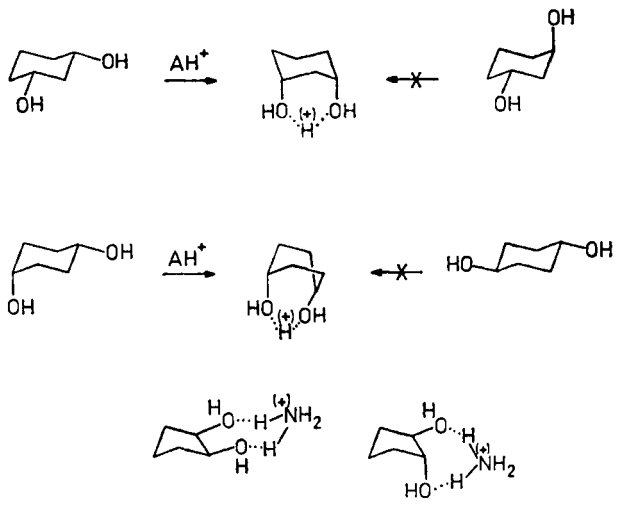
Dependence of the collision efficiency on the energetics of protonation

$= 841\ kJ\ mol^{-1}$)[99] than t-$C_4H_9^+$. In this case, only the *cis*-diols are protonated (Scheme 2), while the *trans*-isomers form mainly $[M + NH_4]^+$ adducts. This



Isobutane-CI						
$[M + H]^+$	68	13	75	19	54	10
$[M + C_4H_9]^+$	-	3	-	3	2	15
Ammonia-CI						
$[M + H]^+$	51	2	64	0.5	0.4	0.4
$[M + NH_4]^+$	29	54	15	19	53	56

The $[M + H]^+$, $[M + C_4H_9]^+$, and $[M + NH_4]^+$ values represent the relative abundances of the corresponding ions

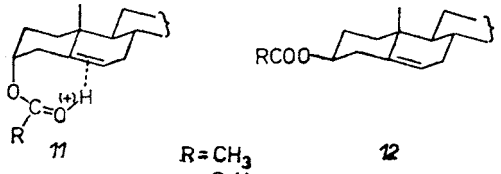


SCHEME 2

stereoselectivity was explained qualitatively by assuming a higher proton affinity for the *cis*-diols because of stabilization of the $[M + H]^+$ ions by proton chelation between the *cis*-oriented hydroxy groups. The subseqeunt quantitative determination of the gas-phase basicities[102] fully confirmed this assumption.

The isomeric cyclopentane-1,2-diols deviate from the above scheme in that both form $[M + NH_4]^+$ adducts, possibly stabilized by intramolecular chelation. Protonation of cyclopentane-1,2-diols is endothermic[102] and does not occur. It should be noted that an analogous chelation of the t-$C_4H_9^+$ ion is impossible, which contributes to better stereodifferentiation of cyclopentanediols when the latter reagent is employed.

Intramolecular proton chelation has been noted in a fast-atom bombardment (FAB) study of maleic and fumaric acids[103], of which the former gave 50–100 times more efficient ion yield.



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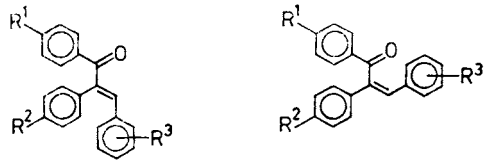
Isomeric 3-acetoxy- and 3-benzoyloxycholest-5-enes (*11*, *12*) differ in the formation of $[M + H]^+$ and $[M + NH_4]^+$ ions in desorption chemical ionization (DCI) mass spectra with NH_4^+ as an acid[104]. The axial 3α-isomers give rise to intense $[M + H]^+$ ions, because of chelation of the proton between the acyl group and the π-orbital of the double bond. The equatorial 3β-isomers afford only $[M + NH_4]^+$ adducts, as do saturated 3α- and 3β-acyloxy steroids, too[104].

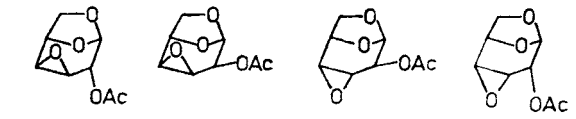
Although stereochemical effects caused by different proton affinities of stereoisomers are well-documented, there is also a possibility of observing steric effects due to steric hindrance in ion–molecule reactions[105–11]. This has nicely been demonstrated by the recent work of Houriet and Rolli[105] who examined the kinetics of protonation of pyridine and 2,6-di-tert-butylpyridine. Using a series of gaseous acids of different acidity they have shown that even at the same or comparable exothermicity of proton transfer, the protonation of the hindered 2,6-di-tert-butylpyridine occurred at much slower rate than that of pyridine. This steric effect was explained by the existence of a barrier to protonation of 25 kJ mol^{-1} in 2,6-di-tert-butylpyridine, which was attributed to entropy effects[105].



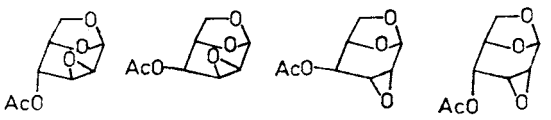
13 14

(*E*)- and (*Z*)-Isomers of triarylbutenones *13* and *14* have been reported to show different relative abundance of $[M + H]^+$ and $[M + NH_4]^+$ ions in ammonia CI mass spectra[112]. The (*E*)-isomers invariably displayed more abundant $[M + H]^+$ ions, which was interpreted as being due to different gas-phase basicities of the geometrical isomers[112].

Beside the structural features that affect the formation of protonated species, the competition between protonation and adduct formation can be influenced by factors that stabilize the adduct. Stereoisomeric 1,6-anhydrohexopyranose derivatives *15*–*22*



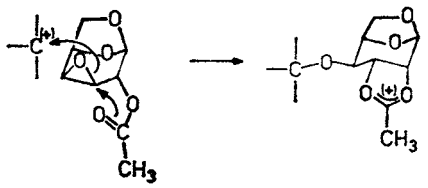
	15	*16*	*17*	*18*
$[M + C_4H_9]^+$	67	2	92	8



	19	*20*	*21*	*22*
	58	1.5	68	2

The $[M + C_4H_9]^+$ values represent the relative abundances of the corresponding ions normalized to the intensity of the base peak

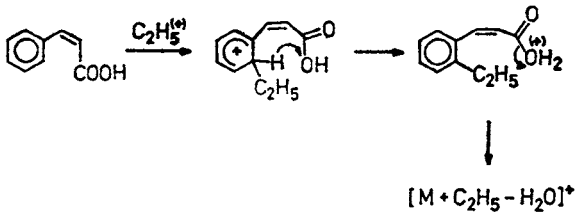
react[113] differently with $C_4H_9^+$ in isobutane CI. Of the whole series, only those isomers in which the oxirane ring and the acetoxy group are *trans*-disposed give abundant $[M + C_4H_9]^+$ adduct ions. The effect is essentially independent of other structure variations, *e.g.* the orientation of the oxirane oxygen and the acetoxy group with respect to the bicyclic skeleton. The remarkably different reactivity of *15*, *17*, *19*, and *21* has been explained by oxirane ring opening upon attack by t-$C_4H_9^+$, assisted



SCHEME 3

by participation of the neighbouring acetoxy group (Scheme 3). Stereoelectronic factors[114] favour such an assistance only in *trans*-isomers in which the rear attack is not precluded by molecular geometry[114].

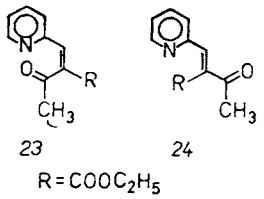
Stereoselective ion–molecule reactions have also been observed for (*E*)- and (*Z*)--3-phenylpropenooic acid[115]. In methane CI mass spectra (*Z*)-3-phenylpropenoic acid shows a peculiar $[M + 11]^+$ ion, the formation of which was rationalized by $C_2H_5^+$ attachment* followed by loss of water (Scheme 4). The preferential reactivity



SCHEME 4

of the (*Z*)-isomer is probably due to an *ortho*-effect[116,117] of the benzene ring which is attacked by $C_2H_5^+$ and then can transfer a proton to the *cis*-oriented carboxy group (Scheme 4). The important point to note here is the absence of *E*, *Z*-isomerization in the strongly acidic medium.

Stereoselective self-protonation, assisted by *ortho*-effect of the pyridine nitrogen atom, takes place in *23* but not in *24* (ref.[118]).



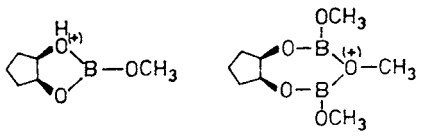
23 *24*

R = $COOC_2H_5$

Ion–molecule reactions other than protonation have been investigated in conjunction with stereoselectivity[107,111]. Chemical ionization in a mixture of water, methane, and trimethylboronate produces $[(CH_3O)_2B(HOCH_3)]^+$, $[(CH_3O)_2B—O(CH_3)—B(OCH_3)_2]^+$ and $[(CH_3O)_2B—OCH_3..H..CH_3O—B—(OCH_3)_2]^+$ which react stereoselectively with isomeric cyclopentane- and cyclohexane-1,2--diols[119]. By analogy with the formation of boronate esters in solution[120], gaseous *cis*-vicinal diols have been shown to react preferentially with the first two reagents to form cyclic boronate ions *25* and *26*. Monosaccharides, *e.g.* glucose, galactose,

* The $C_2H_5^+$ ions are present as minor products of ion–molecule reactions in methane plasma[98].

mannose, and fructose, were also distinguished by their different reactivity with $[(CH_3O)_2B(HOCH_3)]^+$ and the proton-bound dimer. In this case, the formation of cyclic boronate ions was easier when the sugar molecule had one or more pairs of *cis*-vicinal hydroxy groups[119].



25

26

Another analogy with solution chemistry has been reported very recently by the same group[121]. Methane CI mass spectra of stereoisomeric 3-hydroxy steroids in the presence of N,N-diethylaminotrimethylsilane[122] differed in the relative abundance of $[M + 72]^{+\bullet}$ ions, which were produced exclusively from the equatorial isomers. This is in line with the reactivity of the silylating reagent in solution where equatorial cyclic alcohols are silylated selectively, too[122]. Despite this analogy, the published CI mass spectra[121] raise several questions, especially in view of the reported high abundance of odd-electron molecular and $[M + 72]^{+\bullet}$ ions under conditions of CI. The co-evaporation of the highly volatile silane with much less volatile steroid diols and hydroxy ketones also seems to be very peculiar.

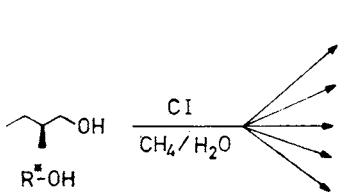
4. ENANTIOSELECTIVE IONIZATION

Another exciting feature of ion–molecule reactions stems from the possibility of enantioselection. The first, though somewhat special, case of enantioselective ion formation was discovered by Fales and Wright who studied proton-bound dimers in the CI mass spectra of tartrate esters[123]. In the experiment, artificial racemates were preformed by mixing equimolar amounts of methyl or isopropyl L- and D-tartrates, discerned by massive labelling. If no stereoselection were to occur in the dimer ion formation, proton-bound dimers $[2L(^2H_0) + H]^+$, $[L(^2H_0) + D(^2H_n) + H]^+$ and $[2D(^2H_n) + H]^+$ should be produced in a statistical 1 : 2 : 1 ratio, as was the case with homochiral mixtures. In fact, the "racemic" form $[L + D + H]^+$ was discriminated by factors of 0·78 (for dimethyl tartrates) and 0·46 (for diisopropyl tartrates) against the homochiral clusters. In spite of the clear enantioselectivity in this case, the effect is not intrinsic to any chiral system, as the enantiomers of camphor and (2-acetylamino-1-propyl)benzene showed no enantioselectivity.

Winkler and co-workers examined recently the enantioselectivity of protonated complex formation with a series of chiral compounds[124]. The formation of proton-bound complexes from mixtures of enantiomers with a chiral auxiliary has been

shown to depend on several structural features, namely, the type, number and location of the proton donor and acceptor sites, molecular rigidity and steric hindrance[124].

