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Unidirectional triple hydrogen rearrangement in the radical cations of electron-rich 3-aryl-1-propanols: further evidence and limitation

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The unidirectional triple-hydrogen (3H) rearrangement of the radical cations of 3-aryl-1-propanols bearing an electron-rich substitutent in the *para*-position was investigated for the diastereomeric 2-(4-dimethylamino)benzylcyclohexanols and 2-(4-dimethylamino)-benzylcyclopentanols and confirmed to be a highly stereospecific feature. Whereas the standard electron ionization (EI) (70 eV) mass spectra of the *trans*-isomers exhibit very minor (~2%–3%) albeit stereospecific peaks for the relevant $C_8H_{13}N^{\bullet+}$ ions (*m/z* 123), the metastable ion [mass-analyzed ion kinetic energy (MIKE)] spectra show these peaks with significant relative intensity (8%–17%). The respective *cis*-isomers do not undergo the 3H rearrangement, be it under standard or under metastable-ion conditions. The stereospecific 3H rearrangement is suppressed in the radical cations of *cis*- and *trans*-3-(4-dimethylamino)phenylcyclohexanol, the mass and MIKE spectra of which are governed by cleavage processes of the cyclohexane ring, which impedes the stereochemical assignment of the isomers by mass spectrometry. A multistep mechanism for the unidirectional 3H rearrangement is discussed in view of the present and previous experimental data.

Keywords: hydrogen rearrangement "triple", hydrogen rearrangement "unidirectional", proton transfer, distonic ions, ion/neutral complexes, radical cations, metastable ions, multistep reactions, stereochemistry, stereospecific fragmentation, anilines, cycloalkanols

Introduction

Mass spectrometric fragmentation processes remain an ever-lasting source of chemical surprise. Although a wealth of insight into the chemistry of unimolecular dissociation of gaseous ions has been accumulated in the past decades,[1–5] the possibility of encountering unexpected mass spectral phenomena—sometimes addressed as "irritating" peaks—has remained remarkably high.[6,7] If the underlying fragment ions are abundant, it is hard to ignore their formation and non-mass spectrometrists may become interested in the origin and chemical logics behind them. If their abundance is low or minute, then such peaks will probably be interpreted as the result of impurities or—no less "irritating"—attributed to the fact that the high-energy conditions of mass spectrometric fragmentation processes are known to give rise to untypical side reactions. The occurrence of side reactions, however, is the very rule for chemical processes carried out in synthesis. However, just as an undesired side reaction may lead to new chemical insights, new methodology, or even novel compounds with unusual structural motifs,[8,9] an unexpected fragmentation reaction in mass spectrometry may yield novel significance for use as an analytical feature. As a consequence,

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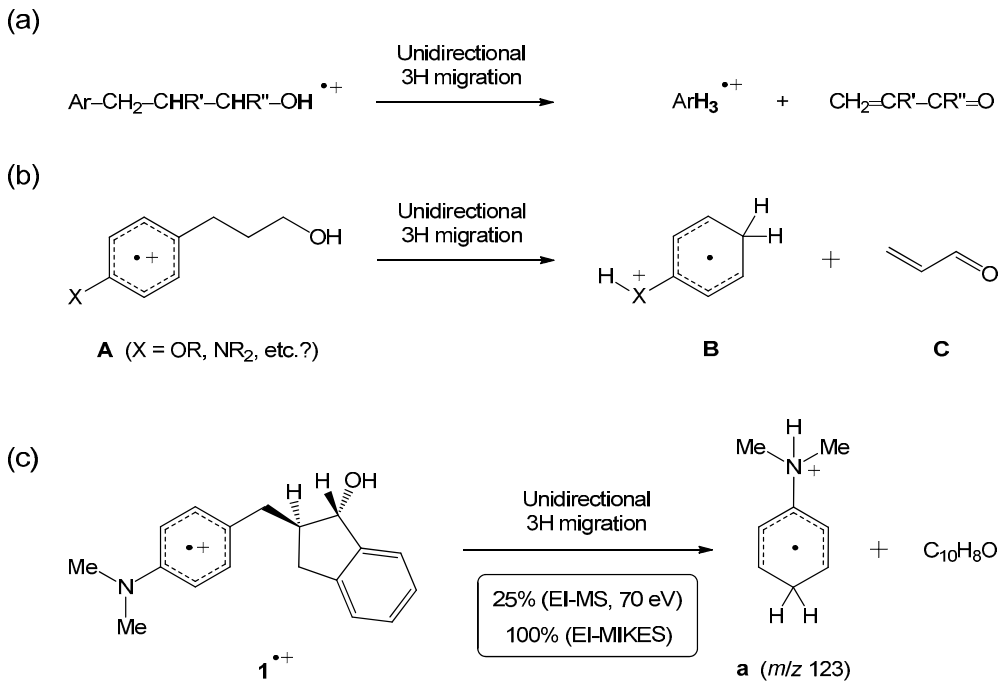
any observation of unusual fragment ion peaks in whatever type of mass spectrum should be taken seriously, and this holds true even more since the advent of modern ionization techniques which have brought us so many and formerly unimaginable sorts of ions, be it positive and negative ions, doubly or multiply charged ions, or adduct ions of any kind.

In this contribution, we will present and discuss a rather peculiar fragmentation reaction of a particular group of "conventional" organic molecular radical cations formed under electron ionization conditions. It concerns the dissociation of 3-aryl-1-propanols bearing a strongly electron-donating substituent in the *para*-position of the aryl residue with concomitant rearrangement of three hydrogens from the alcohol moiety to the arene moiety [Scheme 1(a)].[10] Such a unidirectional triple-hydrogen (3H) rearrangement is extremely rare in organic ions[11–17] and is beyond the quite large variety of unidirectional 2H rearrangements.[18,19] The most consequent simplification of the structural prerequisites required for this process to occur—be it in inferior rates or as an efficiently competing reaction channel—may be illustrated by formula **A** [Scheme 1(b)]. The unique 3H rearrangement involved in this process implies a redox reaction between the alcohol moiety of the radical cation and the arene unit prior to fragmentation, giving what is believed to be an unconventional (distonic) Type **B** fragment ion and a conjugated enone, **C**, as the neutral fragment. Specifically, the most prominent case of the unidirectional 3H rearrangement was encountered in the 70 eV electron ionization (EI) mass spectrum of *trans*-2-(4-dimethylamino)benzyl-1-indanol **(1)**.[10] The standard EI mass spectrum of this isomer exhibits a peak at *m/z* 123 of *ca* 25% abundance relative to the base peak (*m/z* 134 for the $Me_2NC_6H_4CH_2^+$ ion) and the mass-analyzed ion kinetic energy (MIKE) spectrum of the metastable ions $\mathbf{1}^{\bullet+}$ even displays the *m/z* 123 signal as the base peak [Scheme 1(c)]. Extensive deuterium labeling in that case revealed that the three migrating hydrogen atoms originate with high specificity from the carbinol position (C1), the hydroxyl group (OH), and the position β to the carbinol group (C2).[10] Therefore, the formation of an enone as the neutral fragment has been inferred. The structure of the *m/z* 123 ion is speculative, still, but it appears reasonable to assume a dimethylammonium species attached to a cyclohexadienyl ring [**a**, Scheme 1(c)]. Further striking features, in the case of the benzylindanol **1**, showed that neither the molecular ions of the corresponding *cis*-stereoisomer nor those of the respective *meta*-dimethylamino constitutional isomer undergo the 3H rearrangement.

