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Stereospecific Fragmentation Processes in Cycloalkane/Cycloalkene-Fused Isomers of Saturated Pyrrolo[2,1-*b*][1,3]oxazin-6-one Derivatives

Kalevi Pihlaja and Vladimir V. Ovcharenko
Department of Chemistry, University of Turku, Turku, Finland

Géza Stájer
Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, Szeged, Hungary

Electron ionization-induced fragmentations were studied in a set of saturated pyrrolo[2,1-*b*][1,3]oxazin-6-one derivatives fused to either cycloalkane or cycloalkene rings, including seven pairs of *cis/trans* and *endo/exo* annelation isomers. Fragmentation patterns were confirmed by accurate mass measurements and metastable ion spectra. A number of striking differences were observed between the mass spectra of cyclohexene-fused isomers due to highly stereospecific retro-Diels-Alder (RDA) fragmentation of their $M^{+\cdot}$ ions. The observed 90% stereospecificity is abnormally high in the light of the recent classification (A. Mandelbaum, 1994) of stereospecific RDA fragmentations according to the degree of substitution of the cyclohexene ring being cleaved. In the absence of RDA processes, the differences between the mass spectra of cyclohexane-fused isomers originated from heterocyclic fragmentations. The assumed mechanistic interpretation of the observed differences, e.g., in the formation of $[M - C_3H_5O]^+$ ions, was consistent with the condensed-state conformations of these isomers determined previously by NMR and X-ray diffraction studies. Because of rapid RDA decompositions of their rather unstable $M^{+\cdot}$ ions, the spectra of the di*endo*/di*exo* norbornene-fused isomers were virtually identical. (J Am Soc Mass Spectrom 1999, 10, 393–401) © 1999 American Society for Mass Spectrometry

Our earlier studies on the stereochemical aspects of electron ionization (EI)-induced fragmentation processes in partially saturated heterocycles has brought some interesting results. In particular, considerable differences were observed between the 70-eV mass spectra of *cis* and *trans* annelated isomers of cycloalkane- and cycloalkene-fused pyrimidone derivatives [1, 2]. In the present paper, we report on a novel set of heterocycles **1–8** comprising of pairs of stereoisomers (either *cis/trans* or *endo/exo* annelated) of polycyclic saturated pyrrolo[2,1-*b*][1,3]oxazin-6-one derivatives (Figure 1). The absolute stereochemistry and conformations of compounds **1–5** have been determined by NMR and X-ray diffraction studies [3]. An NMR study of compounds **6–8** will be published elsewhere.

It is known that the conformations of the neutral compounds are not necessarily relevant to the reacting configurations of their $M^{+\cdot}$ ions. In our opinion, however, they merit a brief discussion, because most of the stereospecific fragmentations observed in the present work are fairly consistent with the condensed-state structures of the compounds studied. According to the NMR data [3], the pyrrolo[2,1-*b*][1,3]oxazine nucleus of compounds **1–5** is conformationally rigid. In all cases, the five-membered ring has an envelope conformation with C-3a (according to the numbering system previously used in [3], cf. Figure 1) as the flip atom. The oxazine ring of compound **1** is a nearly ideal chair conformation, which becomes more twisted in norbornene- and norbornane-annelated structures **3** and **5**. However, both cyclohexane-annelated isomers **4a,b** have "chair–chair," and their cyclohexene-annelated analogs **2a,b** "chair–(half-chair)" conformations. Interatomic distances obtained from X-ray diffraction data suggest that the lactam C–N bond is shortened and has significant π character. Rigid arrangement of the lactam moiety is also indicated by homoallylic-type five-bond couplings observed between H-2 and H-9a(ax) in compounds **2b** and **4b**. This conformational rigidity has certain implications for the stereospecific formation of $[M - C_3H_5O]^+$ ions in their spectra, which will be discussed later.

Address reprint requests to Professor K. Pihlaja, Department of Chemistry, University of Turku, FIN-20014 Turku, Finland. E-mail: kpihlaja@utu.fi

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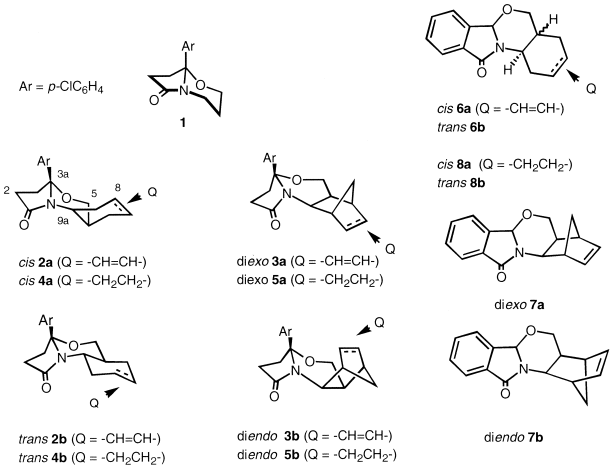
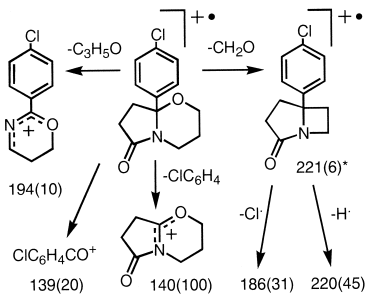


Figure 1. The compounds examined in this study.



Scheme 1. Characteristic fragment ions in the 70-eV EI mass spectrum of 8a-(4-chlorophenyl)perhydropyrrolo[2,1-*b*][1,3]-oxazine **1**. Asterisks denote RA values corrected for isotopic contributions.

Experimental

The low-resolution EI mass spectra were obtained using a VG 7070E mass spectrometer (Manchester, UK) at 70 eV (direct insertion probe, ion source temperature 180 °C). Elemental compositions of fragment ions were determined within an average accuracy of $\sim 3 \times 10^{-4}$ u based on accurate mass measurements performed with a VG ZabSpec instrument at a resolution of 10–12,000 (10% valley definition) using the peak matching technique and perfluorokerosene (PFK) as a reference compound. Metastable ion spectra (B/E and B^2/E linked scans) were recorded on the same instrument. All the fragmentation processes shown in Schemes were observed in the metastable ion spectra. In several cases, collision-induced dissociation (CID)-enhanced spectra of metastable ions were recorded (using B/E scanning) by introducing helium into FFR1.