Su-Ming and co-workers have recently achieved enantioselective ionization by using chiral plasma prepared from water, methane and (*S*)-(−)-2-methyl-1-butanol (R*—OH in Scheme 5) as a chiral auxiliary[125]. Under CI conditions the alcohol



	m/z
$[R^*\text{-}OH_2]^+$	89
$[R^*\text{-}OH\text{-}R^*]^+$	159
$[R^*\text{-}OH\cdot\cdot H\cdot\cdot HO\text{-}R^*]^+$	177
$[R^*_2O\cdot\cdot H\cdot\cdot HO\text{-}R^*]^+$	247
$[(R^*\text{-}OH)_3H]^+$	265

	$[M+H]^+$	$[M+89]^+$	$[M+159]^+$	$[2M+H]^+$
D-(+)-Phe	67	41	3.5	36
L-(−)-Phe	48	18	<2	12
D-(−)-Met	91	32	-	36
L-(+)-Met	63	20	-	17
D-(−)-Mand	-	17.5	25.5	-
L-(+)-Mand	-	<2	<2	-

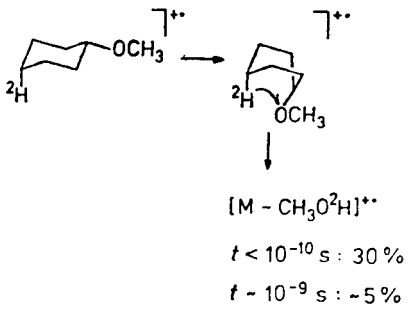
SCHEME 5

produces five chiral ions at *m/z* 89, 159, 177, 247, and 265 (Scheme 5). This motley mixture of chiral reagents has been found to discern enantiomers of phenylalanine, methionine, and mandelic acid (Phe, Met, and Mand in Scheme 5)[125]. The results reveal several interesting features, namely, there is chemoselectivity in these ion–molecule reactions, as the enantiomeric amino acids under study are distinguished upon protonation to form $[M + H]^+$ and $[2M + H]^+$ and adduct formation with $[R—OH_2]^+$, while mandelic acids react enantioselectively with $[R—OH_2]^+$ and $[R—OH—R]^+$ ions.

The great potential of this approach rests on the possibility of identifying a single enantiomer of a chiral compound by using separately both enantiomers of a chiral reagent. A recent preliminary report by Tabet[126] indicates that enantioselective S_N2 substitution of the hydroxy group in (*R*) and (*S*) menthol and mandelic acid takes place upon reaction with chiral amino alcohols. The analysis by collision-induced decomposition (CID)[127] spectra of the diastereoisomeric $[M + AH - H_2O]^+$ products has been quoted to be specific enough to permit quantitative determination of the enantiomers in a mixture[126].

5. STEREOSPECIFIC FRAGMENTATIONS

In addition to the stereoselective formation of ions in the gas phase, stereospecific fragmentations of isomers have been observed for a large number of molecular systems of various types[2-6]. Obviously, there are two basic requirements that have to be fulfilled in order to detect differences in the reactivity of gas-phase ions derived from stereoisomers. First, the stereoisomeric parent ions must retain, at least in part, their structural integrity before the fragmentation. In other words, if there is a fast isomerization which interconverts the isomeric ions prior to decomposition, no differences in the fragmentation patterns are likely to be observed. For instance, no significant differences have been found in the EI mass spectra of stereoisomeric 4-arylcyclohexanamines[128] and in the CI mass spectra of isomeric methyl cyclohexanehexacarboxylates[129]. In both cases, isomerization to common intermediates takes place before decomposition[128,129]. Since the isomerization and the fragmentation are competitive reactions, ion lifetime may also be of importance for detecting stereospecific fragmentations. In a recent paper, Nibbering and co-workers[130] have shown by the field-ionization kinetics technique[131] that the stereospecificity of loss of methanol from methoxycyclohexane decrease dramatically when the lifetime of the molecular ion is prolonged (Scheme 6)[130].



SCHEME 6

The second factor for a stereodifferentiation to be observed is the presence of at least one stereospecific fragmentation reaction. Ion fragmentations are very seldom, if ever, totally stereospecific. As a rule, the mass spectra of stereoisomers display only quantitative differences, in that one stereoisomer decomposes more readily *via* certain reaction channel(s) than does the other. Hence stereodifferentiation through only quantitative differences, in that one stereoisomer decomposes more readily *via* stereospecific fragmentation is always a matter of comparing relative reactivities of isomers.

The nature of stereospecific fragmentations depends on the ion type, *i.e.* different classes of stereospecific reactions are observed for odd-electron ions (radical cations),

even-electron cations[132], and even-electron anions. In the following text these three types of gaseous ions will be treated separately.

5.1. Even-Electron Cations

Even-electron cations are formed under conditions of CI by attachment of proton or a heavier even-electron ion (Eq. (*A*), (*B*))[98], or from odd-electron ions by loss of a radical (Eq. (*C*)).

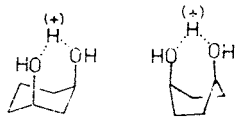
$$A \xrightarrow{H^+} [A + H]^+ \qquad (A)$$

$$A \xrightarrow{R^+} [A + R]^+ \qquad (B)$$

$$[AB]^{+\cdot} \longrightarrow A^+ + B^\cdot \qquad (C)$$

Protonated molecules $[M + H]^+$ can undergo stereospecific unimolecular decompositions in dependence on the relative configuration of functional groups in the isomers. There are two major factors that affect the stereochemistry of gaseous $[M + H]^+$ species containing polar groups, *i.e.* intramolecular proton chelation and anchimeric assistance.

Stereospecificity induced by proton chelation in conformationally flexible bifunctional ions was discovered by Winkler and McLafferty in the CI mass spectra of cyclic diols[133]. *cis*-Isomers, *e.g.* cyclohexane-1,4-diol and 1,3-diol, show much less fragmentation of $[M + H]^+$ ions by loss of dihydrogen or water than do the corresponding *trans*-isomers[133]. The higher kinetic stability of $[M + H]^+$ with the *cis*-diols was explained by intra-ionic solvation of the proton with the *cis*-disposed hydroxy groups (*27*, *28*). Hydrogen bonding had been shown earlier to increase the gas-phase basicities of bifunctional aliphatic compounds[134–136] so that thermodynamic stabilization of intramolecularly chelated $[M + H]^+$ species was well-established.



27 *28*

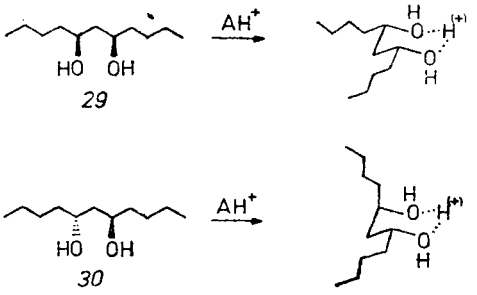
Stereospecific behaviour due to proton chelation has also been found for stereoisomeric diols with the tricyclo[4.3.1.0^{3,8}]decane[137] and bicyclo[4.4.0]decane skeletons[138]. For diacetoxy- and dimethoxytricyclo[4.3.1.0^{3,8}]decanes see ref.[139]. Protonated diols that cannot form any intraionic hydrogen bond behave as simple alcohols in which the loss of water from $[M + H]^+$ is a very rapid process following exothermic protonation[140,141].

Gas-phase basicities of a series of cyclopentane and cyclohexane diols and triols have recently been determined by Houriet and co-workers[102]. These quantitative data clearly reveal the thermodynamic stabilization of chelated $[M + H]^+$ ions, with the differences in the gas-phase basicities of stereoisomers ranging between 17–22 kJ mol^{-1}. *cis*-Cyclohexane-1,3-diols and 1,4-diols must undergo conformational transformations to bring the hydroxyls within a distance enabling hydrogen bond formation in the ions. While intramolecular hydrogen bond is absent in these diols in solution[142], the energy gain upon hydrogen bonding in the corresponding ions *27* and *28* is entirely sufficient to overcome the conformational barriers.

It is worth noting that some diols that can form strong intramolecular hydrogen bond in neutral molecules, *e.g. cis*-cyclopentane-1,2-diol and cyclohexane-1,2-diols[142], are not stabilized as their protonated forms in the gas phase[102]. This may explain the absence of stereospecificity in the water loss from protonated cycloalkane-1,2--diols[133] and pregnane-1,3-diols[143].

The higher stability of protonated (*Z*)-2-butene-1,4-diol *versus* the (*E*)-isomer has also been attributed to proton chelation[144].

Even aliphatic diols, *e.g. meso* and (±)-undecane-5,7-diols (*29*, *30*, Scheme 7) can be discerned by small differences in the relative abundances of $[M + H]^+$, $[MH - H_2O]^+$ and $[MH - 2\,H_2O]^+$ ions[145]. The slightly greater stability of $[M + H]^+$ derived from the *meso*-form *29* was explained by the "diequatorial" position of the butyl groups in the proton-chelated ions (Scheme 7).



SCHEME 7

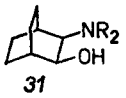
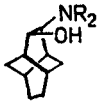
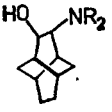
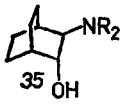
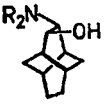
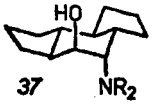
The concept and role of proton chelation in the unimolecular decompositions of conformationally locked bifunctional ions have further been elaborated by Longevialle and co-workers[143,146–148]. In a series of vicinal aminoalcohols of increasing dihedral angle ϑ (compounds *31*–*37*, Table III) the fraction of $[MH - H_2O]^+$ ions produced in isobutane CI mass spectra increased from zero (for *31*, $\vartheta = 0°$) up to 0·45 (for *37*, $\vartheta = 180°$). The gas-phase basicities of *31* (strong hydrogen bonding) and *37* (no bonding) were found to differ by as much as 29 kJ mol^{-1} (ref.[147]). Thorough kinetic[148] and thermodynamic studies[147] with the same series of amino-

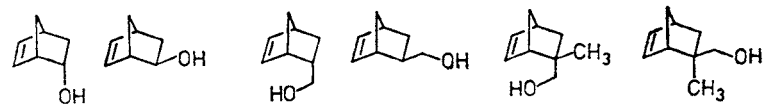
alcohols provided detailed picture of the competition between the loss of water and proton transfer from the less basic hydroxyl to the amino group[148].

Stabilization of $[M + H]^+$ ions can also be achieved through hydrogen bonding between a hydroxyl and a double bond suitably located in the molecule[149]. Jalonen and Taskinen have recently reported on the relative stabilities of $[M + H]^+$ ions in the isobutane CI mass spectra of stereoisomeric norbornenols *38–47* (*ref.*[150]).

TABLE III

Dependence of the $[MH - H_2O]^+/\{[MH]^+ + [MH - H_2O]^+\}$ abundance ratios on the dihedral angle in cyclic aminoalcohols

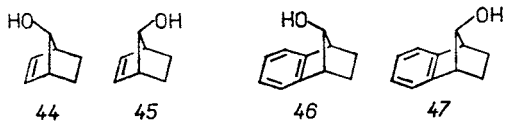
Compound	$[MH - H_2O]^+/\{[MH]^+ + [MH - H_2O]^+\}$		
	$\vartheta°$	R = H	R = CH_3
 *31*	0	0·005	—
 *32*	30	0·01	0
 *33*	60	0·01	0
 *34*	90	0·02	0·07
 *35*	120	0·045	0·21
 *36*	150	0·31	0·675
 *37*	180	0·45	0·61



38 39 40 41 42 43

2 (CH_4-CI) 4 3

9 (i-C_4H_{10}-CI) 4 6



44 45 46 47

6 0.1

22 4

Upper values: $[MH]^+_{endo}/[MH]^+_{exo}$ or $[MH]^+_{cis}/[MH]^+_{trans}$ abundance ratios for the corresponding stereoisomers in the methane CI mass spectra. Lower values: The same data from the isobutane CI mass spectra

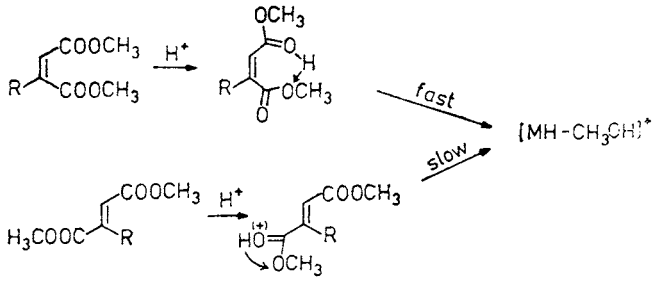
Since the norbornene double bond is more basic (GB = 811 kJ mol^{-1})[99] than the hydroxy group (*e.g.* GB(OH) = 805 kJ mol^{-1} in cyclohexanol)[102], a rapid proton transfer to the former can stabilize the $[M + H]^+$ ions with the *cis* and *endo*-geometry. The corresponding *trans* and *exo*-isomers behave like the saturated analogues, giving only minor $[M + H]^+$ ions and very intense $[MH - H_2O]^+$. In benzonorbornenols *46*, *47* the stereochemical effect curiously depends on the exothermicity of protonation. The benzene ring is less basic than the hydroxy group (*e.g.* GB(*o*-xylene) = 786·6 kJ mol^{-1})[99], so the protonated aromatic system can act as an intramolecular acid donor to protonate the *cis*-oriented hydroxyl[150]. As a result, the water loss from $[M + H]^+$ ions is more frequent in the *cis*-isomer *46*, if a gas-phase acid capable of protonating the aromatic ring is employed. When the hydroxyl in *46* and *47* is protonated selectively by using a weaker acid ($C_4H_9^+$), preferential elimination of water occurs from the *trans*-isomer, possibly because of stabilization of the *cis*-$[M + H]^+$ by a weak hydrogen bond between the hydroxyl and the aromatic ring[150].