Here, we disclose some more evidence of the occurrence of the unidirectional 3H migration and also of the limitation of this peculiar fragmentation route. In a cursory exploration, we synthesized a number of related cycloalkanols bearing either *para*-(dimethylamino)benzyl or *para N,N*-dimethylanilino residues. Both standard EI mass spectra and EI-MIKE spectra were recorded to check for the occurrence of the 3H rearrangement under high- and low-energy conditions.

Results and discussion

The set of cycloalkanols studied is displayed in Scheme 2. The mixture of the racemic *cis*-2-(4-dimethylamino)-



Scheme 1. The unidirectional 3H migration: (a) the generalized process with the migrating hydrogens highlighted, (b) the simplest structural preconditions and (c) the specific and most prominent case.

benzylcyclohexanol (*cis*-**2**) and the racemic *trans*-isomer (*trans*-**2**) was synthesized by a conventional three-step sequence starting from cyclohexanone and *para*-dimethylaminobenzaldehyde. The diastereomers were obtained in pure form after chromatography of the *cis*/*trans*-**2** mixture. Similarly, the corresponding racemates of *cis*-2-(4-dimethylamino) benzylcyclopentanol (*cis*-**3**) and the respective *trans*-isomer (*trans*-**3**) were prepared, starting from cyclopentanone. Furthermore, the 3-(4-dimethylamino)- phenylcyclohexanols *cis*-**4** and *trans*-**4** were synthesized by copper(I)-mediated Michael addition of *para*-dimethylaminophenyllithium to cyclohexen-3-one, subsequent reduction with lithium aluminium hydride and chromatographic separation of the diastereomeric alcohols. Finally, a mixture of 3-(4-dimethylamino)phenylcyclopentanols, *cis*/*trans*-**5**, was synthesized by the same sequence starting from cyclopenten-3-one without accomplishing chromatographic separation.

The stereochemical purity of the diastereomers *cis*-**2** to *trans*-**4** was determined by ^{1}H nuclear magnetic resonance (NMR) spectroscopy. Whereas the stereochemical assignment of the arylcyclohexanols *cis*-**4** and *trans*-**4** was straightforward, that of some of the benzylcycloalkanols was not. As will be shown, the unidirectional 3H rearrangement observed by EI mass spectrometry turned out to be useful as a complementary tool for the identification of the diastereoisomeric 2-benzylcycloalkanols *cis*-**2** to *trans*-**3**, whereas this method fails in the case of the 3-phenylcycloalkanols **4** and **5**.

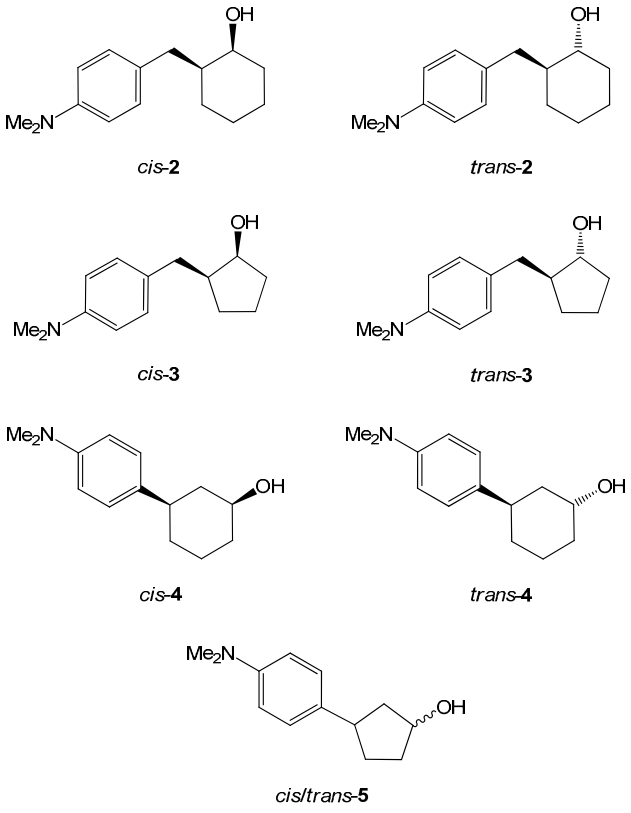


Chart 1.

The standard (70 eV) EI mass spectra of the benzylcyclohexanols *cis*-**2** and *trans*-**2** are reproduced in Figure 1. Not surprisingly, the peak due to the ionic fragment of the benzylic cleavage, $Me_2NC_6H_4CH_2^+$ (*m/z* 134), dominates in both cases. It appears that this process is much more favorable than elimination of water which, remarkably, is almost absent in both cases (rel. abundance 2–3%). Considering the fact that the molecular ions (*m/z* 237) and also the other fragment ions (*m/z* 118) have very similar relative abundances in both spectra, it appears as if the diastereomers *cis*-**2** and *trans*-**2** were indistinguishable by EI mass spectrometry. However, the peak at *m/z* 123 due to the unidirectional 3H rearrangement does make a significant difference. While being absent in the spectrum of the *cis*-isomer, this signal amounts to ~2% in the spectrum of the *trans*-isomer. In fact, considering the peak groups *m/z* 118–123 in both spectra, the peak intensity at *m/z* 123 makes the only significant difference. Hence, again, formation of the underlying $C_8H_{13}N^{\bullet+}$ ions (*m/z* 123) is a characteristic, albeit rather inconspicuous, feature of the *trans*-stereoisomer, *trans*-**2**.

Very similar findings were obtained with the EI mass spectra of the diastereomeric benzylcyclopentanols *cis*-**3** and *trans*-**3** (Figure 2). Again, the two spectra are almost indistinguishable (for example, water loss ⩽1% in both cases), but the peak corresponding to the unidirectional 3H rearrangement (m/z 123) appears exclusively in the case of the *trans*-isomer, *trans*-**3**, with minor relative abundance (~2%).

Considering the fact that the migration of three hydrogen atoms (possibly including the migration of a proton, see below) should be entropically disfavored compared to the simple benzylic cleavage giving the dominant $C_9H_{12}N^+$ ions (*m/z* 134), the fragmentation of long-lived, metastable ions was expected to give enhanced relative abundances of the *m/z* 123 ions. In fact, the MIKE spectra of the *trans*-cycloalkanols, *trans*-**2** and *trans*-**3**, were found to exhibit relatively pronounced peaks for the 3H rearrangement at *m/z* 123, as well as the still predominating peaks at *m/z* 134 indicating the simple benzylic cleavage (Figure 3). The $C_8H_{13}N^{\bullet+}$ ions (*m/z* 123) amount to ~7.5% of the total fragmentation of the metastable molecular ions, trans-$\mathbf{2}^{\bullet+}$, of the cyclohexanol derivative. In the case of the cyclopentanol homolog, the relative abundance of the $C_8H_{13}N^{\bullet+}$ ions is increased to even ~17% of the total fragmentation of the *trans*-$\mathbf{3}^{\bullet+}$ ions. In contrast, the metastable ions of the corresponding *cis*-isomers both exclusively undergo benzylic cleavage giving the $C_9H_{12}N^{\bullet+}$ ions (*m/z* 134) (the minute contribution at *m/z* 123 in the spectrum of *cis*-**2** is attributed to an impurity of *trans*-**2**). It is also noteworthy that, similar to the standard EI mass spectra, elimination of water is a negligibly minor process for the metastable ions in all cases.

