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Stereospecificity and Concertedness of Retro-Diels–Alder Fragmentation in Some Diester Systems Upon Chemical Ionization

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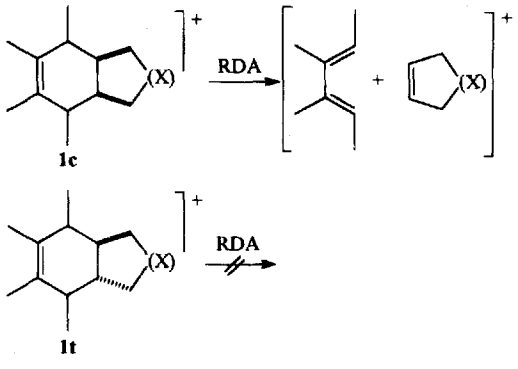
Retro-Diels–Alder (RDA) fragmentation of *cis*- and *trans*-2,3-diethoxycarbonyl-5,6,7,8-dibenzobicyclo[2.2.2]octanes under isobutane and methane chemical ionization conditions is highly stereospecific, giving rise to protonated diethyl maleate and fumarate, respectively. This behaviour indicates a single-step concerted mechanism, analogous to the ground-state RDA process that occurs in neutral molecules in the condensed phase. The analogous dissociation is partially stereospecific in stereoisomeric *endo*-, *exo*- and *trans*-2,3-diethoxycarbonylbicyclo[2.2.1]heptanes and non-stereospecific in *endo*-, *exo*- and *trans*-2,3-diethoxycarbonyl-5,6-benzobicyclo[2.2.2]octanes, indicating the involvement of a stepwise mechanism in the latter two systems. The different behaviour of the above systems is explained in terms of the energy of the RDA fragmentation. The differentiation and quantitative estimates of protonated diethyl maleate and fumarate were obtained from collision-induced dissociation measurements.

KEYWORDS: retro-Diels–Alder fragmentation; stereochemical effects; reaction mechanism; chemical ionization mass spectrometry; collision-induced dissociation

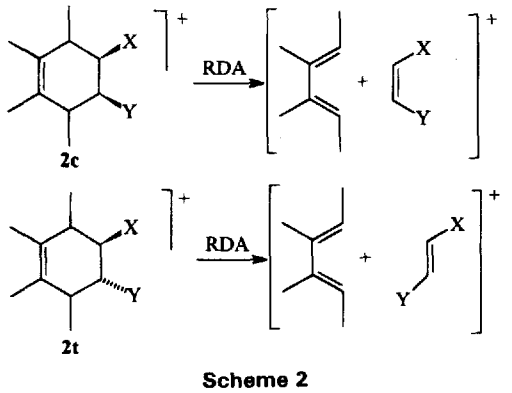
INTRODUCTION

The mechanism of the Retro-Diels–Alder (RDA) fragmentation of organic gas-phase ions has been explored by a number of groups since the early days of organic mass spectrometry. The question that was posed was whether this fragmentation takes place by a single-step concerted mechanism, analogous to the ground-state process known in neutral molecules in the condensed phase, or whether it is a stepwise dissociation.[1] Stereochemistry has been used by numerous groups as a natural probe in this problem.[1]

The concertedness of the RDA fragmentation may be manifested in two ways. (i) In bicyclic systems such as **1**, the concerted RDA process will take place only in the ionized *cis*-isomers **1c**, affording a *cis*-double bond in the charged or neutral cyclic product, originating from the non-cyclohexene portion of the precursor (the original dienophile). The high energy requirement of a *trans* double bond in small-sized rings will suppress this process in ionized **1t** (see Scheme 1). (ii) In systems resulting in acyclic dienophiles, such as **2**, the concerted RDA process will take place in both stereoisomers, but the original *cis* or *trans* configuration will be retained in the charged or neutral product, originating from the non-cyclohexene portion of the precursor (see Scheme 2). Thus, geometrically isomeric ene fragments will be formed by a concerted RDA reaction, *cis* from **2c** and *trans* from **2t**, if isomerization does not take place under the conditions of the experiment. Route (ii) is a more direct probe for the concertedness of the RDA process