Gas-phase methylation of bifunctional cyclohexane derivatives, *e.g.* cyclohexane-1,4-diols, 4-chlorocyclohexanols, and cyclohexane-1,2-dicarboxylic acids, has been shown to distinguish stereoisomers even in cases where isobutane chemical ionization gave identical spectra of $[M + H]^+$ ions[151].

The rate of decomposition of an $[M + H]^+$ ion can be augmented by intra-ionic interaction of two functional groups, if one of these can participate in the elimination of the other by forming a new chemical bond in the product[114]. Long-range participation of remote functional groups in the elimination of water or methanol from protonated acids and methyl esters, respectively, has been investigated, though not

from a stereochemical point of view, and found to depend on the number of carbon atoms connecting the interacting groups[152,153]. Stereochemical implications may be found in the decompositions of even-electron ions derived from macrocylic polyethers[154,155], which show some stereospecificity resulting from interaction of formally remote functional groups[156].

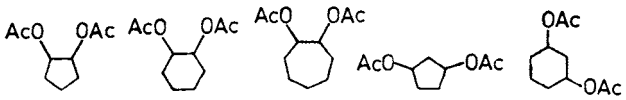
Stereochemical effects induced by proximity of functional groups have been observed in the low-energy CID spectra of protonated methyl and ethyl maleates, fumarates, citraconates, and mesaconates[157]. Upon collisional activation, stable $[M + H]^+$ ions with *cis*-disposed ester groups lose a molecule of the alcohol much easier than do the *trans*-isomers, in line with the behaviour of more energetic $[M + H]^+$ ions in the ion source[158,159]. This stereospecific behaviour was rationalized by assuming a proton transfer from the carbonyl oxygen of one ester group to the alkoxyl of the other ester group *via* a seven-membered transition state (Scheme 8).



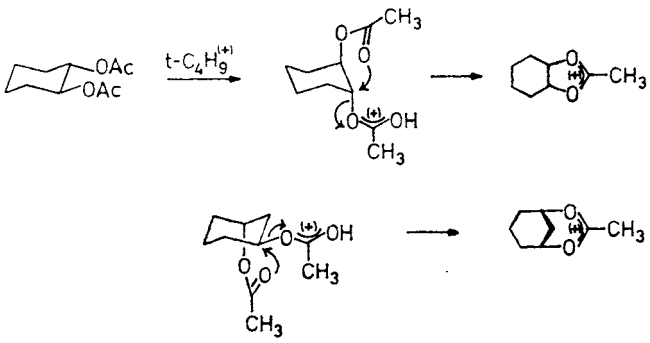
SCHEME 8

This is impossible to accomplish in the (*E*)-isomers which can lose alcohol following a high-energy 1,3-proton transfer within one ester group[157]. It is worth noting here that the enhanced reactivity of the (*Z*)-isomers may well be due to assistance of oxygen atoms at one ester group in the cleavage of the other C—O(H)R bond.

Neighbouring group participation in the loss of molecules from bifunctional $[M + H]^+$ ions is one of the major phenomena that induce stereospecificity in CI mass spectra[7]. With cyclic systems, both the ground-state and the higher-energy conformations may be important in the transition state of elimination, as exemplified with the loss of acetic acid from protonated *trans*-1,2- and 1,3-diacetoxycyclohexanes in isobutane CI mass spectra (Scheme 9)[160,161]. A number of cyclic compounds and some aliphatic systems have been scrutinized (for a detailed discussion see ref.[6]). Major differences in the behaviour of stereoisomers have been discovered in the loss of acetic acid from protonated 1,2- and 1,3-diacetoxycyclohexanes and cyclopentanes[160,161], and 2-methyl-1,3-diacetoxycyclopentanes and cyclohexanes[162], in the loss of methanol from protonated 1-acetoxy-2-methoxycyclopentanes[163], 1,3-dimethoxy-2-methylcyclopentanes[162], and 1-methoxy-3-methoxycarbonylmethylcyclo-



$\frac{[MH-AcOH]^+}{[MH]^+}$	*cis*	0.8	0.59	8.78	0.99	3.34
	trans	1.77	1.56	5.79	∞	23.4

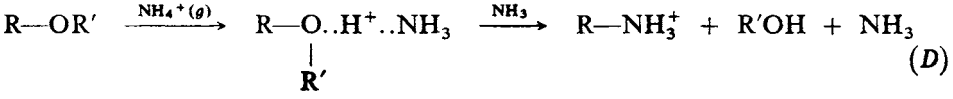


SCHEME 9

Upper values: $[MH - CH_3COOH]^+/[MH]^+$ abundance ratios for the *cis*-isomers; lower values: The same ratios for the *trans*-isomers

pentanes[164], loss of trimethylsilanol from protonated 1,3-bis(trimethylsilyloxy)-4,5--dimethylcyclopentanes[165], loss of methyl boronic acid from protonated 4,5-dimethylcyclopentane-1,3-diol methylboronates[165], and with other systems[166]. It should be noted that the different behaviour of $[M + H]^+$ ions from stereoisomers of the above type is often due to a combination of proton chelation, which stabilizes the *cis*-isomers, and neighbouring group participation which enhances the reactivity of the *trans*-isomers[148,162]. Both these effects have been employed for elegant structure elucidations of cycloalkenone photodimers[167] and photoadducts of cyclopentenone with electron-rich olefins[168,169], where head-to-head and head-to-tail isomers, as well as stereoisomers were easily distinguished through their CI mass spectra[167,168].

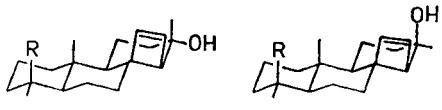
An interesting means of stereodifferentiation was discovered in the gas-phase reaction of $[M + NH_4]^+$ adducts, prepared from alcohols, ethers, and esters with ammonia[170]. The gas phase basicity of OR groups is usually lower than tht of ammonia, so that simple protonation is highly disfavoured. The ion–molecule reaction (Eq. (*D*))



(*D*)

has been shown convincingly to proceed *via* an S_N2 mechanism[171] (for earlier mechanistic suggestions see refs[172,173]). Since the substitution products generated from alcohols have the same nominal m/z values as ionized alcohols (substitution of OH by NH_3), the former ions have been denoted $[M_sH]^+$ to avoid confusion[149]. There are several structural requirements for the S_N2 reaction with ammonia to proceed in the gas phase[104,174–176]. Secondary carbon atoms, *e.g.* $C_{(3)}$ in saturated terloids, are very little reactive[104], while activation thereof by an allylic or homosallyic double bond is sufficient to promote the substitution. The ability of the group OR to act as a leaving group is also important[104]. Tertiary carbon atoms, even those of a neopentyl type such as $C_{(17)}$ in steroids, are reactive (refs[175,176]). This suggests that the nucleophilic substitution in $[M + NH_4]^+$ ions with ammonia proceeds closer to a borderline S_N2 mechanism with a highly polarized C—O bond which, however, retains its configurational identity. The presence of another functional group in the molecule of a higher basicity than that of the OR group (*e.g.* the 7-oxo group in steroids[104]) has a deleterious effect on the formation of $[M_sH]^+$ ions, since the more basic group is preferentially protonated[104].

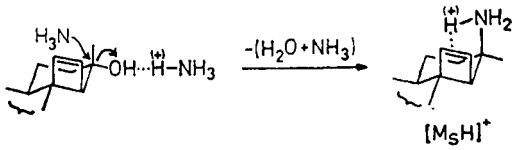
The different behaviour of stereoisomers in the nucleophilic substitution in the gas phase is often due to intra-ionic interactions that can affect the stabilityu ad further reactivity of $[M_sH]^+$ ions[149]. Stereoisomeric sesquiterpenoids *48* and *49*



48 *49*

R = CH_3, $COOCH_3$

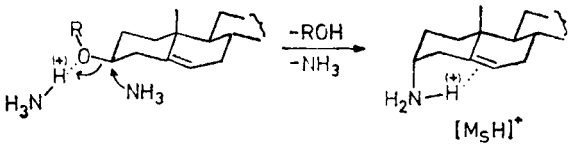
exerted striking differences in their ammonia CI mass spectra, owing to the formation of $[M_sH]^+$ substitution products[149]. The α-isomers *48* gave more abundant $[M_sH]^+$ than did the β-isomers *49*, which was explained by stabilization of the ammonium group through a hydrogen bridge to the double bond (Scheme 10)[149]. In contrast, the saturated analogues afforded very similar CI mass spectra regardless of the configuration of the hydroxy group[149].



SCHEME 10

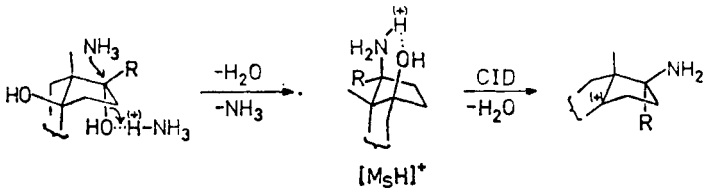
Stabilization *via* hydrogen bonding onto the 4- or 5-double bond has been invoked to explain the higher stability of $[M_sH]^+$ ions from 3β-hydroxy, alkoxy, and acyloxy

steroids, compared with the corresponding 3α-isomers[174]. Following nucleophilic substitution of the 3β-OR group and Walden inversion, the axial 3α-ammonium group can form a hydrogen bond onto the double bond in a ground-state conformation of the A-ring (Scheme 11), which is excluded in a 3β-configuration[174].



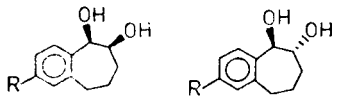
SCHEME 11

Steroidal 14β,17-diols also differ in their ammonia CI mass spectra, depending on the configuration at $C_{(17)}$[175]. The 17α-isomers generally afford more abundant $[M_sH]^+$ ions than do the 17β-isomers, because of stabilization of the newly formed 17β-ammonium group *via* hydrogen bond to 14β-OH. When the $[M_sH]^+$ ions are selected by mass and activated by glancing collisions with helium (CID spectra), those from the 17α-OH isomers undergo much easier loss of water, compared with their counterparts prepared from the 17β-OH isomers. This stereospecific water elimination from $[M_sH]^+$ was explained by intra-ionic proton transfer from the 17β-NH_3^+ group to the *cis*-oriented 14β-hydroxyl upon collisional activation (Scheme 12)[175].



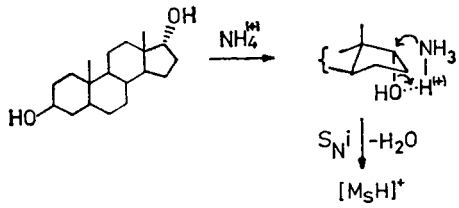
SCHEME 12

Modest differences have also been observed in the ammonia CI mass spectra of stereoisomeric diols *50* and *51*, of which the *trans*-isomer *51* showed the higher relative abundance of $[M_sH]^+$ (ref.[177]).