The EI mass spectra of the three-(dimethylamino) phenylcyclohexanols, *cis*-**4** and *trans*-**4**, reveal quite different fragmentation behaviour (Table 1). In both cases, a number

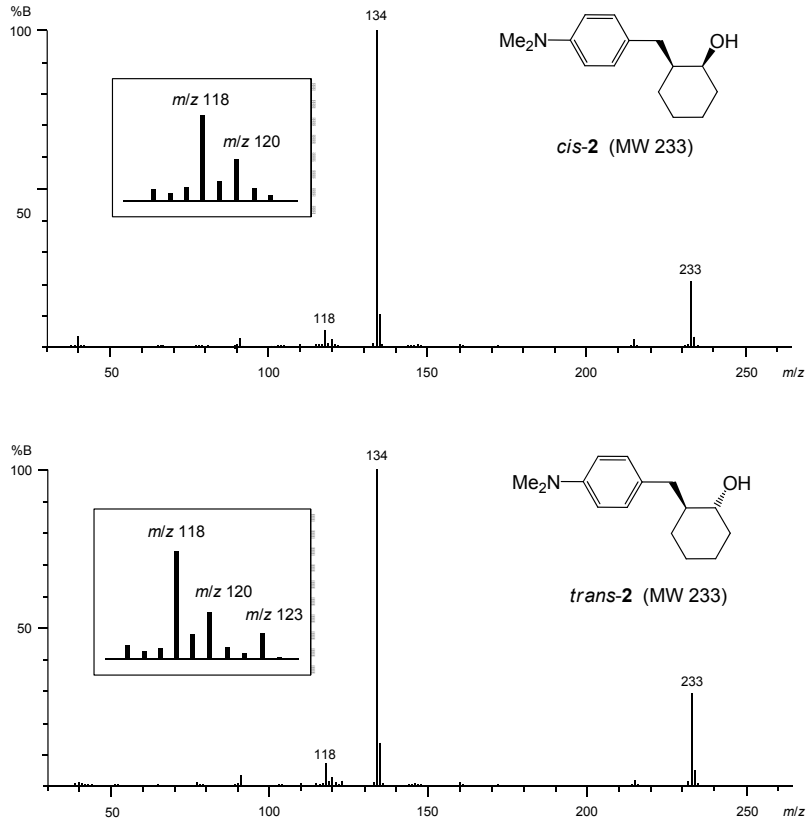


Figure 1. EI (70 eV) mass spectra of the diastereoisomeric *para*-(dimethylamino)benzylcyclohexanols *cis*-2 (top) and *trans*-2 (bottom).

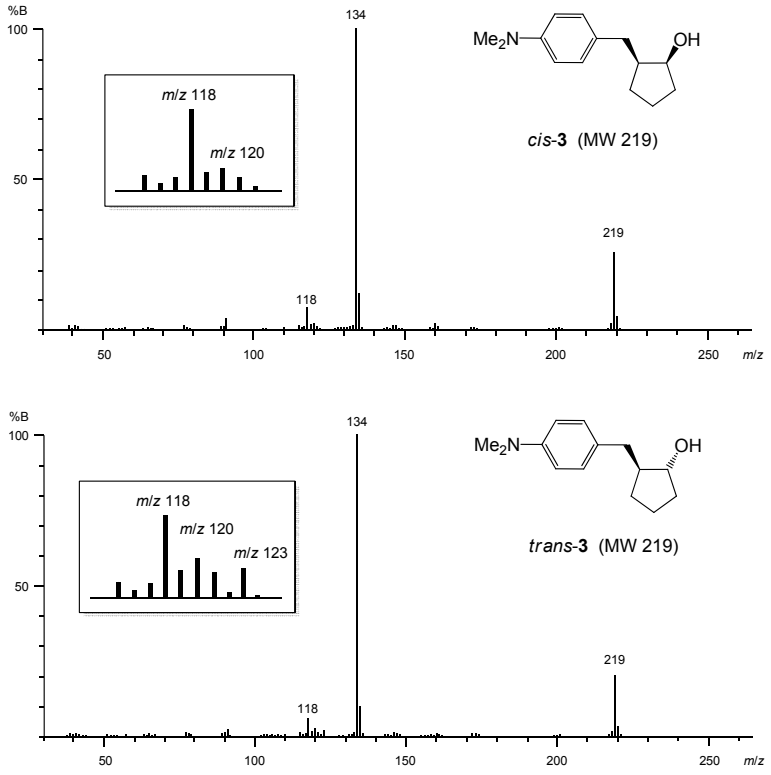


Figure 2. EI (70 eV) mass spectra of the diastereoisomeric *para*-(dimethylamino)benzylcyclopentanols *cis*-3 (top) and *trans*-3 (bottom).

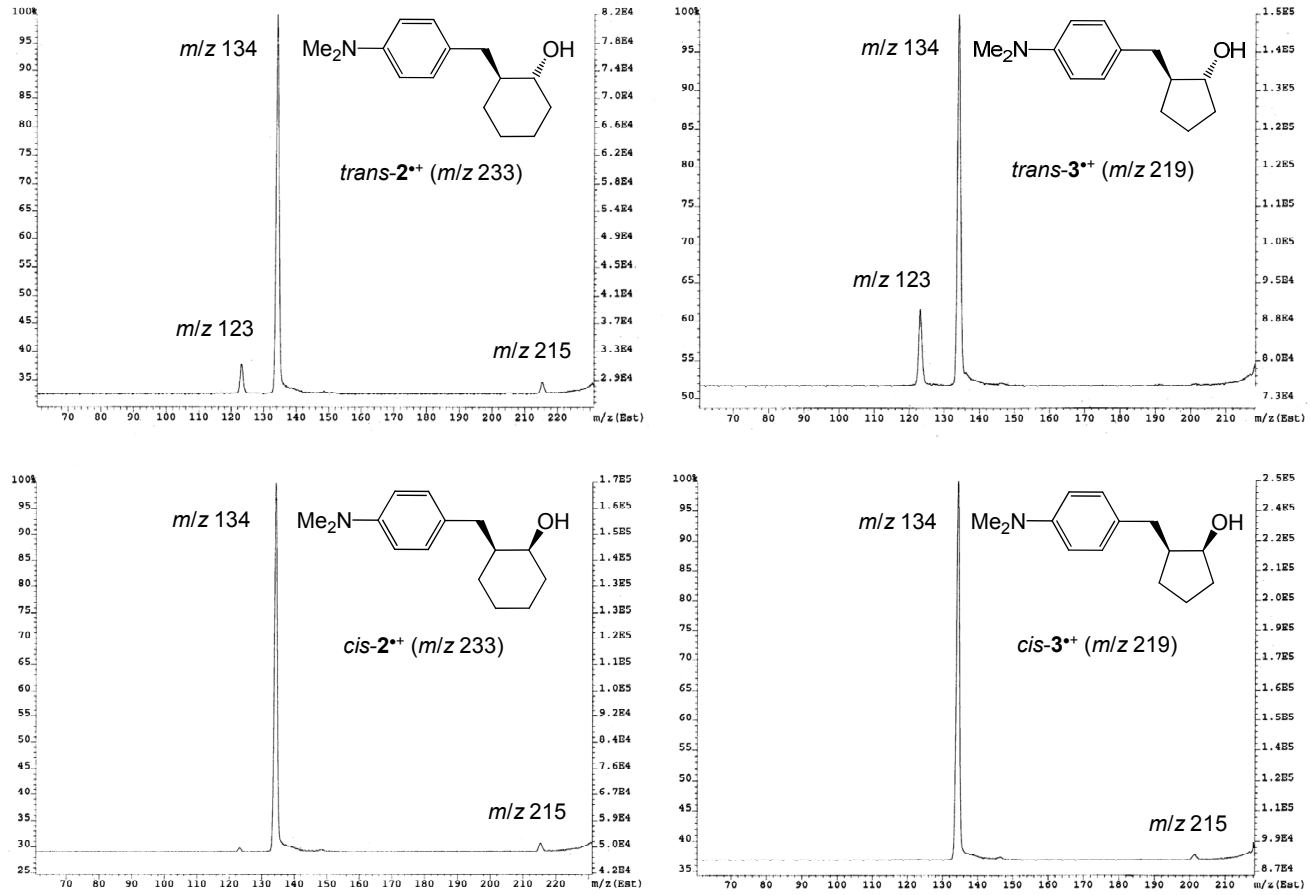


Figure 2. Metastable ion mass spectra (EI-MIKE spectra, 70 eV) of the *trans-para*-(dimethylamino)benzylcycloalkanols, *trans*-2 and *trans*-3 (top), and the corresponding *cis*-isomers, *cis*-2 and *cis*-3 (bottom). The peaks of the precursor molecular ions at *m/z* 233 and *m/z* 219, respectively, have been suppressed.

of competing fragmentation channels are accessible even for the metastable ions, including that for the elimination of water (*m/z* 201) and the loss of $C_3H_7^{\bullet}$ (*m/z* 176), a typical multistep fragmentation of cyclohexane derivatives.[4] In the latter case, particularly stable 1-arylallyl cations, *p*-$Me_2NC_6H_4CHCHCH^+OH$, are formed.