Scheme 1



Scheme 2

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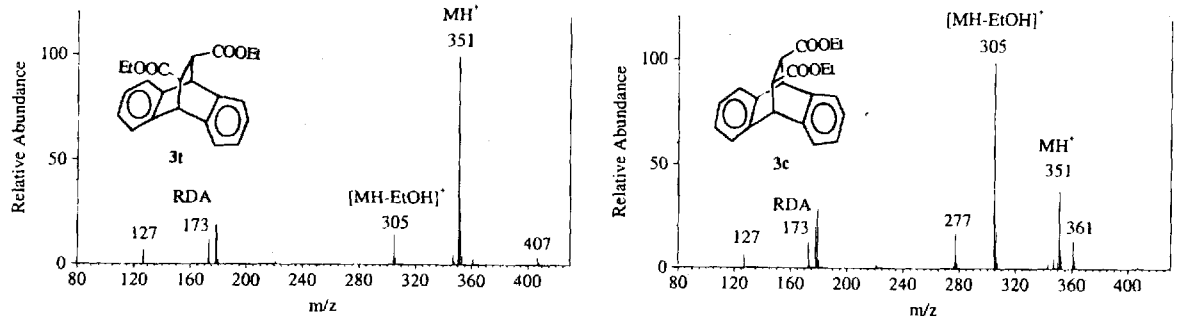


Figure 1. Isobutane CI mass spectra of **3c** and **3t**. The *m/z* 407 and 361 peaks correspond to $[M + C_4H_9]^+$ and $[M + C_4H_8 - C_2H_5OH]^+$ attachment ions, respectively.

since both stereoisomers give rise to the expected fragments.

Numerous examples of the application of route (i) have been reported. A number of bi-, tri-, tetra- and pentacyclic systems exhibit highly stereospecific RDA fragmentation upon electron impact (EI) and chemical ionization (CI) conditions, which takes place exclusively in the *cis*-isomers following the pattern indicated in Scheme 1.[1] This stereospecific nature of the RDA process is indicative of a concerted single-step mechanism.[1] Route (ii) is limited to systems which afford RDA charged or neutral fragments whose configuration can be assigned by mass spectral techniques. There has been one report on the concerted nature of an EI-induced RDA fragmentation accompanied by a hydrogen transfer (RDA + H), which has been determined by configurational assignment of the protonated fragment.[1,2] To the best of our knowledge, there has been no analogous report on an EI- or CI-induced normal RDA fragmentation. In this paper we present two cases in which configurational assignment of the fragments led to the conclusion that RDA fragmentation under CI conditions takes place mainly or partially by a concerted mechanism, and a third case in which the RDA fragment ion is formed largely by a stepwise process.

RESULTS AND DISCUSSION

Cis- and *trans*-7,8-diethoxycarbonyl-2,3,5,6-dibenzo [2.2.2]bicyclooctanes (**3c** and **3t**), *endo*-, *exo*- and *trans*-2,3-diethoxycarbonyl-bicyclo[2.2.1]heptenes (*endo*-**4c**, *exo*-**4c** and **4t**) and *endo*-, *exo*- and *trans*-2,3-diethoxycarbonyl-5,6-benzobicyclo[2.2.2]octanes (*endo*-**5c**, *endo*-**5c** and **5t**) exhibit RDA fragmentation under methane and isobutane CI conditions giving rise to *m/z* 173 protonated diethyl butenedioate species. The isobutane CI mass spectra of the above diesters are shown in Fig. 1–3. Elimination of ethanol from the MH^+ ions is the most significant fragmentation of these materials, occurring to a much greater extent in the *cis*-isomers **3c**, **4c** and **5c** than in the *trans* counterparts. This behaviour results from the different distances between the ester groups in the *cis*- and *trans*-isomers.[3] The *m/z* 178 and 179 ions in the mass spectra of **3c** and **3t** correspond to RDA fragmentation with retention of the charge and the proton, respectively, in the anthracene moiety. The