50 R = H, OCH_3 *51*

Androstane-3,17-diols display some differences in the reactivity of $[M + NH_4]^+$ adducts[178]. In unimolecular decompositions of mass-selected metastable ions[179], the $[M + NH_4]^+$ adducts from the 17α-isomers lose water more readily than do the ions from the 17β-isomers, regardless of the configuration at $C_{(3)}$ and $C_{(5)}$[178]. Since S_N2 substitution is excluded under unimolecular conditions, the authors suggested an S_Ni mechanism for the loss of water in this case (Scheme 13)[178]. Again, there is no differentiation between stereoisomeric 3-oxo derivatives which produce identically behaving $[M + H]^+$ ions[178].



SCHEME 13

Less pronounced, but still discernible stereochemical effects have been found in the CID spectra of protonated crotonic acids[180], steroid fragments[181], and iron–alkene complexes[182]. For other recent examples of stereochemical behaviour in CI mass spectra see refs[183–186].

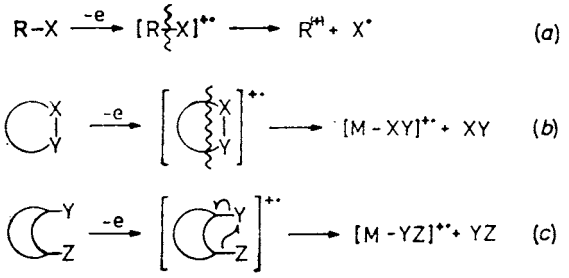
In summarizing this section, it is clear that the fragmentations of even-electron ions, especially of those formed by protonation in a CI ion source, can exert pronounced stereochemical effects within certain classes of organic compounds, as outlined above. The electronic effects behind the stereochemistries observed are familiar to organic chemists, since the ractivity of gas-phase cations is often analogous to that of cations in solution.

From a different point of view, the ionizing medium as produced in conventional high-pressure CI ion sources often affords mixtures of primary ions of different nature and reactivity, so that the conventional spectra resulting from ion source decompositions may be less clear. The studies employing unimolecular or collision-induced decomposition of mass-selected ion species have been of great help in this respect, and striking differences in the reactivity of stereoisomeric ions have often been revealed even if the conventional spectra were closely similar. Ion cyclotron resonance experiments represent another extremely fruitful approach in that they provide good-quality kinetic and thermodynamic data. A more extensive use of these powerful techniques for stereochemical problems is anticipated and wellcome.

5.2. Radical Cations

Gaseous radical cations are generated by electron impact ionization of molecules in the coventional ion source of a mass spectrometer. Ionization with non-threshold

electrons, *e.g.* at 70, 75 or 100 eV as commonly used, is accompanied by excitation of the molecular ions formed which then decompose *via* competitive and consecutive reactions. The chemistry and stereochemistry of gaseous radical cations share some common features with the chemistry of radicals in solution[1]. For our purposes it is practical to distinguish decompositions proceeding *via* simple bond cleavage (Scheme 14) of one (*a*) or two (*b*) bonds, and rearrangements that involve intra-ionic



SCHEME 14

transfer of a molecular fragment which is eventually lost in the molecule or radical eliminated (Scheme 14, (*c*)). In decompositions of the first type the dissociation energy of the R—X bond becomes important, and other factors that can affect the dissociation energies in the radical cations will be important for the stereochemistry, as well. The stereochemistry of the fragmentations of the second type (rearrangements) depends on the ease of the intra-ionic interaction between Y and Z to form a new chemical bond in the neutral molecule YZ. It should be noted that fragmentations that formally appear as proceeding *via* simple bond cleavage may in fact involve rate-determining rearrangements[187,188], so the knowledge of the reaction mechanism is essential for the discussion of subtle effects, such as stereochemistry.

5.2.1. *Decompositions With Simple Bond Cleavage*

Depending on the presence and nature of functional groups in the parent ion, the stereochemistry of simple-cleavage reactions can be affected by bonding and non-bonding interactions that evolve or are relieved, respectively, in the transition state. The latter possibility can be demonstrated with the loss of an alkyl radical R· from stereoisomeric hydrocarbons AR and BR. Let us consider that AR and BR differ in the relative configuration at two asymmetric centers, one of which vanishes upon loss of R·. If non-bonding repulsive interactions owing to presence of R are greater in AR than in BR ($\Delta H_f(\mathrm{AR}) < \Delta H_f(\mathrm{BR})$), the energetics of the simple bond cleavage to $A^+ + R^\cdot$ and $B^+ + R^\cdot$ can be depicted in the conventional[2] diagram (Fig. 4). Following the loss of R· the products A^+ and B^+ become identical. If the order of

stability is preserved in the ionized state ($\Delta H_f([AR]^{+\cdot}) < \Delta H_f([BR]^{+\cdot})$, *i.e.* if the ionization energies of the isomers do not differ much, the decomposition of $[AR]^{+\cdot}$ will require a lower critical energy[189] than that of $[BR]^{+\cdot}$. Consequently, the decomposition of $[AR]^{+\cdot}$ will be faster than that of $[BR]^{+\cdot}$ had the isomers acquired the same amount and distribution of internal energy upon ionization, and at the time of leaving the ion source the relative abundance of undecomposed $[AR]^{+\cdot}$ will be lower than that of $[BR]^{+\cdot}$ (ref.[190]).

This simple concept, which relates the thermochemistry of neutral molecules with the kinetics of ionic decompositions, was introduced in the early days of organic mass spectrometry (ref.[190]) and since then has been the subject of many controversies[2]. In some systems[191–198] correlations have been found between the relative intensity of molecular ions and the ΔH_f of the neutral molecules, while examples of inverse correlation[199–202] or even no correlation have also been reported[2]. Although the differences in the EI mass spectra due to different thermochemical stabilities of stereoisomers are often very small, their very existence is of some analytical value, since the isomers can be identified through their fragmentation patterns even in very complex mixtures by gas chromatography–mass spectrometry. Nevertheless, the predictive power of the enthalpy–reactivity correlations is low.

Stereochemical effects in simple-cleavage reactions become more pronounced in the presence of control elements. The control element may be a neighbouring group that can participate with its non-bonding electrons at the reaction center, thus promoting elimination of the leaving group (Scheme 15, (*a*)) (ref.[114]). Alternatively, the participating orbital may be located in the vicinity of the reaction center and its orientation with respect to the dissociating bond may affect the reactivity through stereoelectronic control[203,204] (Scheme 15, (*b*)). Obviously both the neighbouring

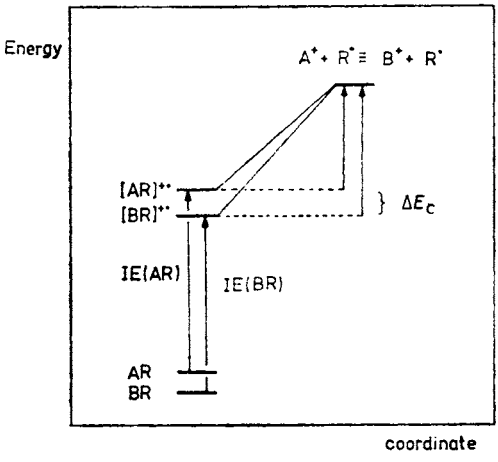
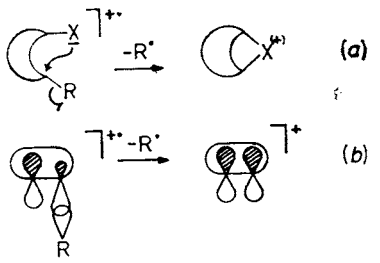


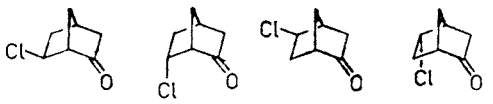
FIG. 4
Energy diagram for the decomposition of stereoisomers $[AR]^{+\cdot}$ and $[BR]^{+\cdot}$ *via* simple bond cleavage

group participation and the stereoelectronic assistance are based on the development of a bonding orbital overlap in the transition state that can decrease the overall critical energy of the decomposition.



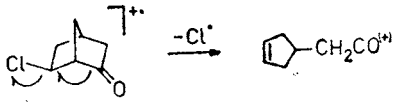
SCHEME 15

Neighbouring group participation has been encountered in the loss of halogen radicals from molecular ions with bridged skeletons by analogy with the well-known solvolytic reactions (ref.[205]). Of the isomeric chlorobicyclo[2.2.1]heptanones *52*–*55*,



52 *53* *54* *55*

the *exo*-isomer *52* gives the highest abundance of $[M - Cl]^+$ ions, which was explained by neighbouring participation of the antiperiplanar skeletal σ-bond in the cleavage of the C—Cl bond (Scheme 16)[206].



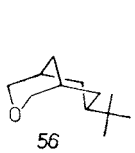
SCHEME 16

The faster loss of bromine from *exo*-isomers of 2-bromobicyclo[2.2.1]hept-5-enes[207] and 2-bromobicyclo[2.2.1]heptanes[208] has also been attributed to neighbouring group participation. Other examples comprise the different rates of bromine loss from stereoisomeric 1,2-dibromocyclopentanes[209], 1,2-dibromocyclohexanes[209], 1,2-dibromo-4-tert-butylcyclohexanes[6], 2,3-dibromobutanes[209], and 1-bromo-2-chlorocyclopentanes and cyclohexanes[210].

A non-bonding orbital on a heteroatom can assist the elimination of a suitably oriented tert-butyl group, as in *cis*-4-tert-butyl-1-bromocyclohexane which gives more abundant $[M - C_4H_9]^+$ ions than does the *trans*-isomer[211].

Stereoisomeric 7-tert-butyl-3-oxabicyclo[3.3.1]nonanes *56*, *57* lose the tert-butyl radical to a different extent[212]. Moreover, the unimolecular decompositions of metastable $[M - C_4H_9]^+$ ions from *56* and *57* gave distinct kinetic energy spectra indicating different structures for these ions[212].

The carboxyl group suitably located and oriented on the bicyclo[3.3.1]nonane skeleton can also assist the loss of the tert-butyl group, as in *58* and *59*. Curiously, the orientation of the tert-butyl group does not play a role[213].



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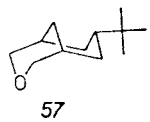

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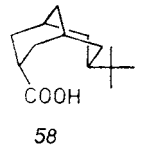

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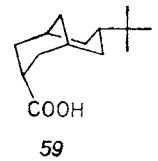
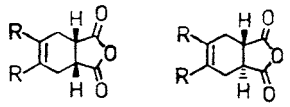


59

Neighbouring group participation by a carbon–carbon double bond has been postulated as an explanation of the different behaviour of stereoisomeric anhydrides *60* and *61* upon electron impact[214,215]. The *cis*-annulated isomers *60* exhibit abundant $[M - CO]^{+\bullet}$ ions which are almost absent in the spectra of the *trans*-isomers *61* (ref.[215]). The loss of CO is suppressed in the spectra of the saturated analogues which, in turn, show negligible stereochemical effects[215].

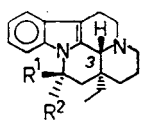
The stereoelectronic control of dissociations proceeding *via* simple bond cleavage depends on the conformational properties of the underlying σ-bond skeleton[204]. In conformationally locked systems major stereochemical effects have been observed for the loss of a hydrogen atom or an alkyl group.



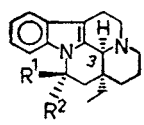
60

61

R = H, CH_3



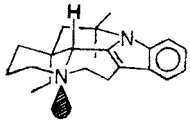
62

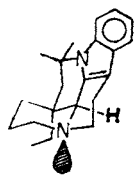


63

R^1, R^2 = H, OH, $COOCH_3$

Synthetic analogues of eburnane alkaloids *62*, *63* (ref.[216]) may serve as a recent example documenting the stereoelectronic control. The 3β-isomers *62* in which the axial $C_{(3)}$—H bond is antiperiplanar with respect to the p_z orbital at the bridgehead



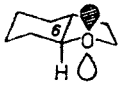


SCHEME 17

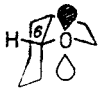
nitrogen atom regularly display more abundant $[M - H]^+$ ions than do the 3α--isomers with a synclinal $C_{(3)}$—H bond (Scheme 17)[216]. The stereospecificity of the hydrogen atom loss from *62*, *63* is remarkable indeed, since the $C_{(3)}$—N bond in eburnane derivatives is thought to undergo rapid cleavage following electron impact ionization[217]. It should be noted, however, that appropriate deuterium-labelled derivatives were unavailable to establish unequivocally the loss of $H_{(3)}$ from ionized *62*, *63*.