Mass-analyzed ion kinetic energy (MIKE) spectra were obtained on the same instrument using air as a collision gas at a pressure in the MIKES cell (located in the FFR2) providing 50% transmission of the initial ion beam. Parent ions were manually selected at a resolu-

Table 1. The 70-eV EI mass spectra, showing peaks of >5% relative abundance (RA), of compounds **1–8**

Compd.	*m/z* (%RA)
1	253(12) 252(6) 251(36, M) 222(16) 221(12) 220(45) 196(7) 194(10) 186(31) 158(6) 141(13) 140(100) 139(20) 138(6) 137(6) 112(12) 111(10) 84(5) 75(8) 58(15) 56(11) 55(11) 43(27) 41(9)
2a,b	*cis* **2a:** 305(25) 304(16) 303(80, M) 251(27) 250(14) 249(84) 248(13) 246(15) 223(6) 222(33) 221(17) 220(100) 207(12) 205(36) 197(11) 196(24) 195(35) 194(66) 193(13) 192(58) 150(7) 141(23) 140(9) 139(67) 138(44) 137(22) 116(6) 115(10) 113(9) 111(27) 110(18) 100(25) 93(26) 92(17) 91(15) 82(7) 80(7) 79(24) 78(8) 77(30) 75(12) 67(6) 65(6) 56(18) 55(23) 54(11) 53(11) 51(8) 41(16)
	trans **2b:** 305(17) 304(9) 303(52, M) 218(7) 197(10) 196(35) 195(30) 194(100) 193(6) 192(31) 139(16) 138(6) 111(9) 100(7) 93(14) 92(17) 91(10) 79(13) 77(14) 55(8) 41(7)
3a,b	di*exo* **3a:** 315(<1, M) 252(13) 251(35) 250(40) 249(100) 223(6) 222(31) 221(17) 220(97) 207(10) 205(30) 195(7) 194(7) 192(10) 141(14) 139(49) 138(41) 137(17) 115(6) 111(16) 110(15) 100(6) 91(12) 77(8) 75(7) 66(19) 65(8) 56(17) 55(13)
	di*endo* **3b:** 315(<1, M) 252(12) 251(38) 250(40) 249(94) 223(6) 222(33) 221(19) 220(100) 207(12) 205(35) 195(7) 194(8) 192(11) 150(6) 141(16) 140(7) 139(50) 138(44) 137(18) 115(6) 113(6) 111(18) 110(16) 100(6) 91(10) 77(8) 75(8) 66(20) 65(9) 56(20) 55(14) 41(6)
4a,b	*cis* **4a:** 307(6) 305(20, M) 250(12) 249(8) 248(30) 196(8) 195(14) 194(100) 141(7) 139(23) 111(7) 100(14) 95(22) 67(7) 55(9) 43(11) 41(11)
	trans **4b:** 305(5, M) 277(7) 275(21) 196(23) 195(13) 194(100) 139(10) 100(8) 95(11) 67(6) 55(8) 41(9)
5a,b	di*exo* **5a:** 319(9) 318(6) 317(29, M) 262(10) 261(6) 260(21) 220(6) 218(7) 207(13) 206(100) 195(7) 194(14) 141(15) 139(45) 138(6) 111(10) 107(17) 79(16) 77(6) 67(14) 66(8) 56(6) 55(9) 41(11)
	di*endo* **5b:** 319(9) 318(6) 317(30, M) 262(10) 261(6) 260(20) 220(7) 218(8) 207(15) 206(100) 195(7) 194(13) 141(15) 139(45) 138(6) 111(11) 107(18) 79(17) 77(6) 67(14) 66(8) 56(6) 55(8) 41(12)
6a,b	*cis* **6a:** 242(11) 241(65, M) 188(10) 187(75) 186(11) 159(35) 158(100) 133(25) 132(15) 130(11) 105(15) 104(13) 79(16) 78(6) 77(32) 76(10) 51(10) 41(7)
	trans **6b:** 242(12) 241(74, M) 134(10) 133(100) 132(41) 105(12) 104(10) 92(17) 91(9) 79(36) 78(6) 77(33) 76(8) 51(10) 41(8)
7a,b	di*exo* **7a:** 253(2, M) 188(26) 187(100) 186(9) 159(35) 158(97) 133(8) 130(9) 105(12) 104(9) 91(5) 77(15) 76(6) 66(8) 51(7)
	di*endo* **7b:** 253(1, M) 188(25) 187(100) 186(9) 159(36) 158(92) 133(9) 130(9) 105(12) 104(9) 91(7) 77(16) 76(6) 66(9) 51(7)
8a,b	*cis* **8a:** 244(17) 243(100, M) 242(60) 215(6) 214(14) 213(20) 201(10) 200(69) 186(6) 160(12) 158(10) 148(15) 134(11) 133(58) 132(56) 130(13) 105(20) 104(17) 95(17) 81(19) 79(6) 77(30) 76(13) 67(11) 55(7) 54(8) 53(9) 51(13) 41(26)
	trans **8b:** 244(17) 243(100, M) 242(84) 215(8) 214(14) 213(45) 200(14) 160(18) 148(15) 146(9) 134(15) 133(84) 132(92) 130(14) 105(28) 104(19) 95(16) 90(6) 89(8) 81(30) 79(9) 77(38) 76(15) 67(14) 55(10) 54(11) 53(10) 51(15) 41(32)

Table 2. Abundances (% TIC above m/z 39) of characteristic ions (unrelated to RDA processes) in the mass spectra of *p*-chlorophenyl substituted derivatives **1–5** (Ar = ClC_6H_4)

Compound		$M^{+\cdot}$	$[M - CH_2O]^{+\cdot}$	$[M - C_3H_5O]^+$	$[M - C_7H_9O]^+$	$[M - Ar]^+$	Ar^+	$ArCO^+$
1		10.0	2.9	2.4	···	17.8	2.4	4.7
2a	*cis*	8.3	<0.5	1.4	6.0	3.2	2.4	6.0
2b	*trans*	12.9	<0.5	0.4	21.2	4.9	1.9	3.3
4a	*cis*	7.0	<0.5	8.6	6.1[b]	18.6[a]	2.3	7.0
4b	*trans*	1.8	7.5	0.8	23.5[b]	9.3[a]	1.7	3.5
3a	di*exo*	···	···	···	···	···	2.4	7.0
3b	di*endo*	···	···	···	···	···	2.5	6.8
5a	di*exo*	6.8	<0.5	4.1	2.6[c]	17.5	2.1	8.9
5b	di*endo*	7.5	<0.5	4.2	2.7[c]	15.7	2.2	9.4

Combined abundances ($^{35}Cl + {}^{37}Cl$) are listed for chlorine-containing ions.
[a]Corrected for the contribution from isobaric $[M - C_7H_{11}O]^+$ ions.
[b]$[M - C_7H_{11}O]^+$ ions.
[c]$[M - C_8H_{11}O]^+$ ions.

tion of ~2000 by adjusting ESA1, and their MIKE spectra obtained by scanning ESA2 voltage. The ESA voltage scans were automatically converted to m/z scale by the data acquisition software (VG OPUS). Scans were accumulated until the signal-to-noise ratio of at least 20 was reached. Superimposed parts of MIKE spectra from isomeric $M^{+\cdot}$ ions of compounds **4** and **8** (m/z 305 and 243, respectively) are shown in Figure 3.