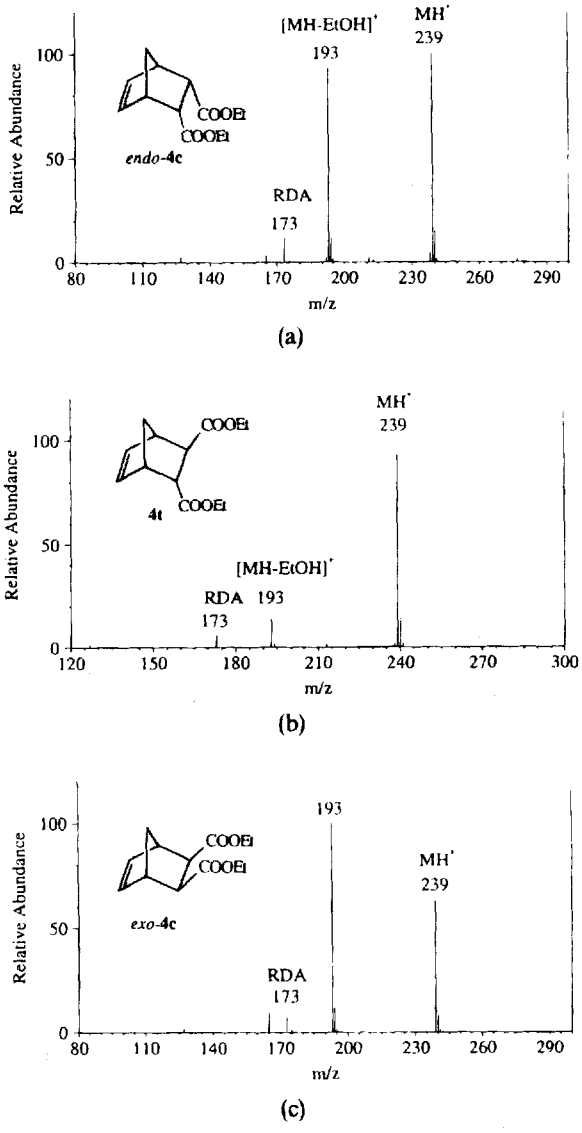


Figure 2. Isobutane CI mass spectra of *endo*-**4**, *exo*-**4** and **4t**.

comparable low-abundance *m/z* 127 ions may be formed in variable proportions by a RDA process of the *m/z* 305 $[MH - EtOH]^+$ ions and by elimination of ethanol from the *m/z* 173 RDA products of protonated **3c** and **3t**.

It has been shown previously that the *m/z* 173 MH^+ ions of the two geometrically isomeric diethyl butene-

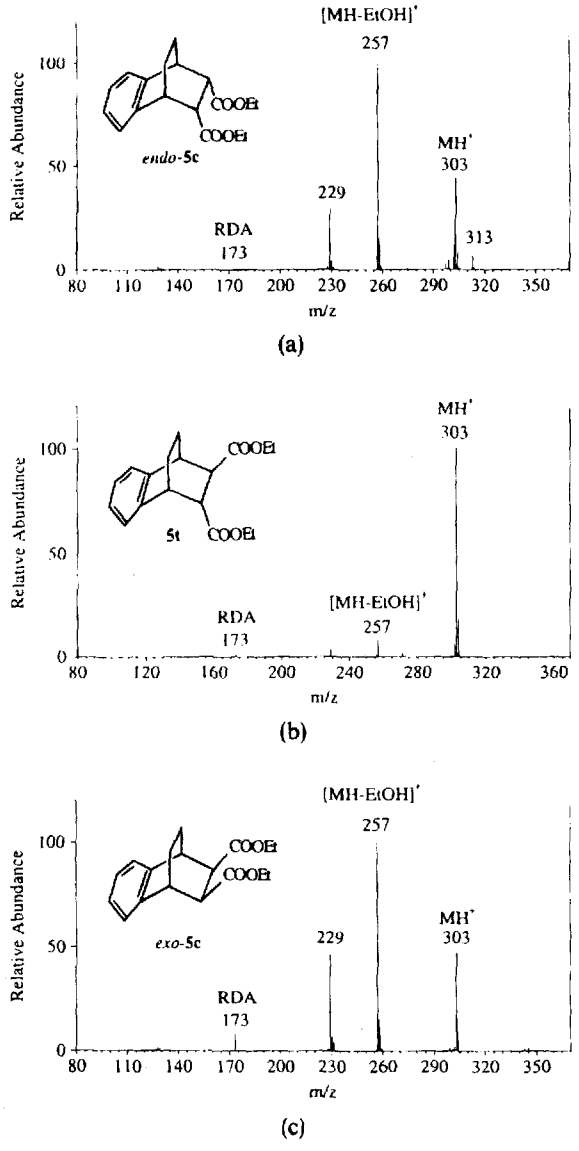


Figure 3. Isobutane CI mass spectra of *endo*-**5**, *exo*-**5** and **5t**. The *m/z* 313 peak in the mass spectrum of *endo*-**5** corresponds to the $[M + C_4H_9 - C_2H_5OH]^+$ attachment ion.