Similarly, losses of $C_3H_7O^{\bullet}$, C_4H_8O and $C_5H_9O^{\bullet}$, probably all triggered by particularly favorable benzylic cleavage steps, give rise to very stable ions *p*-$Me_2NC_6H_4CHCHCH_2^+$ (*m/z* 160), *p*-$Me_2NC_6H_4CHCH_2^{\bullet+}$ (*m/z* 147) and, here again, *p*-$Me_2NC_6H_4CH_2^+$ (*m/z* 134), respectively. The efficient competition of most of these fragmentation channels is certainly due to the prevailing cleavage of the cyclohexanol ring of ions *cis*-**4**$^{\bullet+}$ and *trans*-**4**$^{\bullet+}$ in the primary dissociation step, in contrast to the highly selective *exocyclic* benzylic cleavage in the cases of the *N,N*-dimethylaminobenzyl-substituted cycloalkanol ions *cis*-**2**$^{\bullet+}$ to *trans*-**3**$^{\bullet+}$. Noteworthy, however, is the finding that particularly facile *endocyclic* ring cleavage of the (*N,N*-dimethylamino)-phenylcyclohexanol ions *cis*-**4**$^{\bullet+}$ and *trans*-**4**$^{\bullet+}$ also suppresses the unidirectional 3H migration. In fact, the peak expected for the formation of the characteristic $C_8H_{13}N^{\bullet+}$ ions (*m/z* 123) is completely absent in the EI spectra of both diastereomers. This also holds true for the corresponding MIKE spectra, which exhibit the peaks for most of the various fragmentation channels discussed above but are void of the *m/z* 123 signal. As a result, and in contrast to the 2-benzylcycloalkanols *cis*-**2** to *trans*-**3**, the EI and EI-MIKE spectra of diastereomeric 2-arylcycloalkanols, such as *cis*-**4** and *trans*-**4**, cannot be used for stereodifferentiation.

The multifaceted fragmentation behaviour found for the 2-(4-dimethylamino)phenylcyclohexanols *cis*-**4** and *trans*-**4** was also encountered in the case of the cyclopentanol homologue, *cis*/*trans*-**5**, which, however, was analysed as a mixture of diastereomers only (Table 2). Again, besides water elimination, the losses of radicals as well as the expulsion of C_3H_6O, all being triggered by facile benzylic cleavage of the cyclopentane ring, compete in this case. This holds also true for the metastable ions. Remarkably, the MIKE spectrum of the molecular ions, *cis*/*trans*-**5**$^{\bullet+}$, does exhibit a minor signal at *m/z* 123, suggesting the occurrence of the unidirectional 3H rearrangement in the case of the *trans*-isomer. Unfortunately, stereochemical assignment in this case was impeded by experimental restrictions.

Table 1. Fragmentation of the diastereomeric 2-(4-dimethylamino)phenyl-cyclohexanols, *cis*-4 and *trans*-4, under EI (70 eV) and EI-MIKES (70 eV) conditions.

m/z	*cis*-4		*trans*-4		Fragment ion (tentative)[b,c]	Neutral fragment
	Rel. abundance		Rel. abundance			
	EI	(EI-MIKES)[a]	EI	(EI-MIKES)[a]		
219	100		100			
201	7	(28)	9	(35)	$[M-H_2O]^{\bullet+}$	H_2O
176	36	(33)	33	(32)	$Ar-CHCHCH^+OH$	$C_3H_7^{\bullet}$
160	27	(3)	24	(3)	$Ar-CHCHCH_2^+$	$C_3H_7O^{\bullet}$
147	25		26		$Ar-CHCH_2^{\bullet+}$	C_4H_8O
146	22		21			
134	97	(100)	86	(100)	$Ar-CH_2^+$	$C_5H_9O^{\bullet}$
123	⩽ 1		⩽ 1			
122	5	(⩽ 2)	5	(⩽ 2)		
121	12	(8)	14	(11)		
120	8		7			
118	8		5			
91	5		5			
77	7		6			

[a]Relative abundances in the MIKE spectrum derived from peak intensities.

[b]"Ar" denotes the *para*-(dimethylamino)phenyl residue.

[c]Structural assignment based on the accepted fragmentation mechanisms of cyclohexane derivatives under EI conditions (Reference 4).

Mechanistic aspects

A mechanistic interpretation of the unidirectional 3H rearrangement was given previously on the basis of the *trans*-stereospecificity of the process, the clear cut electronic influence of substituents both at the benzyl residue and the carbinol center and, in particular, on the basis of extended deuterium labeling.[10] The latter technique was applied to the radical cations of *trans*-2-(4-dimethylamino) benzyl-1-indanol, **1**$^{\bullet+}$, for which the 3H rearrangement was found to be most prominent [Scheme 1(c)].[10] In addition, kinetic isotope effects shed some light on the mechanistic interpretation. It is our understanding that this unusual and complicated process involves both highly specific steps via distonic ion intermediates[20] but, necessarily, also ion/neutral complexes[21,22] as crucial intermediates. There is no doubt that the successive transfer of three hydrogen atoms (or protons) from the indanol moiety to the dimethylaniline moiety of ions **1**$^{\bullet+}$ starts with the stereospecific transfer of the carbinol H atom, which is oriented *cis* with respect to the electron-rich benzyl group. Most importantly, and at variance from the usual migration of such a γ-positioned H atom to one of the *ortho*-positions of the benzyl group—a path crucial to the well-known McLafferty reaction of higher alkylbenzenes, including 2-benzylindanes[23–25]—the *para*-dimethylamino substituent navigates the migrating carbinol γ-H atom to the *ipso*-position of the benzyl residue, giving rise to a particularly stable *para*-protonated benzenium ion.[26,27]