Results and Discussion

EI mass spectra of compounds **1–8** are listed in Table 1. $M^{+\cdot}$ ions of all compounds studied, except norbornene-fused **3** and **7**, are fairly stable under EI. Compound **1** mainly decomposes by losing the aryl substituent (Scheme **1**). A characteristic loss of CH_2O from the heterocyclic part was observed, and it proved to be a common fragmentation in this series of compounds: apart from compound **1**, abundant $[M - CH_2O]^{+\cdot}$ ions were also observed with cyclohexane-fused derivatives **4b**, **8a,b**. For compound **1**, another characteristic process, a one-step loss of $C_3H_5O^{\cdot}$ from $M^{+\cdot}$ ions, could involve either the pyrrolo or the oxazine ring. The latter possibility was, however, excluded, because peaks of $[M - C_3H_5O]^+$ ions were also present in the spectra of compounds **2a**, **4a**, and **5**, where their formation by the oxazine ring cleavage would have involved two hydrogen transfers and two C–C bond ruptures. The $[M - C_3H_5O]^+$ ions are also completely absent from the spectra of compounds **6–8**, where the pyrrolo ring is benzo fused. Hence the loss of C_3H_5O from $M^{+\cdot}$ ions of compounds **1**, **2**, **4**, **5** involves the pyrrolo rings to form aryloxazolidinium ions (Scheme **1**). A number of common fragment ions are listed in Tables 2 and 3 for aryl-substituted derivatives **1–5** and benzo-fused compounds **6–8**. The data in Table 2 show that $[M - ClC_6H_4]^+$ ions are very stable and, together with $ArCO^+$ and Ar^+ ions, they generally provide the largest contributions to total ion current (TIC) in the absence of RDA processes (cf. compounds **1**, **4**, **5**). However, the RDA fragmentation processes make the spectra of cyclohexene-fused compounds **2** and **6** particularly noteworthy.

Stereospecific RDA Fragmentations

A striking difference can be seen between the 70-eV mass spectra of stereoisomers with *cis*- and *trans*-fused cyclohexene rings (Figure 2). Thus, *cis*-fused isomers **2a**, **6a** readily undergo retro-Diels-Alder fragmentation to form $[M - C_4H_6]^{+\cdot}$ ions, and the base peaks in their spectra correspond to $[M - C_4H_6 - HCO]^+$ ions. The abundance of these characteristic ions is decreased by an order of magnitude in the spectra of *trans*-fused isomers, which are dominated by peaks of $[M - C_7H_9O]^+$ (**2b**) and $[M - C_7H_8O]^{+\cdot}$ (**6b**) ions formed in

Table 3. Abundances (% TIC above m/z 39) of characteristic ions (unrelated to RDA processes) in the mass spectra of benzo-fused derivatives **6–8**

Compound		$M^{+\cdot}$	$[M - H]^+$	$[M - CH_2O]^{+\cdot}$	$[M - C_3H_7]^+$	m/z 133 (C_8H_7NO)	m/z 133 ($C_8H_5O_2$)	m/z 132 (C_8H_6NO)	$C_6H_5^+$
6a	*cis*	10.2	0.3	0.8	···	3.6[a]	···	2.3	4.7
6b	*trans*	14.5	1.0	0.2	···	18.0[a]	···	7.7	6.2
7a	di*exo*	0.4	···	···	···	···	1.7[a]	1.0	3.0
7b	di*endo*	0.3	···	···	···	···	1.8[a]	1.2	3.1
8a	*cis*	12.9	6.5	2.2	7.5	3.4[a]	2.3[a]	6.1	3.3
8b	*trans*	11.1	7.9	4.2	1.4	5.4[a]	1.6[a]	8.7	3.6

[a]Corrected for isotopic contributions.