dioates, maleate and fumarate, retain their original configurations, resulting in different fragmentation behaviour under collision-induced dissociation (CID) conditions: the protonated maleate gives rise to *m/z* 127 and 99 ($[MH - EtOH]^+$ and $[MH - EtOH - C_2H_4]^+$) ions, while the protonated fumarate affords *m/z* 145 and 117 ($[MH - C_2H_4]^+$ and $[MH - 2C_2H_4]^+$) fragments.[4] The CID behaviour of this pair of geometrical isomers permits the easy configurational assignment of these two ions, and also a quantitative estimate of their relative concentrations, if they are formed as mixtures in the gas phase.[5] Such estimates may be utilized as a simple analytical tool in structural assignments and in mechanistic studies.[5–7]

The *m/z* 173 ions are of significant abundance in the isobutane and methane CI mass spectra of *cis*- and *trans*-2,3-diethoxycarbonyl-5,6,7,8-dibenzobicyclo[2.2.2]octanes (**3c** and **3t**). The CID spectra of the *m/z* 173 ions (Tables 1 and 2) show that this ion, when formed from

Table 1. CID[a] mass spectral data[b] of *m/z* 173 RDA fragment ions obtained from stereoisomeric precursors 3–5 upon isobutane CI

Sample	*m/z* 173	*m/z* 145	*m/z* 127	*m/z* 117	*m/z* 99	% *trans*	% *cis*
3c	100	1.8	25.7	0.5	16.1	5	95
3t	100	36.0	0.9	10.0	1.4	96	4
endo-**4c**	100	3.0	24.5	1.0	13.7	9	91
exo-**4c**	100	3.0	29.3	0.7	19.0	7	93
4t	100	26.2	7.2	7.6	6.4	71	29
endo-**5c**	100	3.9	27.2	0.8	20.1	9	91
exo-**5c**	100	1.0	23.2	1.0	17.9	5	95
5t	100	2.5	20.3	<0.5	12.8	7	93

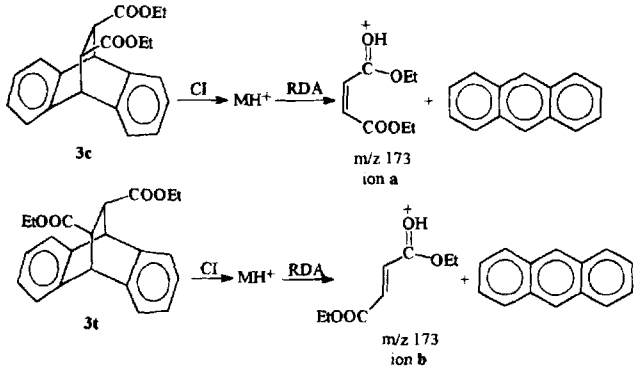
[a] Collision energy 30 eV.
[b] Relative ions abundances (%), normalized to the most abundant ion.

3c, has the maleate structure **a**, whereas that obtained from **3t** is protonated fumarate **b** (Scheme 3). This structural assignment leads to the conclusion that the RDA fragmentation of the 2,3-dialkoxycarbonyl-5,6,7,8,-dibenzobicyclo[2.2.2]octane system **3** is a highly stereospecific (>95%) process with retention of the original configuration of the precursor in the product ions. The high stereospecificity suggests that this fragmentation

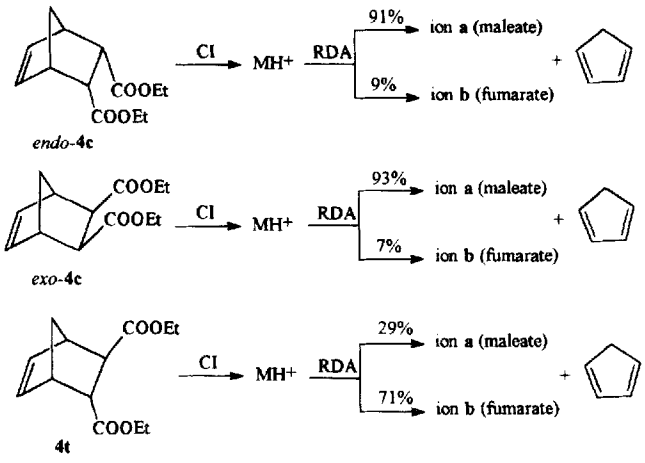
Table 2. CID[a] mass spectral data[b] of *m/z* 173 RDA fragment ions obtained from stereoisomeric precursors 3–5 upon methane CI