It is obvious that the fragmentation of the molecular ions of the *trans*-2-(4-dimethylamino)benzylcycloalkanols, *trans*-**2**$^{\bullet+}$ and *trans*-**3**$^{\bullet+}$, starts with the same stereospecific γ-H atom transfer (Scheme 2). Compared to the case of the indanol-derived ions **1**$^{\bullet+}$, the lack of benzylic activation ("localized bond activation")[28,29] leads to an attenuated relative fragmentation rate with respect to the simple benzylic cleavage giving ions $C_9H_{12}N^{\bullet+}$ (*m/z* 134). It can be envisioned that the comparably flat cyclopentane ring in ions *trans*-**3**$^{\bullet+}$ is a favorable factor for the initial γ-H atom transfer compared to the cyclohexane homolog, *trans*-**2**$^{\bullet+}$, in which conformational effects may slow down this step. In any case, the distonic ion **b** generated by the γ-H atom transfer to the *ipso*-carbon atom of the *N,N*-dimethylanilino residue should be by far the most stable among the *ring*-protonated tautomeric intermediates.[27] Heterolysis of the C^{α}–C^{ipso} bond in ion **b** corresponds to the well-known proton-induced cleavage of alkylbenzenium ions giving the respective alkyl cation and the neutral benzene derivative.[30–32] However, it is also known that concomitant transfer of a hydrogen atom (formally as H^+) can compete efficiently if the arene moiety is sufficiently basic.[27,32] This channel gives rise to formation of an alkene and the protonated benzene derivative. In the present case, it appears that the H^{β} atom takes on this role, migrating from the tertiary C2 position at the cycloalkane ring to the dimethylaniline fragment being released. It also appears reasonable to assume that there is a concerted mechanism via ion **c**, possibly as a transition state. In this way, the first two hydrogen transfer steps are believed to generate the

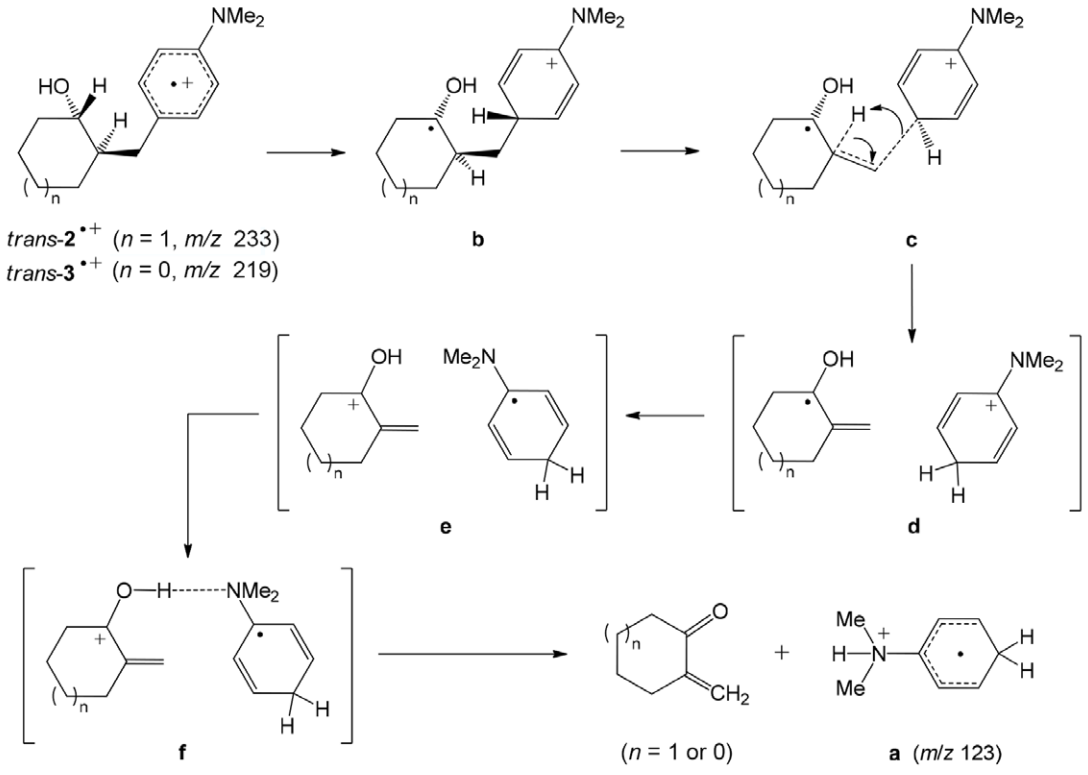
Table 2. Fragmentation of the 2-(4-dimethylamino) phenylcyclopentanols *cis/trans*-5 (mixture of diastereomers) under EI (70 eV) and EI-MIKES (70 eV) conditions.

m/z	*cis/trans*-5		Fragment ion (tentative)[b,c]	Neutral fragment
	Rel. Abundance			
	EI	(EI-MIKES)[a]		
205	100			
187	8	(100)	$[M-H_2O]^{\bullet+}$	H_2O
186	9			
176	14	(46)	Ar–CHCHCH$^+$OH	$C_2H_5^{\bullet}$
160	41	(81)	Ar–CHCH$_2^+$	$C_2H_5O^{\bullet}$
147	27	(12)	Ar–CH$_2^{\bullet+}$	C_3H_6O
146	19			
134	53	(46)	Ar–CH$_2^+$	$C_4H_7O^{\bullet}$
123	1	(7)		
122	4	(~3)		
121	7	(~1)		
120	6			
118	5			
117	6			
91	5			

[a]Relative abundances in the MIKE spectra derived from peak intensities.

[b]"Ar" denotes the *para*-(dimethylamino)phenyl residue.

[c]Structural assignment based on the accepted fragmentation mechanisms of cycloalkane derivatives (Reference 4) and alkylbenzenes (References 1, 2 and 5) under EI conditions.



Scheme 2. Suggested mechanism for the unidirectional 3H migration (see discussion).

first ion/neutral complex, intermediate **d**, consisting of *para*-protonated dimethylaniline, a particularly stable arenium ion,[27] and a rather stable cyclic 1-hydroxyallyl radical. Intra-complex charge transfer and internal rotation may lead to the electromeric[33] I/N complex **e**, in which a strong O···H···N hydrogen bond (*cf*. ion **f**) should facilitate the final transfer of a proton to the nitrogen atom. According to this mechanistic view, the α-distonic[20] radical cation **a** is formed along with the corresponding methylenecycloalkanone.

Admittedly, this mechanism is tentative, still, and extended theoretical calculations may be required to substantiate this model. However, the model is based on previous experimental findings. The present experimental findings made with the 2-(4-dimethylamino)benzylcycloalkanols *cis*-**2** to *trans*-**3** further demonstrate that the unidirectional 3H rearrangement does represent a stereospecific fragmentation route under EI conditions of cycloalkanols bearing an electron-rich benzyl residue at the position C2. However, this process is easily suppressed if energetically and entropically more favorable fragmentation reactions compete. Hence, as shown in this work for the case of the 3-(4-dimethylamino)phenylcycloalkanols *cis*-**4** and *trans*-**4**, structural preconditions for the unidirectional 3H rearrangement are quite delicate.

Conclusion

The unidirectional rearrangement of three hydrogen atoms within the molecular radical cations of 3-aryl-1-propanols, bearing suitably activating substituents at the *para*-position of the arene moiety, has been shown to operate stereospecifically in the cases of the *trans*-isomers of 2-(4-dimetylamino)benzylcyclohexanol, *trans*-**2**, and 2-(4-dimetylamino)benzylcyclopentanol, *trans*-**3**. Although being of minor (or even minute) relative abundance under standard (70 eV) EI conditions, the relevant fragment ions, $C_8H_{13}N^{\bullet+}$ (*m/z* 123), give rise to valuable analytical information. This holds particularly true for the low-energy, long-lived metastable ions, *trans*-**2**$^{\bullet+}$ and *trans*-**3**$^{\bullet+}$, which undergo the 3H rearrangement with a significant relative abundances. The related 3-(4-dimethylamino)phenylcyclohexanols do not show this process. The mechanism of the unique 3H rearrangement appears to be very complicated, still, and there is no doubt that theoretical modeling of this multistep process will be a challenging task.

Experimental

Syntheses (General)

Melting points (uncorrected): Electrothermal melting point apparatus. TLC: silica (Kieselgel 60) on aluminum foil with fluorescence indicator F_{254}, thickness 0.2 mm (Merck). ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75.4 MHz) were measured on a Bruker AM 300 instrument ($CDCl_3$/TMS).