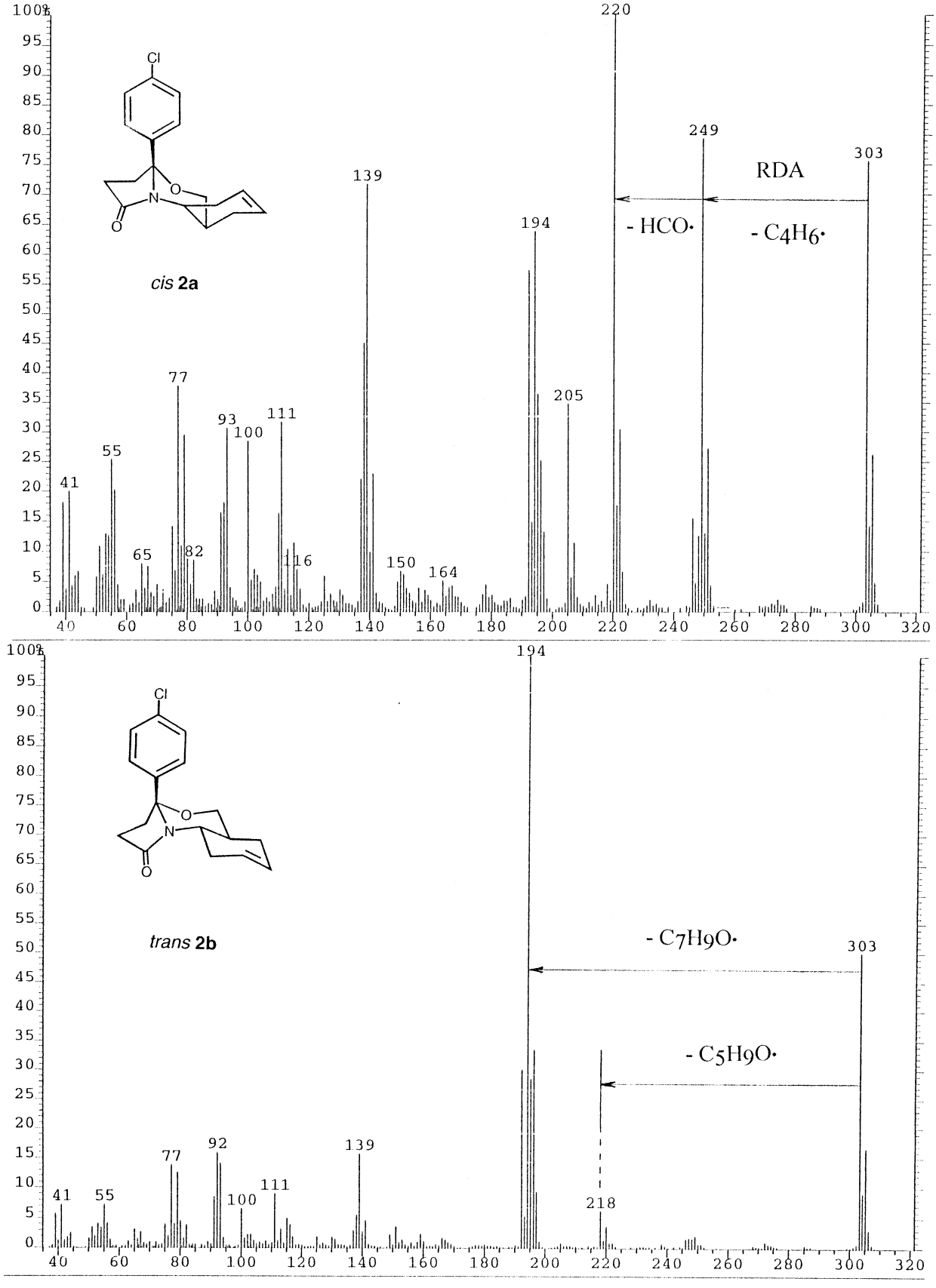
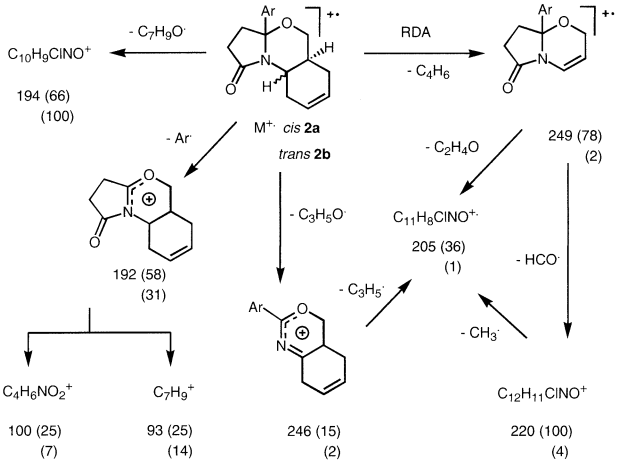


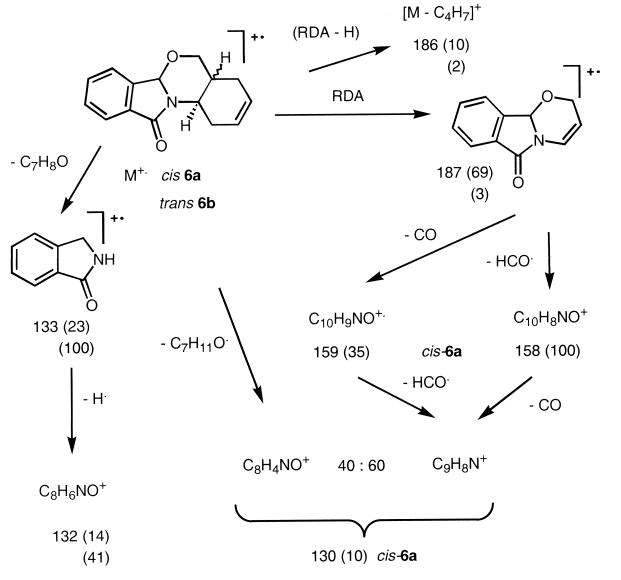
Figure 2. Comparison of 70-eV EI spectra for the *cis/trans* annelation isomers (top) **2a** and (bottom) **2b**.



Scheme 2. Characteristic fragmentation patterns in the 70-eV mass spectra of isomeric compounds **2**. Relative abudances of fragment ions are shown in parentheses, the top value corresponding to *cis* **2a**.

one step from the respective $M^{+\cdot}$ ions (Schemes **2** and **3**). Accordingly, the total share of all the RDA-related ions (those formed by the RDA decomposition of $M^{+\cdot}$ ions and the products of their further fragmentation) in TIC is by an order of magnitude greater in the spectra of *cis* isomers. The RDA-related fragment ions are listed in Table 4. The even-electron dienophile cations resulting from RDA fragmentations accompanied by hydrogen transfer are referred to as either (RDA + H) or (RDA − H) whether the hydrogen atom was added to or abstracted from the dienophile.

The stereospecificity of an RDA fragmentation has been defined [4] as a normalized difference between the



Scheme 3. Characteristic fragmentation patterns in the 70-eV mass spectra of isomeric compounds **6**. Relative abudances of fragment ions are shown in parentheses, the top value corresponding to *cis* **6a**.

abundances of the same RDA ions produced from either isomer, $(I_{cis} - I_{trans})/(I_{cis} + I_{trans})$. We have found the observed RDA stereospecificity to equal 90% for both pairs of cyclohexene-fused compounds **2** and **6**, which is quite high and, according to the literature, rather unusual for polycyclic systems comprising cyclohexene rings with unsubstituted allylic positions [4]. The concurrent (RDA − H) fragmentation leading to $[M - C_4H_7]^+$ ions is only significant for **6a** (1.7% TIC) and occurs with a lower stereospecificity of ~70%. In the case of compounds **2a,b**, $[M - 55]^+$ peaks were found to be doublets corresponding to $[M - C_4H_7]^+$ and $[M - C_3H_3O]^+$ ions, the former species contributing only 0.5% and <0.1% TIC in the spectra of *cis* **2a** and *trans* **2b**, respectively.