Alkaloid skeletons have been fruitful in providing examples of stereoelectronic control of the loss of bridgehead hydrogen atoms from molecular ions. Striking stereochemical effects have been reported for isomeric deacylcylindrocarpols[218], corynanthene synthons[219], and substituted indoloquinolizidines[220].

Stereoelectronic effects on the loss of bridgehead hydrogen atoms have been scrutinized quantitatively with stereoisomeric 7-oxabicyclo[4.3.0]nonanes *64* and *65* (ref.[89]). The *trans*-annulated isomer *64* eliminates the axial $H_{(6)}$ more easily than does the *cis*-isomer, in which the $C_{(6)}$—H bond can adopt an equatorial position. The identity of the $H_{(6)}$-loss was established by specific deuterium labelling[89]. Appearance energy measurements of $[M - H]^+$ indicated that the loss of $H_{(6)}$ was easier in the *trans*-isomer by c. 50 kJ mol^{-1}. Some differences have also been found in the decompositions of long-lived metastable molecular ions, the *cis*-isomer decomposing to $[M - H]^+$ and H$^\cdot$ with a greater kinetic energy release. This indicates that achieving the transition state of decomposition in the latter isomer may require conformational excitation which contributes to the higher critical energy for the hydrogen loss.



64



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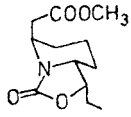

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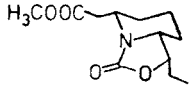


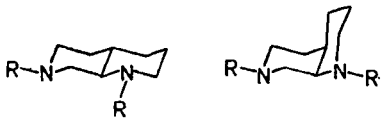
67

Loss of groups other than hydrogen can also be assisted by stereoelectronic factors. The mass spectra of bicyclic carbamates *66*, *67* were reported[212] to differ in the relative abundance of $[M - CH_2COOCH_3]^+$ ions, with the axial isomer decomposing more easily.

The loss of methyl from $C_{(3)}$ in stereoisomeric 2-azabicyclo[4·4·0]decanes has been investigated for a large number of derivatives[222–230]. The stereochemical effects observed in the mass spectra were largely due to the configuration at $C_{(3)}$, with axial methyl groups having been split off more easily than the equatorial ones. As established from appearance energy measurements, the loss of an axial methyl requires 15–18 kJ mol^{-1} less energy than the elimination of an equatorial methyl[93,231].

Bicyclic ethers[232,233], sulfides[234], lactones[235], and quinolizidines[236] bearing methyl groups in the vicinity of the heteroatom also display stereochemical effects in the loss of methyl.

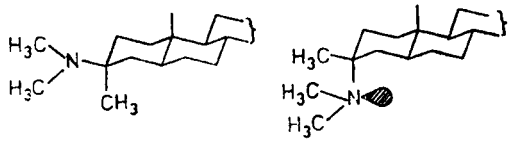
Stereoelectronically assisted skeletal cleavage in 2,9-diazabicyclo[4.4.0]decane derivatives *68*, *69* was employed for stereochemical assignment[237].



68 R = $COCH_3$, $COCF_3$, COC_6H_5 *69*

In monocyclic saturated heterocycles the conformation of the ring is not fixed, and conformational changes are possible in molecular ions that possess enough energy to decompose *via* simple bond cleavage. With the conformational ring inversion being possible, the orientation of the splitting bond and the control orbital is not well-defined in the transition state with respect to the ground-state geometry, and so the situation becomes less clear. In spite of this, modest stereochemical effects have been observed in the mass spectra of stereoisomeric pyran[238], thian[239], dioxan[240–242], and oxathian derivatives[82].

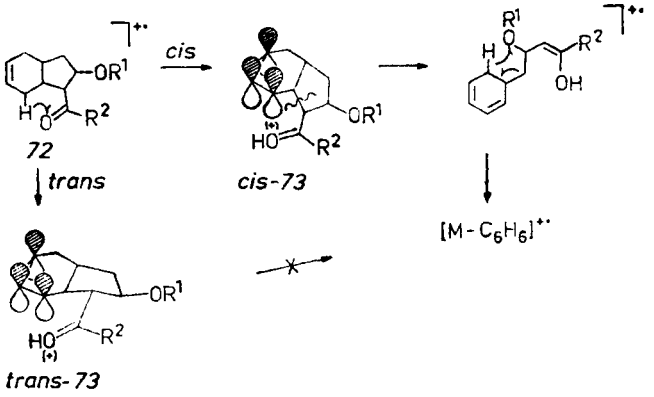
Even a rotational barrier of the bulky N,N-dimethylamino group has been reported to fix the conformation of the latter and lead to stereoelectronic assistance, as reported for the loss of the $C_{(3)}$-methyl from stereoisomeric 3-methyl-3-dimethylamino steroids *70*, *71* (ref.[243]).



70 *71*

Carbon–carbon double bonds can serve as control elements in promoting the rupture of suitably oriented allylic bonds. *cis*-Annulated bicyclo[4.3.0]non-3-ene derivatives *72* (R^1 = H; CH_3; C_2H_5, R^2 = H; OH; OCH_3; OC_2H_5, Scheme 18) uniformly decompose by eliminating benzene, while the fragmentation of the corresponding *trans*-annulated isomers depends on the nature of the substituents[244–246]. The facile elimination of benzene in the *cis*-series is triggered by stereoelectronically promoted rupture of the $C_{(6)}$—$C_{(7)}$ bond in the allylic ion *cis-73* (Scheme 18). The stereoelectronic assistance is hampered in analogous ions of the *trans*-series (*trans*-

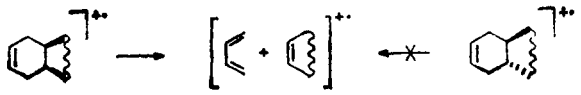
-*73*), as the $C_{(6)}$—$C_{(7)}$ bond of the *trans*-annulated seleton is held perpendicular to the control π-orbital[246].



SCHEME 18

5.2.2. *Cleavage of Two Bonds Without Hydrogen Transfer*

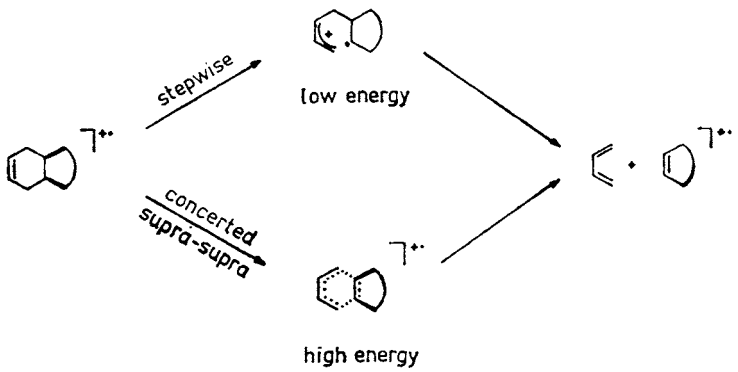
The simultaneous or step-wise cleavage of two single bonds in radical cations is a typical feature of electrocyclic ring fragmentations. Out of various types of electrocyclic retrogressions, *e.g.* (2 + 2), (3 + 2), (4 + 1), (4 + 2), (6 + 2), (6 + 4), *etc.*, the retro-Diels–Alder (RDA) fragmentation has attracted the most intense attention (ref.[247]). The stereochemical aspects of the RDA reaction of radical cations in the gas phase have usually been based on a formal similarity with an analogous reaction of molecules which is known to obey the Woodward–Hoffmann rules[248]. According to the conservation of orbital symmetry, an RDA decomposition should be facile in the ground electronic state of a *cis*-annulated cyclohexene derivative, while being forbidden in the corresponding *trans*-annulated isomer (Scheme 19). In reality, bi- and tricyclic systems have been found which underwent highly stereospecific RDA



SCHEME 19

fragmentations[249–254]. On the other hand, the RDA decomposition of other bicyclic compounds showed only moderate stereospecificity, giving more abundant diene or ene fragments from the *cis*-annulated isomers than from the *trans*-annulated ones[247]. Frequent examples of non-stereospecific RDA decompositions have also been reported (ref.[247]).

The validity of the symmetry-conservation rules is ambiguous with radical-cations, as follows from a formally constructed correlation diagram (Fig. 5) which predicts incorrectly formation of charged ethylene and neutral butadiene from the cyclohexene radical-cation. As discussed earlier[255], the basis set of orbitals that are used to construct correlation diagrams may not be adequate to correctly describe an open-shell system[256]. Recent theoretical work, supported by experimental data[38,87,88,255–258]



SCHEME 20

has shed more light on the mechanism of the RDA decomposition in radical cations. In ionized cyclohexene derivatives containing unsubstituted allylic positions, the pseudo-π orbitals of the allylic methylene groups mix considerably with the π(C=C) orbital. This interaction stabilizes the radical cation through hyperconjugation[255]. The stabilization is dramatically lessened in the transition state of a concerted RDA decomposition in which both allylic C—C bonds are partially interrupted. The transition state of the concerted process thus becomes energetically disfavoured against

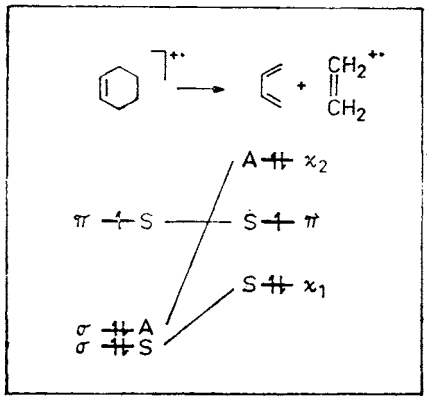
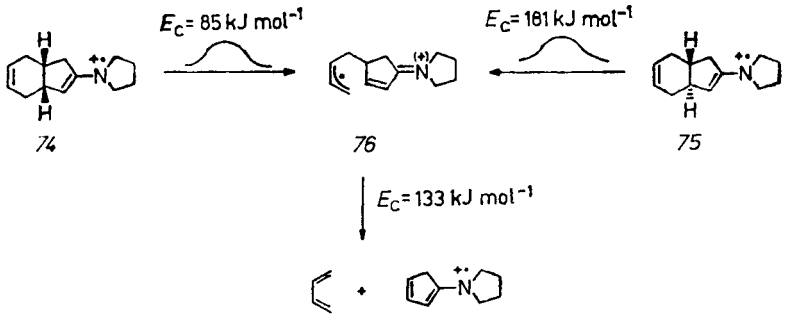


FIG. 5

Formal correlation diagram for the retro-Diels–Alder decomposition of cyclohexene radical-cation

that of a stepwise route (Scheme 20)[87,255,257,258]. Stepwise RDA decomposition is, of course, possible in both *cis*- and *trans*-annulated isomers, which results in decreased stereospecificity (see below). The importance of the hyperconjugative effects points to the role of substituents located in the allylic positions of the cyclohexene moiety. In the absence of allylic substituents the hyperconjugative interaction predominates and the RDA reaction follows a stepwise path (ref.[87,88,255,257]). The stereospecificity of the decomposition (if any) is governed by factors other than orbital symmetry correlations. The stereochemistry can be affected by control elements positioned outside the cyclohexene ring.