Mass spectrometry

Mass spectra were obtained by using a double-focusing AutoSpec X mass spectrometer[34] of EBE geometry. Standard EI mass spectra were recorded at 70 eV electron energy and with an acceleration voltage of 8 kV, at an ion source temperature of 200°C, and by using the direct inlet probe. MIKE spectra of the molecular ions generated at 70 eV were obtained by focusing the ions the 3rd field free region (FFR) between the magnet and the 2nd electrostatic analyzer (ESA) and then scanning the deflection voltage of the 2nd ESA. The spectra recorded by a multiplier were processed using the Origin 8 program.[35]

Cis- and *trans*-2-(4-dimethylaminobenzyl) cyclohexanols (*cis*-2 and *trans*-2)

(1) Cyclohexanone (10.0 g, 102 mmol) and *para*-*N*,*N*-dimethylaminobenzaldehyde (5.01 g, 33.5 mmol) were reacted in a solution of potassium hydroxide (2.1 g) in water (45 mL) under reflux for 20 h. Work-up and recrystallization of the precipitated product gave 2-(4-dimethylaminobenzylidene) cyclohexanone as yellow crystals (2.89 g, 38%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.52 (s, 1H), 7.37 (d, *J* = 8.9 Hz, 2H), 6.66 (d, *J* = 8.9 Hz, 2H), 2.98 (s, 6H), 2.84 (t, *J* = 4.6 Hz, 2H), 2.47 (t, *J* = 6.6 Hz, 2H), 1.87 (m, 2H), 1.74 (m, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 201.2 (C), 150.4 (C), 137.1 (CH), 132.6 (C), 131.6 (CH), 123.4 (C), 111.5 (CH), 40.0 (CH_3), 39.9 (CH_2), 29.0 (CH_2), 23.8 (CH_2), 23.1 (CH_2).

(2) The benzylidenecyclohexanone (780 mg, 3.4 mmol) was hydrogenated in 1,4-dioxane solution (90 mL) in the presence of Pd/C catalyst (100 mg, 10% Pd) at 25°C (H_2 take-up 1.0 equiv.). Work-up gave 2-(4-dimethylaminobenzyl)cyclohexanone as a yellow oil (360 mg, 46%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.00 (d, *J* = 8.5 Hz, 2H), 6.67 (d, *J* = 8.5 Hz, 2H), 3.11 (m, 2H), 2.86 (s, 6H), 1.74–2.39 (m, 9H).

(3) The benzylcyclohexanone (360 mg, 1.6 mmol) was reduced in anhydrous tetrahydrofuran (3.5 mL) with lithium aluminium hydride (70 mg, 1.75 mmol) by heating the suspension under reflux for 2 h. Careful hydrolysis and work-up gave a mixture of the 2-(4-dimethylaminobenzyl) cyclohexanols, which were separated by column chromatography (silica).—The first fraction was assigned to be the *cis*-isomer, *cis*-**2a**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.08 (d, *J* = 8.6 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), 3.81 (s, 1H), 2.92 (s, 6H), 2.55 (m, 2H), 1.42–1.76 (m, 10H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 148.6 (C), 129.6 (CH), 129.0 (C), 112.8 (CH), 68.5 (CH), 43.6 (CH_2), 40.8 (CH_3), 37.5 (CH_2), 33.1 (CH), 26.3 (CH_2), 25.2 (CH_2), 20.3 (CH_2). EI-MS (70 eV): *m/z* (%) 234 (4, $^{13}C_1$–M$^{\bullet+}$), 233 (21, M$^{\bullet+}$), 135 (10) , 134 (100), 120 (2), 118 (6), 91 (3).—The second fraction was assigned to be the *trans*-isomer, *trans*-**2a**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.06 (d, *J* = 8.5 Hz, 2H), 6.66 (d, *J* = 8.6 Hz, 2H), 3.82 (s, 1H), 2.90 (s, 6H), 2.30 (m, 2H), 0.88–1.70 (m, 10H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 149.0 (C), 129.9 (CH), 128.7 (C), 112.8 (CH), 74.6 (CH), 47.1 (CH_2), 40.9 (CH_3), 38.0 (CH_2), 35.6 (CH), 30.1 (CH_2), 25.5 (CH_2), 24.9 (CH_2). EI-MS (70 eV): *m/z* (%) 234 (5, $^{13}C_1$–M$^{\bullet+}$), 233 (30, M$^{\bullet+}$), 135 (12), 134 (100), 123(2), 120 (3), 118 (7), 91 (4).

Cis- and *trans*-2-(4-dimethylaminobenzyl) cyclopentanols (*cis*-3 and *trans*-3)

(1) Cyclopentanone (8.6 g, 102 mmol) and *para*-*N*,*N*-dimethylaminobenzaldehyde (5.02 g, 33.5 mmol) were reacted in a solution of potassium hydroxide (2.1 g) in water (45 mL) under reflux for 20 h. Work-up and recrystallization of the precipitated product gave 2-(4-dimethylaminobenzylidene)cyclopentanone as orange crystals (4.55 g, 63%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.33 (s, 1H), 6.68 (d, *J* = 7.8 Hz, 2H), 2.99 (s, 6H), 2.92 (t, *J* = 7.1 Hz, 2H), 2.35 (t, *J* = 7.8 Hz, 2H), 1.97 (m, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 208.1 (C), 150.9 (C), 133.3 (CH), 132.4 (C), 131.0 (CH), 123.2 (C), 111.7 (CH), 40.0 (CH_3), 37.7 (CH_2), 29.3 (CH_2), 20.1 (CH_2).

(2) The benzylidenecyclopentanone (1.05 g, 4.86 mmol) was hydrogenated in 1,4-dioxane solution (130 mL) in the presence of Pd/C catalyst (130 mg, 10% Pd) at 25°C (H_2 take-up 1.0 equiv). Work-up gave 2-(4-dimethylaminobenzyl)cyclopentanone as a yellow oil (740 mg, 70%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.01 (d, *J* = 8.6 Hz, 2 H), 6.65 (d, *J* = 8.7 Hz, 2 H), 2.89 (s, 6 H), 1.21–1.76 (m, 9 H).

(3) The benzylcyclopentanone (739 mg, 3.4 mmol) was reduced in anhydrous tetrahydrofuran (7.0 mL) with lithium aluminium hydride (130 mg, 3.50 mmol) by heating the suspension under reflux for 2 h. Careful hydrolysis and work-up gave a mixture of the two-(4-dimethylaminobenzyl)-cyclohexanols, which were separated by column chromatography (silica).—The first fraction was assigned to be the *cis*-isomer, *cis*-**3a**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.13 (d, *J* = 6.1 Hz, 2H), 6.72 (d, *J* = 6.1 Hz, 2H), 4.11 (s, 1H), 2.94 (s, 6H), 2.69 (m, 2H), 1.27–2.01 (m, 8H). EI-MS (70 eV): *m*/*z* (%) 220 (4, $^{13}C_1$–$M^{\bullet+}$), 219 (26, $M^{\bullet+}$), 135 (12), 134 (100), 118 (8), 91 (4).—The second fraction was assigned to be the *trans*-isomer, *trans*-**3a**. H NMR ($CDCl_3$, 500 MHz): δ 7.10 (d, *J* = 8.1 Hz, 2H), 6.72 (d, *J* = 8.1 Hz, 2H), 3.92 (s, 1H), 2.94 (s, 6H), 2.58 (m, 2H), 1.29–3.03 (m, 8H). EI-MS (70 eV): *m*/*z* (%) 220 (3, $^{13}C_1$–$M^{\bullet+}$), 219 (21, $M^{\bullet+}$), 135 (10), 134 (100), 123 (2), 120 (3), 118 (6), 91(3).