Stereospecificity of RDA fragmentation in polycyclic systems has been correlated with the degree of substitution of the cyclohexene ring involved in this process [4]. In particular, the degree of substitution at the bonds that are cleaved in the RDA fragmentation was supposed to be crucial for RDA stereospecificity, the explanation of the phenomenon being based on the assumedly different effect of substitution on the critical energies of the RDA processes in the respective *cis* and *trans* isomers. Low RDA stereospecificity in both high- and low-substituted systems was rationalized by assuming that the critical energies for RDA in *cis* and *trans* isomers are either both low (when the substitution is high) or both high (when it is low), whereas "medium" substitution selectively increases the critical energy for RDA in *trans* isomers with respect to *cis* isomers, thus leading to higher RDA stereospecificity. The somewhat blurred definition of "medium" (and "low-medium") substitution adopted [4] for the purpose may be questionable, but this does not invalidate, of course, the whole concept of interpreting the RDA stereospecificity in terms of critical energy differences. Because the cyclohexene rings in compounds **2** and **6** are completely unsubstituted, we only state here that the apparently large gaps between the critical energies for RDA processes in these two pairs of *cis/trans* isomers arise from structural differences other than ring substitution patterns.

Nonstereospecific RDA Fragmentations

The RDA decomposition of $M^{+\cdot}$ ions in *cis*-annelated *endo/exo* isomers **3a,b** and **7a,b** was found to be the predominant fragmentation pathway lacking any significant stereospecificity. Indeed, the 70-eV EI spectra of the corresponding isomers are nearly identical (Table 1) and dominated by $[M - C_5H_6]^{+\cdot}$ and $[M - C_5H_6 - HCO]^+$ ions. The latter species have much higher APs than the initial RDA fragments, as is demonstrated by low-energy EI spectra of isomers **3a,b**. At 12 eV, the abundances of $[M - C_5H_6 - HCO]^+$ and $[M - C_5H_6 - C_2H_4O]^{+\cdot}$ ions are roughly equal and reduced to 5%–10% of the abundance of $[M - C_5H_6]^{+\cdot}$ (RDA) ions, which still provide the base peak at this ionization

Table 4. Abundances (% TIC above m/z 39) of RDA-related ions in the mass spectra of cyclohexene- and norbornene-annelated stereoisomers **2**, **3**, **6**, **7**

Compd.	$M^{+\cdot}$	RDA $[M - C_4H_6]^{+\cdot}$	(RDA − H) $[M - C_4H_7]^+$	$[M - C_4H_6 - HCO]^+$	$C_4H_6^{+\cdot}$	$C_4H_7^+$
cis **2a**	8.3	7.4	0.5	9.1	0.4	...[a]
trans **2b**	12.9	0.3	<0.1	0.8	0.4	...[a]
cis **6a**	10.2	11.5	1.7	16.6	0.4	0.2
trans **6b**	14.5	0.6	0.3	0.8	0.3	0.1
	$M^{+\cdot}$	RDA $[M - C_5H_6]^{+\cdot}$	(RDA + H) $[M - C_5H_5]^+$	$[M - C_5H_6 - HCO]^+$	$C_5H_6^{+\cdot}$	$C_5H_5^{+\cdot}$
di*exo* **3a**	<0.1	14.9	3.7[b]	14.4	2.1	0.9
di*endo* **3b**	<0.1	13.7	4.0[b]	14.6	2.1	0.9
di*exo* **7a**	0.4	21.6	2.6[b]	21.0	1.3	0.9
di*endo* **7b**	0.3	22.4	2.8[b]	20.6	1.6	1.0

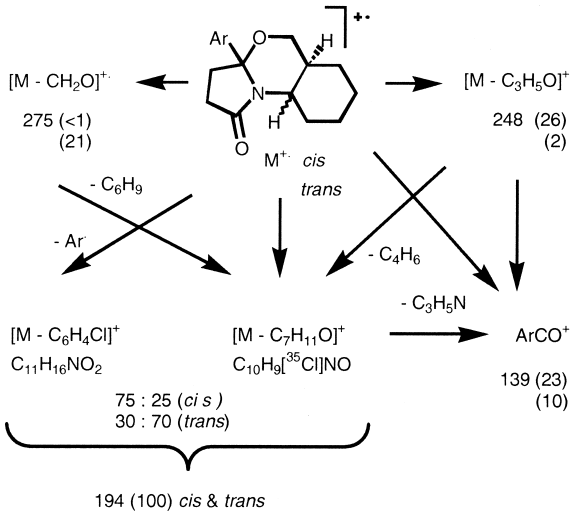
Combined abundances ($^{35}Cl + {}^{37}Cl$) are listed for chlorine-containing ions.
[a] m/z 55: $C_3H_3O^+$.
[b] Corrected for isotopic contributions.

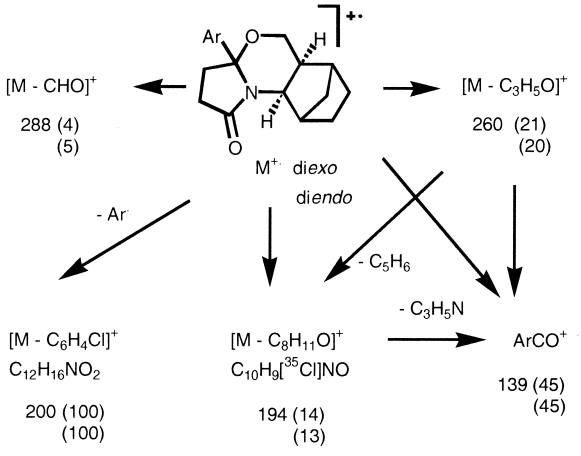
energy. The peaks of $M^{+\cdot}$ ions are negligible in the range of the ionization energies from 70 eV down to 10 eV. However, because of the high sensitivity of the VG ZabSpec instrument, the metastable ion spectra (linked B/E scanning) to find daughter ions originating from $M^{+\cdot}$ could be recorded with excellent signal-to-noice ratio not only for compounds **7**, but also for **3** ($I_M < 1\%$ RA). In all cases, the most abundant metastable ions corresponded to (RDA + H) processes leading to the formation of $[M - C_5H_5]^+$ ions, although the metastable ions for the RDA process with the loss of C_5H_6 were also present. The contributions of $[M - C_5H_5]^+$ ions to the $[M - 65]^+$ peaks were estimated by direct observation at a sufficiently high resolution. It is seen from Table 4 that (RDA + H) fragment ions constitute only ~3% TIC in the spectra of compounds **3** and **7**, regardless of the norbornene orientation (*endo* or *exo*), whereas RDA without hydrogen transfer is the most important fragmentation process in all cases. Significant amounts of $C_5H_6^{+\cdot}$ ions were also formed (but not necessarily from $M^{+\cdot}$ ions, because no corresponding transitions were observed in the metastable spectra).