For instance, stereoisomeric 8-(N-pyrrolidyl)bicyclo[4·3·0]nona-3,7-dienes (*74*, *75*, Scheme 21) differ in the extent of RDA decomposition to $[C_9H_{13}N]^{+\cdot}$ and butadiene[88]. Mapping of the reaction energy hypersurface by a TMO-CI calculation[259]

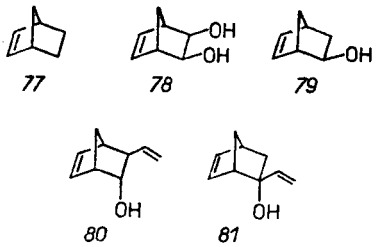


SCHEME 21

revealed that both isomers undergo exothermic ring opening to a common distonic intermediate *76* (Scheme 21) which then decomposes to the products. However, the rate-determining steps are different for the stereoisomers. With the *cis*-annulated compound *74*, the highest-energy saddle point on the hypersurface lies between the open-ring intermediate *76* and the products, as supported by critical energy measurements[88]. In contrast, the *trans*-isomer *75* requires 48 kJ mol^{-1} more energy to decompose *via* the RDA channel, because of a higher barrier in the first, ring-opening step. The much more difficult dissociation of the doubly allylic C—C bond in ionized *75* was explained by the absence of stereoelectronic assistance as a result of unfavourable skeletal geometry[88]. Similar conclusions have been arrived at with stereoisomeric bicyclo[4.3.0]nona-3,7-dienes[87]. In the absence of control elements the stepwise RDA reactions lack stereospecificity, which accounts for the very similar behaviour of some annulation isomers (refs[6,247]).

The influence of substituents in the cyclohexene ring on the course of an RDA fragmentation has recently been investigated with bicyclo[2.2.1]heptene deriva-

tives[38]. Because of bridging these compounds lack allylic pseudo-π orbitals, so there are no *a priori* electronic effects to force the system into a stepwise RDA reaction. In compounds with roughly balanced dissociation energies of the cyclohexene allylic bonds (*77–80*) the RDA fragmentation was found to proceed at the corresponding thermochemical thresholds[38]. The estimated individual dissociation energies of the

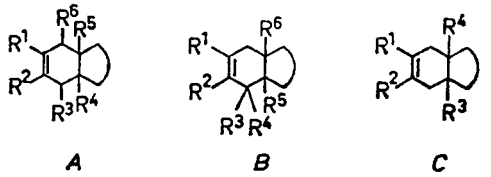


77 *78* *79* *80* *81*

allylic bonds were higher than the corresponding critical energies of decomposition, indicating a concerted mechanism[38]. If one of the allylic bonds was made extremely weak by proper substitution, *e.g.* the $C_{(1)}$—$C_{(2)}$ bond in *81*, the RDA reaction required 58–67 kJ mol^{-1} more energy to proceed than calculated for a threshold process. This is a typical feature of stepwise RDA reactions which have non-negligible barriers over the corresponding thermochemical thresholds (refs[87,88,255]).

The existence of a concerted RDA reaction in cyclohexene derivatives with symmetrically substituted allylic positions has gained support from the studies of Mandelbaum and co-workers[249–254]. It is noteworthy that all cases of highly stereospecific RDA fragmentations have been encountered with compounds of this structure type. The structure factors that govern the mechanism and stereospecificity of the RDA decomposition of radical cations can be summarized as follows (Scheme 22):

1) Compounds with symmetrically substituted allylic positions (type A, R^3 and R^4 need not be identical) can fragment *via* a concerted RDA reaction, provided none of the cyclohexene bonds extremely weak. Strong stereochemical effects can be expected.



A *B* *C*

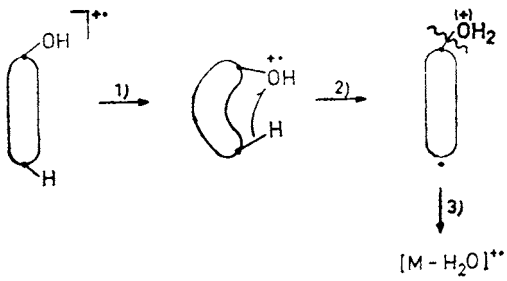
SCHEME 22

2) Unsymmetrical allylic substitution (type B) can diminish or suppress stereochemical effects, if it results in deep weakening of one of the ring allylic bonds.

3) Compounds with allylic methylene groups (type C) decompose *via* stepwise RDA reactions. Stereochemical effects, if they occur, are ruled by control elements other than symmetry conservation.

5.2.3. *Stereospecific Decompositions With Transfer of Molecular Fragments*

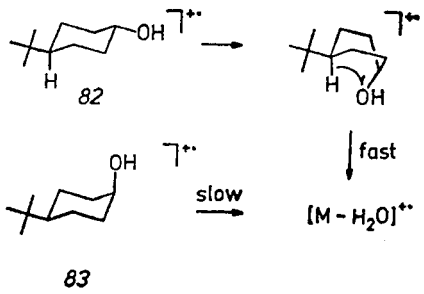
Fragmentations involving intra-ionic transfer of atoms or functional groups belong to the most important stereodifferentiating reactions of gaseous radical cations. Reactions of this type are generally referred to as rearrangements[260]. Rearrangements often have low critical energies, but require highly-ordered transition states in which the interacting groups are brought together. Both these factors favour stereochemical effects to occur. In order to illustrate the subtleties of stereospecific rearrangements we shall consider the individual phases that evolve in the loss of water from an ionized cyclic alcohol (Scheme 23)[261]. A unimolecular loss of water requires that a hydrogen



SCHEME 23

atom be transferred to the hydroxy group. In phase 1 conformational excitation may be necessary to carry the hydrogen atom to the hydroxy group. In phase 2 the original C—H or X—H bond is broken with simultaneous formation of the new O—H bond. Eventually, (phase 3) the C—OH_2 bond dissociates yielding an $[M - H_2O]^{+\cdot}$ ion and a molecule of water. The last step may be accompanied by hidden rearrangements that tend to decrease the heat of formation of the resulting $[M - H_2O]^{+\cdot}$ ion. However, the stereochemistry of the water elimination is mostly governed by the first two steps.

Since the elimination of water competes with other decompositions of molecular ions, an efficient formation of $[M - H_2O]^{+\cdot}$ requires that there be a low-energy route to bring a hydrogen atom to the hydroxyl. In stereoisomeric 4-tert-butylcyclohexanols *82*, *83* (Scheme 24), the *trans*-isomer *82* can lose water by transferring the *cis*-oriented H-4 in a boat-like transition state[262-264]. This low-energy path is unattainable in the *cis*-isomer *83* and, as a consequence, the loss of water occurs to a much lower extent than in *82* and proceeds *via* different mechanisms[264].



SCHEME 24

A large number of molecular systems undergoing stereospecific loss of water have been found[265-278]. In general, there are two important energy factors that can affect the reaction course. First, to bring a skeletal hydrogen atom to the hydroxyl necessitates vibrational and rotational excitation of the ion, so the conformational properties of the molecular skeleton should determine the corresponding increase in energy in the transition state. Second, hydrogen atoms weakly bound to the skeleton, *e.g.* those at allylic, benzylic and tertiary carbon atoms, can be transferred to the hydroxyl over a longer distance than inactivated hydrogen atoms, so that the conformational strain in the transition state is relieved. Effects of both kinds have been observed[279].

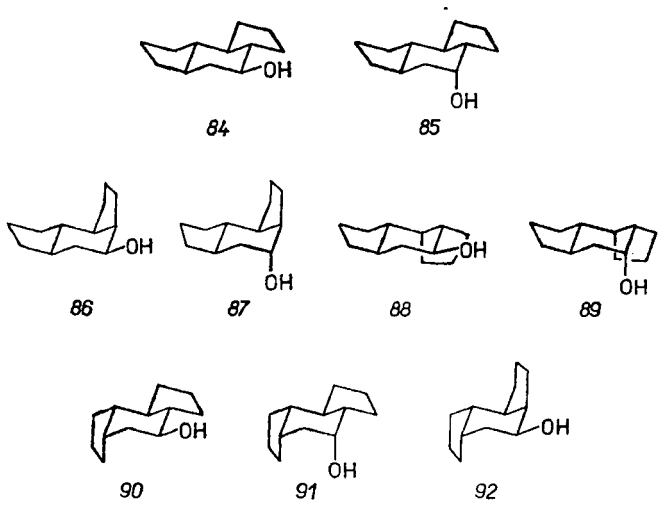
While in cyclohexanol the transfer of *cis*-H-3 is non-stereospecific and probably takes place after ring opening[3], in cycloheptanol a stereospecific transfer of the *cis*-H-3 is observed, although the stereospecificity is not high[279]. The cycloheptane ring is more flexible than that of cyclohexane[280], so that a *cis*-oriented hydrogen atom at $C_{(3)}$ in the former can approach the hydroxyl in a less-strained transition state.

Stereoisomeric 3-tert-butylcyclohexanols lose water to a markedly different extent following electron impact ionization[263]. This indicates that a stereospecific 1,3--transfer of hydrogen atom is possible in the cyclohexane ring, if the $C_{(3)}$—H bond has a low dissociation energy[281]. Stereoisomeric tert-butylcycloheptanols also differ in the relative abundance of $[M - H_2O]^{+\cdot}$ ions in their mass spectra[282].

Aryl groups activate positions $C_{(3)}$ and $C_{(4)}$ in the corresponding arylcyclohexanols, inducing specific transfer to the hydroxyl of the *cis*-oriented hydrogen atoms, as confirmed by deuterium labelling[283].

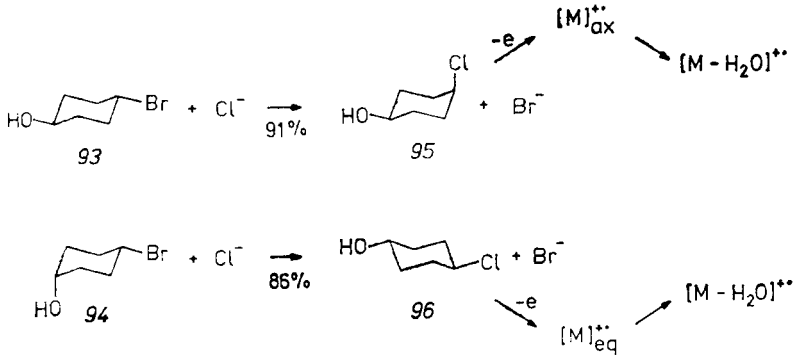
In systems containing more than two chiral centers the elimination of water from stereoisomeric alcohols depends on the number and nature of hydrogen atoms that are accessible for transfer onto the hydroxyl. The conformational properties of the skeleton also play a role[284]. Simple conformational analysis with molecular models has been used to account for the differences in the mass spectra of stereoisomeric tricyclo[7.3.0.$0^{2,6}$]dodecan-7-ols *84–92* (ref.[284]). The isomers with the rigid *trans*-

-*anti-trans* annulated skeleton (*84*, *85*) afford $[M - H_2O]^{+\cdot}$ ions of relative abundance one to two orders of magnitude lower than do the isomers with the more flexible *cis-syn-trans*, *cis-anti-trans*, and *cis-anti-cis* skeletons (*86*–*92*). Some



differences in the relative abundance of $[M - H_2O]^{+\cdot}$ exist in the spectra of the latter compounds and can be related to the nature of transferrable hydrogen atoms[284].

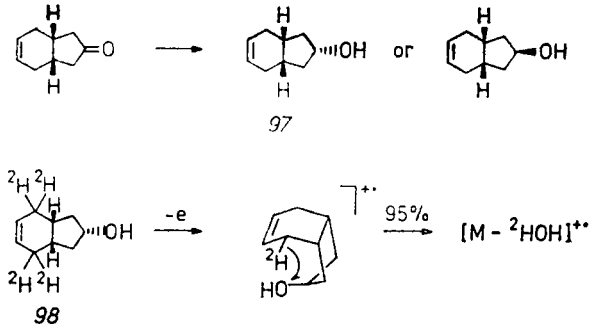
The stereospecific loss of water from cyclic alcohols has been utilized in structure elucidation based on two strategies. If the molecular skeleton is known, the reactivity of the stereoisomers can be correlated with the expected course of water elimination[285]. Both stereoisomers are as a rule necessary to make possible a reliable stereochemical assignment. A nice example is provided by the structure elucidation of the



SCHEME 25

products of nucleophilic substitution in 4-bromocyclohexanols in the gas phase[286] (Scheme 25). The reaction of *93* and *94* with chloride anions was studied in an ion cyclotron spectrometer under conditions which excluded isolation and off-line identification of the products. In an ingenious time-resolved experiment, the polarity of the trapping field was reversed from the negative to positive mode, and the neutral products were ionized with a pulsed electron beam. The $[M - H_2O]^{+\cdot}/[M]^{+\cdot}$ abundance ratios in the mass spectra of *95* and *96* were then used to establish the diastereoisomeric purity of the products[286].