Cis- and *trans*-2-(4-dimethylaminophenyl) cyclohexanols (*cis*-4 and *trans*-4)

(1) A solution of 4-bromo-*N*,*N*-dimethylaniline (6.80 g, 17 mmol) in anhydrous tetrahydrofuran (50 mL) was stirred and cooled to –78 °C under argon and *tert*-butyllithium (2.18 g, 23 mL, 34.0 mmol) were added quickly through a septum. After stirring for 1 h, the viscous colorless solution formed was diluted with THF and a solution of copper(I) iodide (2.60 g, 14.0 mmol) in the same solvent (15 mL) was added at 0°C. The color of the solution first turned dark and then slightly yellow–green. After stirring at 0°C for 2 h, the mixture was cooled to –78°C again and a solution of cyclohexen-3-one (1.30 mg, 14.0 mmol) in anhydrous THF (10 mL) was added through the septum. The reaction mixture was allowed to warm to 0°C and stirred under GC-MS monitoring. After 18 h, the mixture was hydrolyzed by the addition of saturated aqueous ammonium chloride (pH ≈ 7). The product was extracted with diethyl ether (3 × 100 mL) and the combined extracts were washed with water and then brine, dried over magnesium sulphate and the concentrated to dryness under reduced pressure. The dark oily product was subjected to column chromatography (Chx/EtOAc 70 : 30) and recrystallized from *n*-pentane to give 2-(4-dimethylaminophenyl)cyclohexanone as a colorless solid (600 mg, 8%), mp 65–66°C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 2.93 (s, 6H), 2.85–3.01 (m, 1H), 2.45–2.55 (m, 2H), 2.31–2.43 (m, 2H), 2.02–2.17 (m, 2H), 1.70–1.87 (m, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 211.3 (C), 149.2 (C), 132.8 (C), 127.1 (CH), 113.0 (CH), 49.2 (CH_2), 43.9 (CH_3), 41.2 (CH_2), 40.8 (CH), 33.0 (CH_2), 25.5 (CH_2).

(2) The arylcyclohexanone (350 mg, 1.60 mmol) was reduced in anhydrous diethyl ether (40 mL total volume) with lithium aluminium hydride (17 mg, 450 µmol) by heating the suspension under reflux for 1 h. Careful hydrolysis at 0°C and work-up gave a mixture of the 2-(4-dimethylaminophenyl) cyclohexanols *cis*-**4** and *trans*-**4** as a brownish oil. Separation by column chromatography (silica, Chxn/EtOAc 70 : 30) gave the *trans*-isomer, *trans*-**4**, as the first-eluting fraction (10 mg, 3%) and the *cis*-isomer, *cis*-**4**, as the second fraction (140 mg, 40%). *Cis*-**4**: Colorless solid, mp 71–73°C (from cyclohexane). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 3.65–3.76 (m, 1H), 2.92 (s, 6H), 2.44–2.54 (m, 1H), 2.09–2.19 (m, 1H), 2.01–2.08 (m, 1H), 1.81–1.93 (m, 1H), 1.78 (br s, 1H, OH), 1.42–1.47 (m, 1H), 1.36–1.41 (m, 1H), 1.29–1.35 (m, 1H), 1.20–1.27 (m, 1H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 149.0 (C), 134.9 (C), 127.3 (CH), 113.1 (CH), 71.0 (CH), 43.5 (CH_2), 41.6 (CH), 40.9 (CH_3), 35.3 (CH_2), 33.6 (CH_2), 24.5 (CH_2).

Trans-**4**: Color-less solid, mp < 71°C (from cyclohexane). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.12 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 4.21 (quin, *J* = 2.9 Hz), 2.93 (s, 6H), 2.84–2.99 (m, 1H), 1.81–1.91 (m, 2H), 1.71–1.81 (m, 2H), 1.59–1.70 (m, 2H), 1.42–1.55 (m, 2H).

2-(4-dimethylaminophenyl)cyclopentanol (mixture of *cis*/*trans*-5)

(1) A solution of 4-bromo-*N*,*N*-dimethylaniline (3.40 g, 17 mmol) in anhydrous tetrahydrofuran (50 mL) was stirred and cooled to –78°C under argon and tert-butyllithium (1.09 g, 12 mL, 17.0 mmol) were added quickly through a septum. After stirring for 1 h, the viscous colorless solution formed was diluted with THF and a solution of copper(I) iodide (1.30 g, 7.0 mmol) in the same solvent (15 mL) was added at 0°C. The color of the solution first turned dark and then yellow–green. After stirring at 0°C for 2 h, the mixture was cooled to –78°C again and a solution of cyclopenten-3-one (560 mg, 7.0 mmol) in anhydrous THF (10 mL) was added through the septum. The reaction mixture was allowed to warm to 0°C and stirred under GC-MS monitoring. After 18 h, the mixture was hydrolyzed by the addition of saturated aqueous ammonium chloride (pH ≈ 7). The product was extracted with diethyl ether (3 × 100 mL) and the combined extracts were washed with water and then brine, dried over magnesium sulfate and concentrated to dryness under reduced pressure. The dark oily product was subjected to column chromatography (Chx/EtOAc 70 : 30) and recrystallized from *n*-pentane to give 2-(4-dimethylaminophenyl)cyclopentanone, an orange solid

(480 mg, 20%), mp 72°C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.12 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 3.26–3.40 (m, 1H), 2.94 (s, 6H), 2.57–2.67 (m, 1H), 2.09–2.46 (m, 4H), 1.86–2.02 (m, 1H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 218.8 (C), 149.3 (C), 131.3 (C), 127.3 (CH), 113.1 (CH), 46.0 (CH_2), 41.3 (CH), 40.8 (CH_3), 38.9 (CH_2), 31.4 (CH_2).

(2) The arylcyclopentanone (400 mg, 1.97 mmol) was reduced in anhydrous diethyl ether (40 mL total volume) with lithium aluminium hydride (20 mg, 540 µmol) by heating the suspension under reflux for 1 h. Careful hydrolysis at 0°C and work-up gave a mixture of the 2-(4-dimethylaminophenyl)-cyclopentanols *cis*/*trans*-**5** (370 mg, 92%). Separation by column chromatography (silica) was unsuccessful.