Nonstereospecific RDA and (RDA + H) processes have earlier been reported for mass spectra of maleic anhydride adducts with cyclopentadiene and 1,3-cyclohexadiene [5], as well as in norbornene-condensed 1,3-oxazinones [6]. On the other hand, (RDA + H) and (RDA + 2H) fragmentations were found to be stereospecific in di*exo*/di*endo* isomers of bicyclo [2.2.1]hept-5-en-2,3-dicarboxylates [7]. In the latter case, however, $M^{+\cdot}$ ions were generally stable enough to allow calculation of $I_{(RDA+H)}/I_M$ ratios, which actually revealed the RDA stereospecificity, as the relative abundances of the diagnostic (RDA + H) ions themselves happened to be close and even identical in several cases (e.g., for isomers of dimethyl and diethylbicyclo[2.2.1]hept-5-en-2,3-dicarboxylates [7]). The extremely low stability of $M^{+\cdot}$ ions in the case of compounds **3** and **7**, the predominance of RDA fragmentation over (RDA + H), and the great resemblance between the spectra of their di*endo* and di*exo* isomers indicate a fast (presumably, concerted) RDA decomposition occurring at comparable rates in the $M^{+\cdot}$ ions of both di*exo* and di*endo* isomers. It may be that the stereospecificity of the (RDA + H) and (RDA + 2H) processes reported by Mandelbaum et al. [4, 5, 7] results from lower rates (as those fragmentation processes involve hydrogen transfers and rotation around the C–C bonds) and higher critical energies as compared to the nonstereospecific RDA decompositions observed in norbornene-fused derivatives **3** and **7**. Given that RDA fragmentation with the loss of C_5H_6 clearly prevails over (RDA + H) in the spectra of **3** and **7**, the similarly nonstereospecific RDA and (RDA + H) fragmentations reported for other norbornene-fused 1,3-oxazinones [6] cannot be directly compared to the present case. Indeed, $[M - C_5H_5]^+$ ions corresponding to the (RDA + H) process were always more abundant than $[M - C_5H_6]^{+\cdot}$ (RDA) ions in the earlier reported spectra [6], but there were also present very abundant $C_5H_6^{+\cdot}$ ions giving rise to the base peaks in all spectra except those where the base peaks corresponded to $[M - C_5H_5]^+$ (RDA + H) ions [6]. Thus, the moderate abundance of $C_5H_6^{+\cdot}$ ions in the spectra of compounds **3** and **7** indicates a different charge distribution among the RDA fragments. However, the fact that $M^{+\cdot}$ ions of the compounds reported earlier [6] were invariably of low abundance (1%–2% RA) suggests that the similarly low RDA stereospecificity in 1,3-oxazinones [6] and in compounds **3** and **7** may have a common origin in the low stability of their $M^{+\cdot}$ ions due to low critical energies of RDA decompositions in all isomers of these compounds.

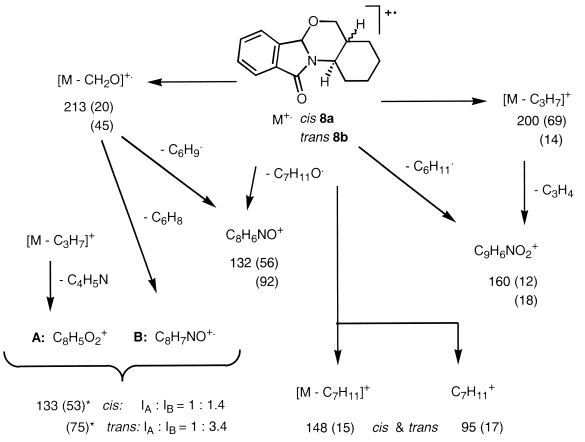
Fragmentation Patterns of Cyclohexane- and Norbornane-Fused Isomers

In the absence of RDA decomposition, a number of stereospecific fragmentation processes were still observed in the mass spectra of saturated (i.e., cyclohexane- and norbornane-fused) analogs of the already discussed compounds. Thus, $[M - CH_2O]^{+\cdot}$ ions were





Scheme 4. Characteristic fragmentation processes in the 70-eV EI mass spectra of compounds **4** and **5**. Relative abundances of the ions are shown in parentheses, the top value referring in each case to either *cis* (**4a**) or di*exo* (**5a**) isomer.



Scheme 5. Characteristic fragmentation patterns in the 70-eV mass spectra of isomeric compounds **8**. Relative abundances of fragment ions are shown in parentheses, the top value corresponding to *cis* **8a**. Asterisks denote RA values corrected for isotopic contributions.

more abundant in the spectra of *trans*-fused isomers, whereas the $M^{+\cdot}$ ions of *cis*-fused compounds preferentially lost either $C_3H_5O^{\cdot}$ or $C_3H_7^{\cdot}$ fragments depending on whether the aromatic moiety was attached as a substituent or benzo fused (Schemes **4** and **5**). As we have already mentioned, the formation of $[M - C_3H_5O]^+$ ions in compounds **1–5** is likely to involve the pyrrolo ring cleavage. This hypothesis is strengthened by a comparison of the spectra of isomers **4**. The abundance of $[M - C_3H_5O]^+$ ions is by an order of magnitude higher in the spectrum of *cis* **4a**. The MIKE spectra of the respective $M^{+\cdot}$ ions (Figure 3a) reveal a much greater difference. The observed substantial difference between the abundances of $[M - C_3H_5O]^+$ ions in MIKE scans from $M^{+\cdot}$ ions of **4a** and **4b** suggests that the critical energy for this fragmentation process must be indeed very low in *cis* **4a**.

The high stereospecificity of $C_3H_5O^{\cdot}$ loss can readily be explained assuming that it involves a regiospecific hydrogen transfer (of H-9a, using the numbering shown in Figure 1) onto the carbonyl oxygen atom (cf. Scheme **6**). This assumption also explains the nonstereospecific loss of $C_3H_5O^{\cdot}$ from isomeric $M^{+\cdot}$ ions of norbornane compounds **5**, since the molecular structures for di*exo* **5a** and di*endo* **5b** obtained from X-ray diffraction analysis [3] show nearly identical spatial arrangement of H-9a with respect to the carbonyl oxygen atom in both cases.