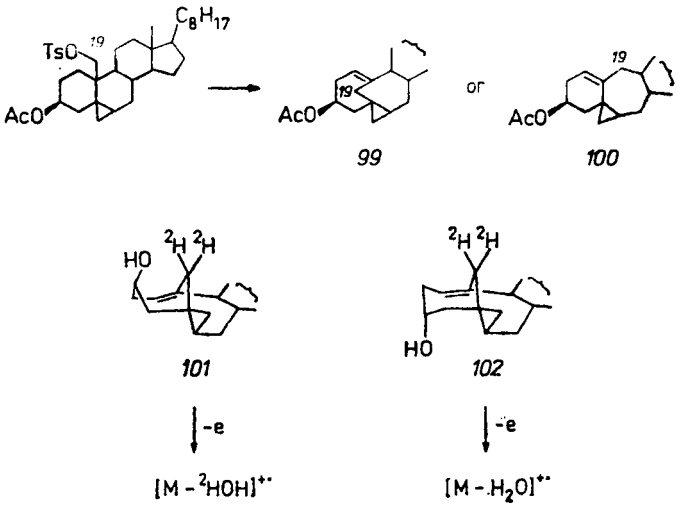
Configurational assignment is also possible to make with a single stereoisomer, if one can prove the mechanism of water elimination by specific labelling. *cis*-Bicyclo-[4.3.0]non-3-en-8-ol (*97*) was obtained as a single isomer by lithium aluminium hydride reduction of the corresponding ketone (Scheme 26), while the configuration



SCHEME 26

at $C_{(8)}$ could not be deduced from the ^1H NMR spectrum, because of the similarity of vicinal coupling constants of the protons on the five-membered ring. The labelled [2,2,5,5-$^2H_4$]analogue *98* showed clean loss of ^{2}HOH (95%) in the mass spectrum which confirmed the *endo*-configuration of the $C_{(8)}$ hydroxyl[278,287].

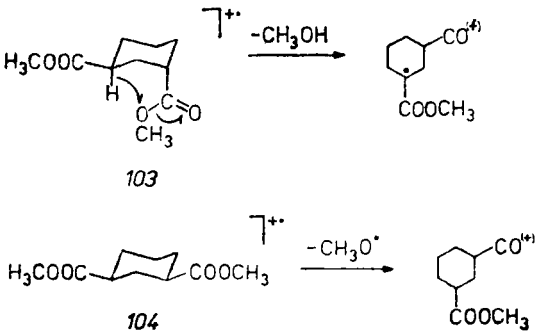
The second strategy in structure elucidation using stereospecific loss of water relies on the knowledge of hyroxyl configuration (*e.g.* from ^1H NMR), and employs the hydroxy group as an intramolecular probe to examine remote chiral centers. Such a procedure was used in the structure elucidation of a product of solvolysis in steroid chemistry, for which two alternative structures (*99* and *100*) could be suggested (Scheme 27)[288]. In a parallel experiment a [19,19-$^2H_2$]-derivative of the acetate *99* was prepared by solvolysis and converted to stereoisomeric alcohols *101*, *102*. The electron impact mass spectrum of the labelled 3β-alcohol *101* displayed clean loss of ^{2}HOH, while the 3α-isomer eliminated mostly H_2O. These results pointed to structure *99* for the product of solvolysis (and *101*, *102* for the related



SCHEME 27

alcohols), since in the alternative structure *100* the 19-deuterium atoms would have been inaccessible for the 3-OH group regardless of its configuration.

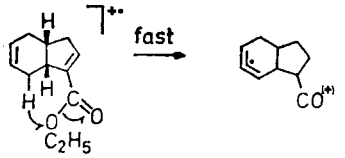
The loss of a molecule of an alcohol from an ionized ester is another stereosensitive reaction which resembles the elimination of water from alcohols. Stereoisomeric esters can be distinguished by the $[M - ROH]^{+\cdot}/[M - OR]^{+}$ abundance ratios[4], since the loss of RO$^{\cdot}$ usually shows little stereospecificity and can be used as a reference reaction. The molecular ion of methyl *trans*-1,3-cyclohexanedicarboxylate (*103*) eliminates mostly methanol, while the *cis*-isomer loses a methoxyl radical (Scheme 28)[289]. The former stereospecific reaction can be explained by the transfer to the methoxyl of the tertiary hydrogen atom from $C_{(3)}$ in a cyclic transition state (Scheme 28)[289]. Stereoisomeric methyl cyclohexanehexacarboxylates differ in the



SCHEME 28

$[M - CH_3OH]^{+\cdot}/[M - CH_3O]^+$ ratios which permit isomer differentiation[290]. For related examples see refs[3-6,278].

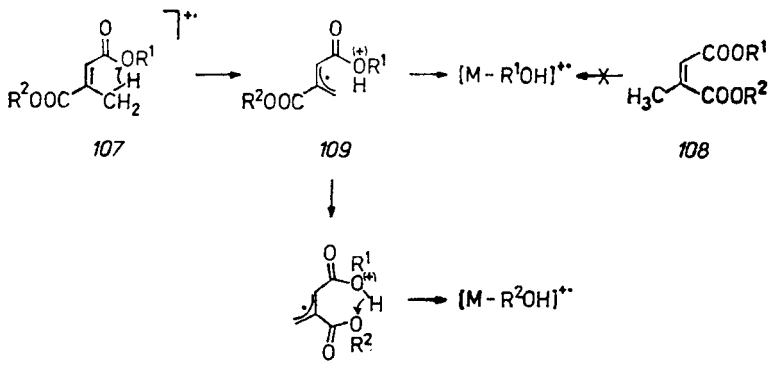
Ring annulation can have an impact on the loss of alcohol from bicyclic esters[287]. With *105* and *106* the *cis*-annulated isomer *105* shows more abundant $[M - C_2H_5OH]^{+\cdot}$ ions in its mass spectrum than does the *trans*-isomer *106* (ref.[287]). While highly regiospecific transfer of an allylic hydrogen atom takes place in both stereoisomers[287], the transition state in the more flexible *cis*-annulated isomer is probably less strained, and the elimination of ethanol proceeds more easily (Scheme 29).



105 *106*

SCHEME 29

Stereospecific elimination of alcohol from geometrical (*E*, *Z*)-isomers has been reported[291]. The electron impact mass spectrum of dimethyl mesaconate (*107*, $R^1 = R^2 = CH_3$) shows a dramatically higher $[M - CH_3OH]^{+\cdot}/[M - CH_3O]^+$



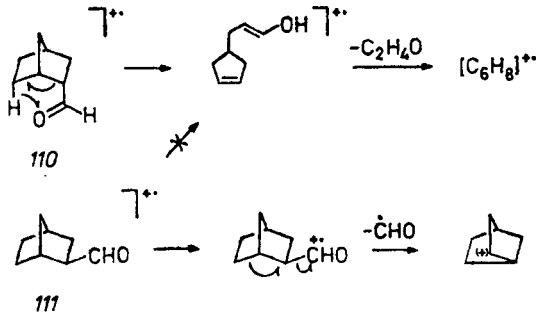
107 *109* *108*

SCHEME 30

ratio (2·1) than observed in the spectrum of dimethyl citraconate *108* (0·29) (ref.[291]). The loss of ROH from mesaconate esters is triggered by hydrogen transfer from the *cis*-disposed methyl group to the ester oxygen. The loss of ROH from the intermediate *109* (Scheme 30) competes with a hidden hydrogen transfer to the other ester moiety, which accounts for the loss of different alcohols from mixed esters[291]. The retention of the original configuration in these and some related ethylene dicarboxylates following electron impact ionization is remarkable, as other stereoisomeric olefins rapidly equilibrate[292].

The carbonyl group in aldehydes and ketones can abstract a γ-hydrogen atom in the well-known McLafferty rearrangement (ref.[293]). This intramolecular reaction has stringent steric requirements[294,295], and often is capable of differentiating stereoisomers[278]. This feature can be documented with two recent examples of stereospecific McLafferty rearrangements in bridged aldehydes[296] and ketones[297,298].

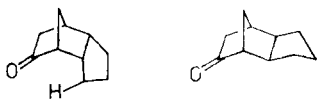
Following ionization, *endo*-bicyclo[2.2.1]heptane-2-carboxaldehyde (*110*, Scheme 31) gives much more abundant $[M - C_2H_4O]^{+\cdot}$ fragments than does the *exo*-isomer *111* (ref.[296]). The preferential elimination of C_2H_4O from the former isomer



SCHEME 31

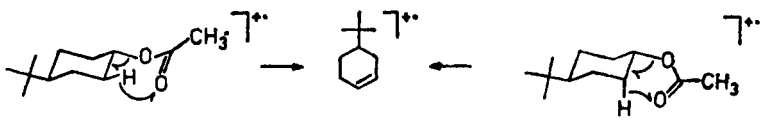
was explained by the stereospecific transfer to the carbonyl of the 6-*endo*-hydrogen atom, which initiated the overall fragmentation sequence (Scheme 31)[296]. The *exo*-isomer *111* loses preferentially the CHO· radical, possibly with anchimeric assistance by the antiperiplanar $C_{(1)}$—$C_{(6)}$ bond.

An analogous situation is encountered with stereoisomeric tricyclo[5.2.1.$0^{2,6}$]-decan-9-ones *112*, *113* of which only the *endo*-isomer *112* can undergo a McLafferty rearrangement (refs[297,298]).



112 *113*

Stereochemical effects have been observed for McLafferty-like decompositions in conformationally flexible 4-tert-butylcyclohexane derivatives[299,300]. The acetyl group in ionized *trans*-4-tert-butylcyclohexyl acetate (Scheme 32) abstracts preferentially the *trans*-equatorial hydrogen atoms at $C_{(2)}$ or $C_{(6)}$ in the course of acetic

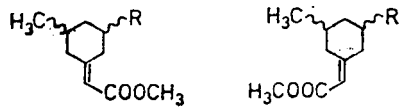


$$\frac{[M-CH_3COOH_{eq}]^{+\cdot}}{[M-CH_3COOH_{ax}]^{+\cdot}} = 3.8$$

SCHEME 32

acid elimination[299], as confirmed by stereospecific labelling[300]. Stereospecific transfer of *trans*-vicinal hydrogen atoms has been found to also take place in tert-butylcyclohexane derivatives with the diethyl malonate, methyl acetate, acetamide, and acetone oxime residues[300]. The nature of the functional group plays a role, since in compounds with the aldehyde, xanthate, and olefin functions *cis*-vicinal hydrogen atoms are transferred preferentially onto the side-chain groups[300]. In *cis*-4-tert-butylcyclohexane derivatives, the *cis*-vicinal hydrogen atoms are uniformly involved in the γ-hydrogen transfer which occurs with markedly higher stereospecificity than in the *trans*-series[300].

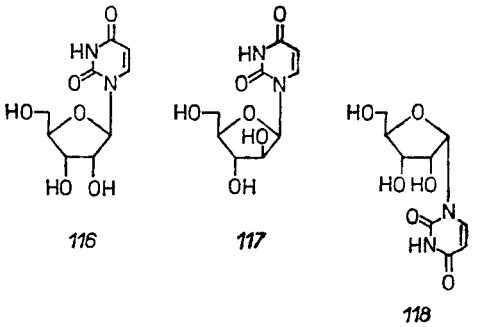
Instead of inducing a loss of a small molecule from the molecular ion, the stereospecific hydrogen transfer may trigger another fragmentation by activating remote bonds for cleavage[301]. Isomeric cyclohexylidene acetates *114*, *115* curiously differ in the loss of methyl radical from the molecular ions, with the (*E*)-isomers *115* giving the higher $[M - CH_3]^+/[M]^{+\cdot}$ ratios[302]. This stereospecific loss of methyl has been explained by a hidden transfer of the allylic hydrogen atom that activates the C—CH_3 bond in the vicinity of the radical center formed. It is notweorthy that the esters *114* and *115* were not available as pure stereoisomers, and the configurational assignment was based exclusively on the postulated mechanism of fragmentation[302].