Sample	*m/z* 173	*m/z* 145	*m/z* 127	*m/z* 117	*m/z* 99	% *trans*	% *cis*
3c	100	0.7	20.3	0	9.4	2	98
3t	100	40.8	0.4	8.2	0.7	98	2
endo-**4c**	100	2.6	24.0	<0.5	13.0	9	91
exo-**4c**	100	3.2	24.0	0.9	12.4	10	90
4t	100	15.8	18.1	4.5	11.5	41	59
endo-**5c**	100	1.5	20.5	<0.5	12.0	4	96
exo-**5c**	100	0.50	17.7	<0.5	8.7	2	98
5t	100	1.7	18.6	<0.5	10.7	5	95

[a] Collision energy 30 eV.
[b] Relative ions abundances (%), normalized to the most abundant ion.



Scheme 3



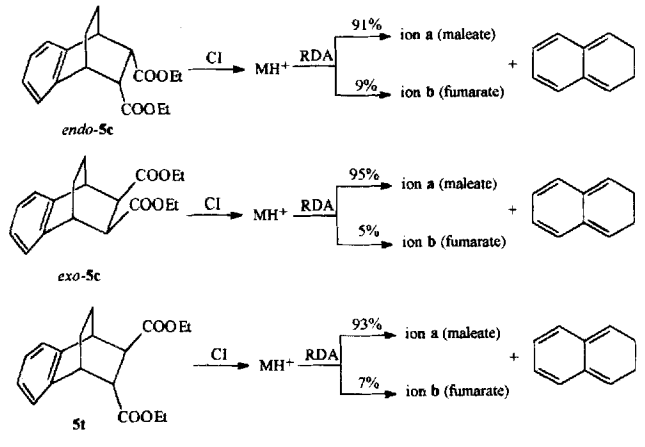
Scheme 4

takes place by a single-step concerted mechanism, analogous to the ground-state RDA reaction of neutral molecules in the condensed phase.

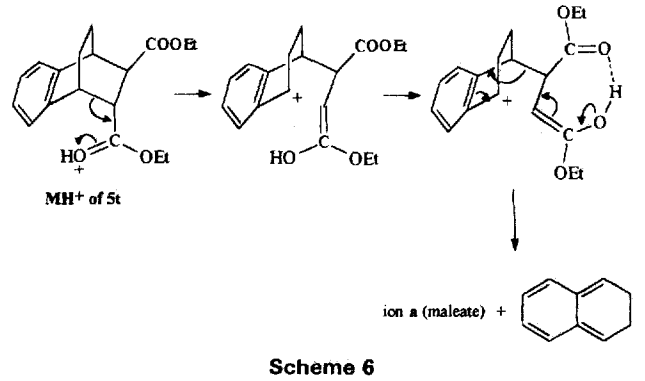
The RDA fragmentation of the MH^+ ions of the stereoisomeric *endo*-, *exo*- and *trans*-2,3-diethoxycarbonylbicyclo[2.2.1]heptenes, (*endo*-**4c**, *exo*-**4c** and **4t**) also results in significantly abundant *m/z* 173 ions under isobutane and methane CI conditions. The CID spectra of the *m/z* 173 ions (Tables 1 and 2) show that these ions formed from the *cis*-isomers *endo*-**4c** and *exo*-**4c** have largely (90–93%) the maleate structure **a**, whereas those obtained from **4t** on isobutane CI are a ~3:7 mixture (6:4 mixture under methane CI) of protonated maleate **a** and fumarate **b** (Scheme 4). This structural assignment leads to the conclusion that the RDA fragmentation of the 2,3-dialkoxycarbonylbicyclo[2.2.1]heptene system **4** takes place with partial stereospecificity. This behaviour suggests two parallel pathways for the formation of the *m/z* 173 ions in system **4**: (a) the single-step concerted mechanism, analogous to the ground-state RDA reaction of neutral molecules in the condensed phase and (b) stepwise non-stereospecific dissociation. The stepwise fragmentation pathway results, at least in part, in protonated maleate (ion **a**) in the case of the *trans*-isomer **4t**, which may be explained by its higher stability compared with protonated fumarate (ion **b**), because of its internal proton-bridged structure. AM-1 calculation suggests a difference of 5.5 kcal mol^{-1} (1 kcal = 4.184 kJ) between the enthalpies of formation of the two protonated isomers (7.04 and 12.6 kcal mol^{-1} for ions **a** and **b**, respectively). The greater extent of the more energetic stepwise process under methane CI may result from the higher internal energy of the MH^+ ions compared with isobutane CI conditions.