The main stereospecific fragmentation processes differentiating between the $M^{+\cdot}$ ions of benzo-fused isomers **8** are the losses of CH_2O and $C_3H_7^{\cdot}$ fragments. Although stereochemical differences are less obvious than in the spectra of isomers **4**, the reversed ratio of $[M - CH_2O]^{+\cdot}$ and $[M - C_3H_7]^+$ ion abundances (also clearly seen in the MIKE spectra, Figure 3b) results in further differences between *cis* **8a** and *trans* **8b** at later stages of fragmentation. For instance, the share of $[M - C_7H_{12}N]^+$ ions ($C_8H_5O_2^+$) in the doublet peak at m/z 133 is much higher for the *cis*-isomer **8a**, as they have abundant $[M - C_3H_7]^+$ ions (69% RA) for the precursor (cf. Table 3 and Scheme **5**). Similarly, there is "hidden" stereospecificity in the formation of $[M - C_7H_{11}O]^+$ ions from chlorophenyl-substituted isomers **4** (Scheme **4**). These ions are formed not only from $M^{+\cdot}$ (which process is likely to be nonstereospecific, as the cyclohexane moiety is cleaved as a whole), but also from $[M - CH_2O]^{+\cdot}$ (characteristic of the *trans* isomer) and $[M - C_3H_5O]^+$ (characteristic of the *cis* isomer) ions. With respect to $[M - Ar]^+$ ions (their formation apparently being nonstereospecific), the abundance of $[M - C_7H_{11}O]^+$ ions is nearly eight times higher in the spectrum of *trans* **4b** than in *cis* **4a** (however, the difference relative to the TIC is smaller: $[M - C_7H_{11}O]^+$ ions contribute 6.1% and 23.5% to the TIC in the spectra of **4a** and **4b**, respectively). Similarly, $[M - C_7H_{11}O]^+$

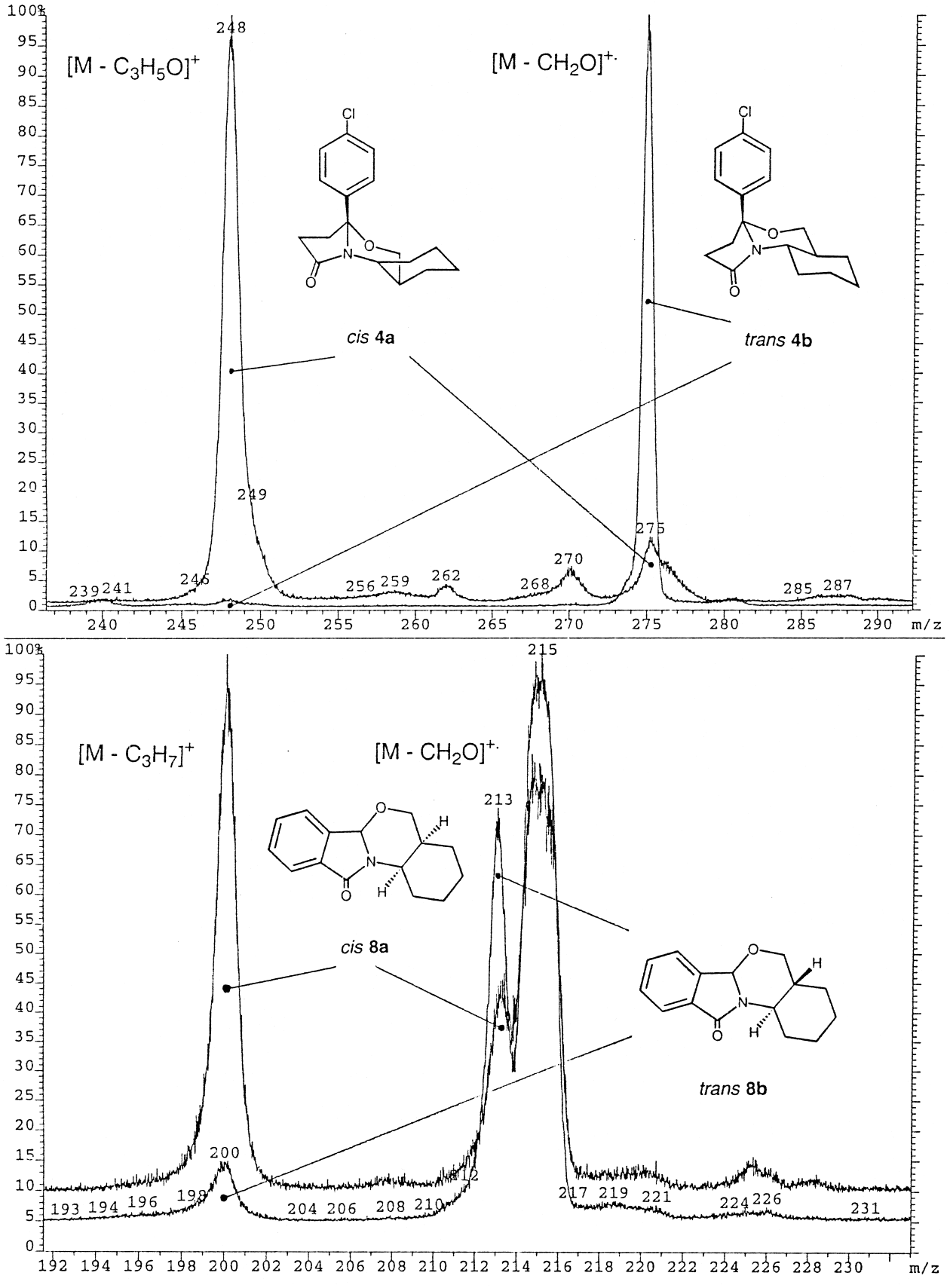
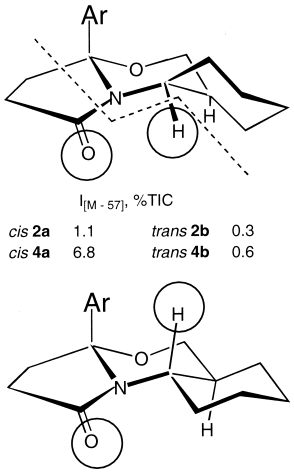


Figure 3. Superimposed MIKE spectra of the *cis/trans* isomers (top) **4** and (bottom) **8**. In each box, the spectra are normalized on the intensity of the most abundant fragment ion peak in the corresponding MIKE spectrum.