114 *115*

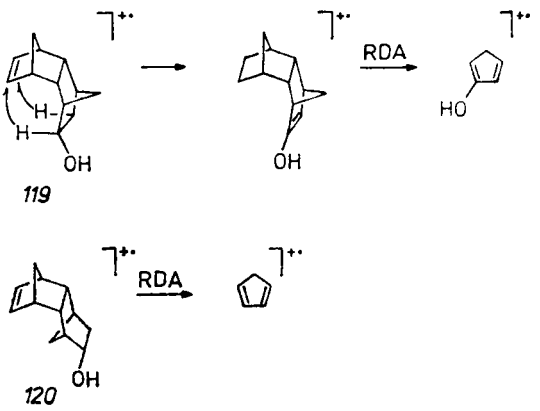
R = C_2H_5, i-C_3H_7

Hidden hydrogen transfers may account for the stereochemical differences in the electron impact mass spectra of nucleosides with *ribo* and *arabo* configuration (*116–118*)[303]. The β-isomers with the *arabo* configuration lose easily a $CH_2OH^{\bullet}$ radical, as do α-isomers of the *ribo*-series. The *cis*-arrangement of the $C_{(2)}$-hydroxyl and the base seems to be requisite for a facile loss of $CH_2OH^{\bullet}$ from these compounds.



116 *117* *118*

The hydrogen transfer can create a new double bond in the parent ion and in this way direct the course of an RDA fragmentation[298,304]. In stereoisomeric alcohols *119*, *120* the *endo*-isomer *119* undergoes dyotropic rearrangement yielding an enolic intermediate (Scheme 33) which decomposes to $[C_5H_6O]^{+\bullet}$ by RDA reaction[304]. An analogous hydrogen rearrangement is unfeasible in the *exo*-isomer *120* which fragments to give $[C_5H_6]^{+\bullet}$ instead.

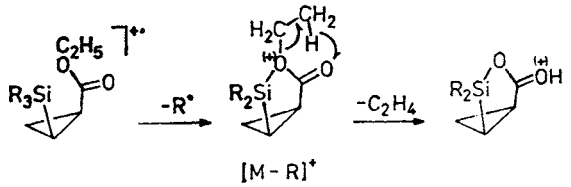


119 *120*

SCHEME 33

Transfer of groups larger than hydrogen, *e.g.* trimethylsilyl or alkoxy, can also introduce stereospecificity into fragmentations of radical cations[305–307]. In tri-

methylsilylated polyols, vicinal *cis*-interaction between the trimethylsilyl groups favours the formation of $[(CH_3)_3Si—O—Si(CH_3)_2]^+$ ions[307]. A different stereochemical effect has been observed for stereoisomeric ethyl trialkylsilylcyclopropanecarboxylates (Scheme 34)[308]. Following loss of the silicon-bound alkyl group, the $[M - R]^+$ ions from the *cis*-isomers eliminate ethylene from the ester ethyl group to form $[M - R - C_2H_4]^+$ which finally decompose to R_2SiOH^+ ions. The $[M - R - C_2H_4]^+$ ions, which are virtually absent in the spectra of the *trans*-isomers, are probably stabilized in the *cis*-isomers by formation of a new siloxane ring (Scheme 34)[308].



SCHEME 34

More or less pronounced differences in the fragmentation patterns of steroid 3α,β-OH, 5α,β-H, 8α,β-H, 14α,β-H, and 17α,β-OH isomers have recently been reported and scrutinized (refs[309-311]). Kinetic energy release data for the loss of methyl from stereoisomeric 3-hydroxyandrostan-17-ones have been investigated and found to differ only very little in dependence on the configuration at $C_{(3)}$ (refs[312,313]).

5.3. Even-Electron Anions

Even-electron anions are produced by ion–molecule reactions, *e.g.* anion attachment (Eq. (*E*)) or proton abstraction (Eq. (*F*)), in a CI ion source[314,315].

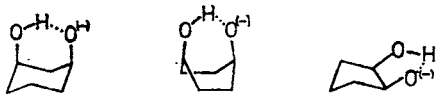
$$M \xrightarrow{X^-} [M + X]^- \qquad (E)$$

$$M—H + Y^- \rightarrow [M - H]^- + HY \qquad (F)$$

Enolizable carbonyl compounds, alcohols, diols, *etc.* can be deprotonated with gaseous hydroxyl anion generated from nitrous oxide and methane in CI plasma[316]. Most of the stereochemical work on gaseous anions has been done with the hydroxyl anion as the base.

Stereoisomeric cyclohexane-1,3- and 1,4-diols and cyclopentane-1,2-diols differ in the relative abundance of $[M - H]^-$ ions produced by proton abstraction with

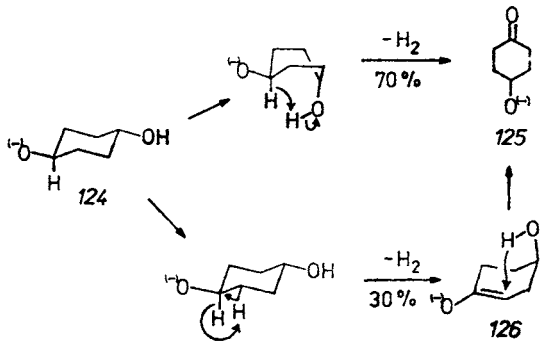
hydroxyl or fluoride anions[101,317]. The *cis*-isomers generally give more abundant $[M - H]^-$ ions, while extensive fragmentation by loss of dihydrogen and water takes place in the *trans*-isomers. The higher stability of $[M - H]^-$ from the *cis*-isomers was attributed to intramolecular hydrogen bonding of the remaining acidic proton between the *cis*-disposed hydroxy groups in *121* – *123* (ref.[101]).



121 *122* *123*

The $[M - H]^-$ ions from stereoisomeric cyclohexane-1,3-diols differ markedly in their unimolecular and collision-induced decompositions[317]. The $[M - H]^-$ ions from the *cis*-isomer decompose mainly by loss of water, while those from the *trans*-isomer eliminate a hydrogen molecule[317].

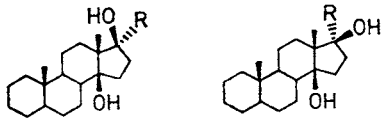
The loss of dihydrogen from $[M - H]^-$ ions prepared from *trans*-cyclohexane-1,4-diol (*124*) was elucidated in detail by means of deuterium labelling and product identification through CID spectra[318]. The major reaction path (70%) proceeds with hydrogen transfer from the alkoxide carbon center (Scheme 35), yielding the



SCHEME 35

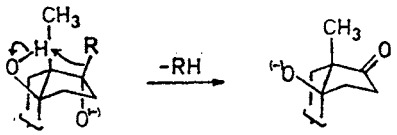
ketolate anion *125*. The minor path (30%) involves 1,2-hydrogen elimination to produce an intermediate enolate anion *126* which rearranges by transferring the hydroxyl proton to the enolate double bond to eventually give the ketolate *125* (ref.[318]).

The $[M - H]^-$ ions prepared from stereoisomeric 17-substituted androstane-14β,17-diols *127* and *128* (R = H, CH_3, C_2H_5, $CH{=}CH_2$, $C{\equiv}CH$) show stereospecific decompositions depending on the configuration at $C_{(17)}$[319]. The 14β,17β-diols *127* with *cis*-disposed hydroxy groups show more abundant $[M - H]^-$ ions than



127 128

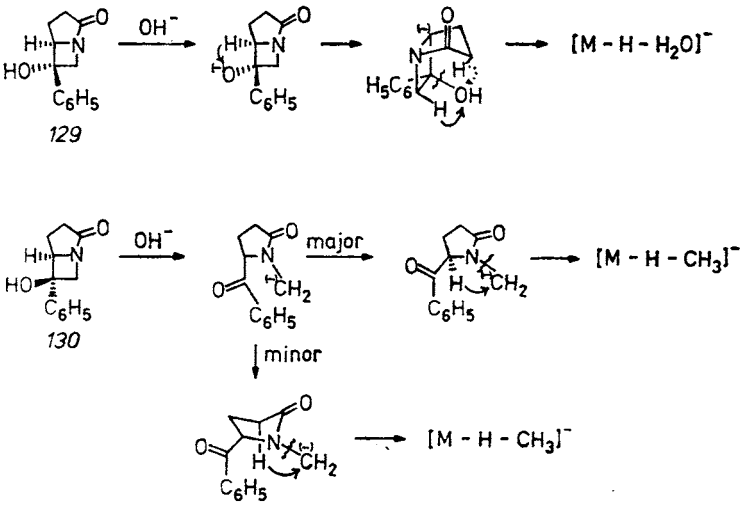
do the *trans*-diols *128*, possibly because of hydrogen bonding in the former ions[319]. The $[M - H]^-$ ions from the 14β,17α-diols *128* eliminate easily RH molecules with the hydrogen atom coming from the 14β-hydroxyl (Scheme 36)[319].



SCHEME 36

Other steroid alcohols and diols, *e.g.* stereoisomeric 5α,14β-androstane-17-ols[319], androstane-3-ols[104], 5α- and 5β-cholestane-3,5-diols[320], and 5-cholestene-3,7-diols[320] show only modest differences in their negative CI mass spectra. By contrast, large stereochemical effects have been reported for the water loss from $[M - H]^-$ ions derived from stereoisomeric monoterpene alcohols[321].

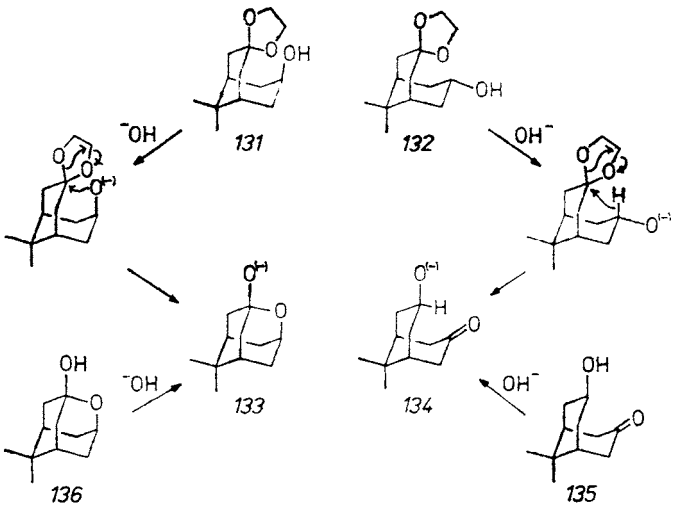
Stereospecific proton transfer reactions in anions have been reported to differentiate isomeric bicyclic lactames, *e.g.* *129*, *130* and their homologues[322]. While only



SCHEME 37

$[M - H]^-$ ions are produced in the ion-source negative CI mass spectra of both stereoisomers[322], unimolecular decompositions of metastable $[M - H]^-$ and CID of stable $[M - H]^-$ ions do differ, depending on the relative configuration at $C_{(5)}$ and $C_{(6)}$ (Scheme 37). The $[M - H]^-$ ion from the *exo*-OH isomer *129* loses water following subsequent transfers of the bridgehead hydrogen atom and another one from the skeleton. The $[M - H]^-$ ion from the *endo*-isomer *130* undergoes ring cleavage and decomposes by losing a methyl to yield isomeric odd-electron anions (Scheme 37)[322].

Intramolecular nucleophilic displacement can distinguish stereoisomeric $[M - H]^-$ ions, as reported for the bicyclo[3.3.1]nonane derivatives *131* and *132* (Scheme 38)[323]. While the negative CI mass spectra of *131* and *132* differ very little[323], the isomers can be differentiated by decompositions of metastable $[M - H]^-$ ions. In *131* the *endo*-alkoxide anion attacks the dioxolane ring which eliminates a C_2H_4O molecule to yield the hemiketal ion *133*. In the *exo*-alkoxide anion the dioxolane ring is cleaved by attack of a hydride ion and loses C_2H_4O to give a ketolate anion *134* isomeric with *133* (Scheme 38). The isomeric $[M - H - C_2H_4O]^-$ ions were distinguished through their CID spectra which also made it possible to assign structure to these ions *via* more straightforward precursors *135* and *136* (ref.[323]).



SCHEME 38

Although examples of stereochemical behaviour of even-electron anions are less numerous than with cations, the stereochemistry of negative ions appears to be a very promising area of reserach with perspective applications in structure elucidation of polyfunctional compounds.

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