References

1. H.M. Grubb and S. Meyerson, "Mass spectra of alkylbenzenes", Chapter 10 in *Mass Spectrometry of Organic Ions*, Ed by F.W. McLafferty. Academic Press, New York, USA, pp. 453–528 (1963).
2. F. McLafferty and F. Turecek, *Interpretation of Mass Spectra*, 4th Edn. Mill Valley, CA, USA (1993).
3. J.L. Holmes, C. Aubry and P.M. Mayer, *Assigning Structures to Ions in Mass Spectrometry*. CRC Press, Boca Raton, Florida, USA (2007).
4. R.M. Smith and K.L. Busch, *Understanding Mass Spectra—A Basic Approach*. John Wiley & Sons Inc., New York, USA (1999).
5. J.B. Lambert, S. Gronert, H.F. Shurvelland and D.A. Lightner, "Anregung und Fragmentierung von Ionen in der Gasphase", Chapter 8, and "Interpretation von Massenspektren" Chapter 9, in *Spektroskopie*, 2nd Edn (revised). Pearson, Munich. Germany (2012).
6. D. Kuck, "From unexpected peaks to unusual fragmentation mechanisms: A potpourri admixed of organic chemistry and organic mass spectrometry", in *Proceedings of the 8th ISMAS Symposium,* Vol. I, Ed by S. K. Aggarwal. Indian Society for Mass Spectrometry, Mumbai, India, pp. 245–260 (1999).
7. D. Kuck, "Scrambling versus specific processes in gaseous organic ions during mass spectrometric fragmentation: elucidation of mechanistic origins by isotope labelling—an overview", *J. Label. Compd. Radiopharm.* **50,** 360 (2007). doi: 10.1002/jlcr.1405
8. D. Kuck, "By cyclodehydration to centropolyindanes: development of a novel class of indane hydrocarbons with three-dimensional molecular frameworks using a classical synthetic tool", *Synlett* **1996(10),** 949 (1996).doi: 10.1055/s-1996-5632
9. D. Kuck, "Three-dimensional hydrocarbon cores based on multiply fused cyclopentane and indane units: the centropolyindanes", *Chem. Rev.* **106(12),** 4885 (2006). doi: 10.1021/cr050546+
10. D. Kuck and U. Filges, "Unidirectional triple and double hydrogen rearrangement reactions in the radical cations of γ-arylalkanols", *Org. Mass Spectrom.* **23(9),** 643 (1988). doi: 10.1002/oms.1210230904
11. S. Meyerson, I. Puskas and E.K. Fields "Organic ions in the gas phase. XXVII. Long-range intramolecular interactions in 4-*n*-alkyl trimellitic esters", *J. Am. Chem. Soc.* **95(18),** 6056 (1973). doi: 10.1021/ja00799a037
12. S. Meyerson, I. Puskas and E. K. Fields, "Triple-hydrogen migration in 4-*N*-alkyl esters of trimellitic anhydride under electron impact", *Chem. Ind.* (*London*) **52,** 1845 (1968).
13. S. Meyerson, I. Puskas and E. K. Fields, "Long-range Intramolecular Interactions in 4-*n*-Alkyl Trimellitic Esters", *Adv. Mass Spectrom.* **6,** 17 (1974).
14. M. Katoh and C. Djerassi, "Mass spectrometry in structural and stereochemical problems. CXC. Electron impact induced triple hydrogen migration in vinyl alkyl ethers, *J. Am. Chem. Soc.* 92, 731 (1970). doi: 10.1021/ja00706a067
15. J. Cable and C. Djerassi, "Mass spectrometry in structural and stereochemical problems. CCIII. The course of a triple hydrogen migration in esters of trimellitic anhydride", *J. Am. Chem. Soc.* **93,** 3905 (1971). doi: 10.1021/ja00745a014
16. H. Vetter-Diechtl, W. Vetter, W. Richter and K. Biemann, "A suitable arginine derivative for mass spectrometry and gas chromatography", *Experientia* **24(4),** 340 (1968). doi: 10.1007/BF02140808
17. C. Schulze and H. Schwarz, "Highly specific interligand triple hydrogen migrations involved in the formation of C_3H_6 from 1-heptyne and bare iron(I) cations. A gas-phase analogue of the crabtree-felkin type of CH bond activation", *Organometallics* **9(7),** 2164 (1990). doi: 10.1021/om00157a030
18. D.G.I. Kingston, J.T. Bursey and M.M. Bursey, "Intramolecular hydrogen transfer in mass spectra. 2. McLafferty rearrangement and related reactions", *Chem. Rev.* **74(2),** 215 (1974). doi: 10.1021/cr60288a004
19. H. Yamaoka, I. Kusagi, K. Isa, Y. Maekawa and N.M.M. Nibbering, "On the double benzylic hydrogen migration in the molecular ion of *N*-(5-phenylvaleryl)-1-azacyclopentane-2-thione", *Int. J. Mass Spectrom.* **234(1–3),** 171 (2004). doi: 10.1016/j.ijms.2004.02.010
20. S. Hammerum, "Distonic radical cations in gaseous and condensed phase", *Mass Spectrom. Rev.* **7(2),** 123 (1988). doi: 10.1002/mas.1280070202
21. T.H. Morton, "Via ion–neutral complexes", in Chapter 6, Collisional Activation and Dissociation in *Encyclopedia of Mass Spectrometry*, Vol. 1, Ed by P.B. Armentrout. Elsevier, Amsterdam, The Netherlands, pp. 467–479 (2003).
22. T.H. Morton, "Theoretical models for ion-neutral complexes in unimolecular ion Decomposition", in Chapter 2 "Structures and Properties of Gas-Phase Organic Ions", in *Encyclopedia of Mass Spectrometry*, Vol. 4, Ed by N.M.M. Nibbering. Elsevier, Amsterdam, The Netherlands, pp. 165–173 (2005).

23. D. Kuck, "Mass spectrometry of alkylbenzenes and related compounds. Part I: Gas-phase ion chemistry of alkylbenzene radical cations", *Mass Spectrom. Rev.* **9(2)**, 181 (1990). doi: 10.1002/mas.1280090203
24. D. Kuck and H.F. Grützmacher, "McLafferty reaction of alkylbenzenes: intramolecular isomerization reactions of the molecular ions of 2-benzylindanes—the effect of substituents on the rate of hydrogen transfer", *Adv. Mass Spectrom.* **8,** 867 (1980).
25. D. Kuck, "Concerning the fragmentation of *ortho*-dimethyl substituted alkylbenzenes Induced by γ-H Migration", *Org. Mass Spectrom.* **24(12)**, 1077 (1989). doi: 10.1002/oms.1210241209
26. E.P. Hunter and S.G. Lias, NIST *Chemistry WebBook, NIST Standard Reference Database Number 69*. National Institute of Standards and Technology, Gaithersburg MD, USA, p. 20899. webbook.nist.gov. (Accessed: 15 August 2013).
27. D. Kuck, "Protonated Aromatics and Arenium ions", in Chapter 2 "Structures and properties of gas-phase organic ions", in *Encyclopedia of Mass Spectrometry*, Vol. 4, Ed by N.M.M. Nibbering. Elsevier, Amsterdam, The Netherlands. pp. 229–242 (2005).
28. S. Meyerson and L.C. Leitch, "Localized activation in bond-forming reactions under electron impact. Internal solvation in isolated molecules", *J. Am. Chem. Soc.* **93(9),** 2244 (1971). doi: 10.1021/ja00738a025
29. S.J. Blanksby and G.B. Ellison, "Bond dissociation energies of organic molecules", *Acc. Chem. Res.* **36(4),** 255 (2003). doi: 10.1021/ar020230d
30. H.W. Leung and A.G. Harrison, "Hydrogen migrations in mass spectrometry. IV—Formation of $[C_6H_7]^+$ in the chemical ionization mass spectra of alkylbenzenes?", *Org. Mass Spectrom.* **12(9),** 582 (1977). doi: 10.1002/oms.1210120912
31. J.A. Herman and A.G. Harrison, "Effect of protonation exothermicity on the chemical ionization mass spectra of some alklybenzenes", *Org. Mass Spectrom.* **16(10),** 423 (1981). doi: 10.1002/oms.1210161002
32. D. Kuck, "Mass spectrometry of alkylbenzenes and related compounds. Part II. Gas-phase ion chemistry of protonated alkbenzenes (alkylbenzenium ions)", *Mass Spectrom. Rev.* **9(6),** 583 (1990). doi: 10.1002/mas.1280090602
33. F.F. Puschmann, J. Harmer, D. Stein, H. Rüegger, B. de Bruin and H. Grützmacher, "Electromeric rhodium radical complexes", *Angew. Chem. Int. Ed.* **49(2),** 385 (2010), and literature cited therein. doi: 10.1002/anie.200903201
34. Fisons Ltd, Manchester, UK.
35. O. Pro 8.6.0, OriginLab Corporation, Northampton, MA 01060, USA.