It is not possible to exclude the possibility that the more stable ion **a** is formed in part by isomerization of ion **b**, which might be obtained by an initial concerted RDA fragmentation from **4t**, if this process is more energetic than that of **3t**. However, it should be noted that the MH^+ ions of diethyl maleate and fumarate retain their structures even when formed under methane CI conditions.[4]

Stereoisomeric *endo*-, *exo*- and *trans*-2,3-diethoxycarbonyl-5,6-benzobicyclo[2.2.2]octanes (*endo*-**5c**, *endo*-**5c** and **5t**) give rise to relatively low-abundance *m/z* 173 ions under isobutane and methane CI conditions. The CID spectra of the *m/z* 173 ions (Tables 1 and 2) show that these ions formed from all the three stereoisomers have largely (91–95%) the maleate structure **a** (Scheme 5). This configurational assignment of the *m/z* 173 ions leads to the conclusion that the RDA fragmentation of the 2,3-dialkoxycarbonylbenzobicyclo[2.2.2]octane system **5** takes place with no significant stereospecificity. This behaviour is consistent with the non-stereospecific stepwise mechanism of formation of the *m/z* 173 ions, which have largely the protonated maleate structure (ion **a**), independent of the configuration of the precursor. A mechanistic pathway for the stepwise process is proposed in Scheme 6.



Scheme 5



Scheme 6

The above results show that the RDA fragmentation takes place by different mechanistic pathways in the three systems examined: it is largely a concerted process in system **3** and stepwise in **5** and the two pathways compete in system **4**. The different behaviours of the three systems may result from differences in the energies of these processes. The aromatic anthracene structure of the neutral fragment obtained in the RDA dissociation of **3** (Scheme 3) suggests a relatively low activation energy compared with system **5**, where a destabilized non-aromatic tetraene is expected as the neutral product of the retro-diene process (see Scheme 5).

CONCLUSION

CID measurements provide a simple and sensitive tool for the quantitative estimation of the relative concentrations of protonated diethyl maleate and fumarate in the gas phase. The examination of the relationship between

the orientation of the ethoxycarbonyl groups in the precursor and product ion(s) made it possible to investigate the problem of stereospecificity of the RDA reaction in gas-phase protonated adducts. The highly stereospecific behaviour observed in the stereoisomeric diesters **3** clearly indicates a concerted mechanism for the RDA fragmentation in this system. It has also been shown that a stepwise mechanism prevails in system **5** where the RDA process is more energetic.

EXPERIMENTAL

Mass spectrometry

Gas chromatographic/CI mass spectrometric analyses and CID measurements were carried out on a Finnigan TSQ-70B triple stage quadrupole mass spectrometer. The stereoisomeric pairs were introduced as mixtures, and separations were performed on a DB-5 (0.25 μm film thickness) 30 m × 0.25 mm i.d. capillary column. The column temperature was programmed from 60 to 280 °C at 25 °C min^{-1}. The scan rate was 1 scan s^{-1}. The *cis* isomers eluted first.

CI measurements were performed at a 150 °C ion source temperature and 0.4 Torr (indicated) reagent gas pressure (1 Torr = 133.3 Pa). CID measurements were performed with argon as the target gas [0.3 mTorr (indicated)] at 20–30 eV collision energy (indicated). All data presented in each figure were obtained on a single day under identical conditions, in order to ensure reliable comparisons.

Materials

Diesters 3. The corresponding anhydride was prepared by Diels–Alder reaction of anthracene and maleic anhydride in boiling xylene. The *cis*-diester **3c** was obtained by esterification of the anhydride with ethanol in the presence of H_2SO_4. The *trans*-isomer **3t** was prepared by treatment of **3c** with sodium ethoxide in ethanol under reflux.

Diesters 4. The *endo*-anhydride was prepared by Diels–Alder addition of cyclopentadiene and maleic anhydride. The *exo*-anhydride was prepared by heating the *endo*-isomer at 190 °C.[8] The esters *endo*-**4**, *exo*-**4** and **4t** were obtained in the same manner as for **3c** and **3t**.[9]

Diesters 5. The *endo*- and *exo*-anhydrides were prepared by Diels–Alder reaction of naphthalene and maleic anhydride in ethyl acetate followed by hydrogenation (10% Pd/C catalyst) at atmospheric pressure.[10] The stereoisomeric esters *endo*-**5**, *exo*-**5** and **5t** were obtained in the same manner as in system **4**.[9]

Acknowledgements

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