Scheme 6. A mechanistic explanation for the stereoselective loss of $C_3H_5O^{\cdot}$ from $M^{+\cdot}$ ions of compounds **2** and **4**.

ions are less abundant in the spectrum of *cis* **8a** than in *trans* **8b** (Scheme **5**). It is seen that $[M - C_7H_{11}O]^+$ ions are always more abundant in the spectra of *trans*-annelated isomers (**4b** and **8b**), in spite of being formed via several independent routes in each case. However, the analogous fragmentation of norbornane-condensed di*endo*/di*exo* isomers **5** to form $[M - C_8H_{11}O]^+$ ions is not stereospecific (Scheme **4**).

Of course, a number of important fragmentation processes in cyclohexane-annelated isomers was predictably nonstereospecific. Thus, for both **8a** and **8b**, the $M^{+\cdot}$ ions dissociate into $[M - C_7H_{11}]^+$ and $C_7H_{11}^+$ ions of essentially the same abundances (15%–17% RA, 1.4%–1.8% TIC) in both cases (cf. Table 1 and Scheme **5**). Apparently, the abundances of these fragments (presumably, having the structures of protonated *o*-phthalimide and norbornyl cation, respectively) depend on their relative stability, gas-phase basicity, etc. rather than on the stereochemistry of the parent $M^{+\cdot}$ ion.

The spectra of norbornane-fused isomers **5** are quite similar to each other, and their fragmentation patterns generally follow those of cyclohexane-fused compounds **4** (Scheme **4**). Surprisingly, the loss of CH_2O from $M^{+\cdot}$ ions of **5** was not as important as with the other compounds. The corresponding metastable ions are present, but $[M - CH_2O]^{+\cdot}$ ions are less abundant than $[M - CHO]^+$ ions (also formed directly from $M^{+\cdot}$ ions), which contribute less than 1% TIC. Apart from the nonstereospecific losses of $C_3H_5O^{\cdot}$, $C_8H_{11}O^{\cdot}$, and $ClC_6H_4^{\cdot}$, $M^{+\cdot}$ ions of compounds **5** undergo no other significant fragmentation processes. Abundant $ClC_6H_4CO^+$ ions are formed from a variety of precursors (Scheme **4**), but their abundances are equal in both spectra. Although the X-ray analyses [3] have shown that the oxazine ring in di*endo* **5b** is more distorted out of an ideal chair conformation than it is in di*exo* **5a**, this structural difference is apparently not substantial enough to be reflected in the fragmentation of the respective isomeric $M^{+\cdot}$ ions.

Conclusion

A number of stereospecific fragmentation processes results in major differences between the 70-eV mass spectra of polycyclic, partially saturated pyrrolo[2,1-*b*][1,3]oxazin-6-one isomers. The observed highly stereospecific RDA decomposition of cyclohexene-annelated derivatives suggests that the stereospecificity of RDA processes, at least in compounds of this type, depends on the molecular geometry (*cis* vs. *trans* annelation) rather than on the degree of substitution in the cyclohexene ring being cleaved. The apparent lack of stereospecificity in the RDA decomposition of norbornene-annelated isomers, as well as low stability of their $M^{+\cdot}$ ions, suggests a fast fragmentation process with low critical energy. In the absence of RDA processes, the highly stereospecific loss of $C_3H_5O^{\cdot}$ from $M^{+\cdot}$ ions of cyclohexane-annelated isomers is in contrast with nonstereospecific fragmentations (including the loss of $C_3H_5O^{\cdot}$ as well) of norbornane-annelated isomers, indicating that it is the annelation geometry (*cis* vs. *trans*) rather than the orientation of the annelated carbocycle (di*endo* vs. di*exo*, the annelation is *cis* in either case) which gives rise to stereospecific fragmentations of these compounds under EI.

References

1. Pihlaja, K.; Himottu, M.; Fülöp, F.; Huber, I.; Bernáth, G.; Ovcharenko, V. V. Stereochemical effects in the EI mass spectra of cycloalkane-(alkene)-fused 2,3-dihydro-5H-thiazolo[3,2-*a*]pyrimidine-5-ones and 3,4-dihydro-2H,6H-pyrimido[2,1-*b*]thiazin-6-ones. *Rapid Commun. Mass Spectrom.* **1996,** *10*, 721–726.
2. Pihlaja, K.; Himottu, M.; Ovcharenko, V.; Gondos, G.; Gera, L.; Bernáth, G. Stereochemical effects in the mass spectra of *cis*- and *trans*-2-aryl-4a,5,6,7,8,8a-hexahydroquinazolin-4(3H)-ones. *Rapid Commun. Mass Spectrom.* **1996,** *10*, 214–219.
3. Tähtinen, P.; Sillanpää, R.; Stájer, G.; Szabó, A. E.; Pihlaja, K. Structures of pyrrolo-1,3-heterocycles prepared from 3-aroylpropionic acid and cyclic aminoalcohols: an NMR and X-ray diffraction study. *J. Chem. Soc., Perkin Trans. 2* **1997**, 597–606.
4. Mandelbaum, A. Stereochemical effects in the retro-Diels-Alder fragmentation. In *Applications of Mass Spectrometry to Organic Stereochemistry*; Splitter, J. S.; Turecek, F., Eds.; VCH: New York, 1994; pp 299–324.
5. Mandelbaum, A.; Weisz, A.; Karpati, A. Nonstereospecific hydrogen migrations accompanying retro-Diels-Alder fragmentations in some adducts of cyclopentadiene and 1,3-cyclohexadiene under EI. *Int. J. Mass Spectrom. Ion Phys.* **1983,** *47*, 415–418.
6. Gömöry, A.; Somogyi, A.; Tamás, J.; Stájer, G.; Bernáth, G.; Komáromi, I. Mass spectrometric and MNDO study of EI-induced fragmentation of some norbornane- and norbornene-condensed pyrimidinones and oxazinones. *Int. J. Mass Spectrom. Ion Processes* **1991,** *107*, 225–246.
7. Weisz, A.; Mandelbaum, A. One and two hydrogen atom migrations in the retro-Diels-Alder fragmentation of norbornene and bicyclo[2.2.2]octene derivatives. *Org. Mass Spectrom.* **1989,** *24*, 37–40.