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DIFFERENTIATION BETWEEN REGIO- AND STEREOISOMERS OF BICYCLO[3,2,0]HEPTANONE-2 DERIVATIVES BY CHEMICAL IONIZATION MASS SPECTROMETRY[1]

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Abstract—The c.i. (isobutane) mass spectral behaviour was examined for a series of bicyclo[3,2,0]heptanone-2 derivatives, produced by $(2\pi+2\pi)$ photocycloaddition reactions. The c.i. (isobutane) data allow unequivocal differentiation between hh- and ht-regioisomers. In some cases, a further assignment of the *syn* or *anti* form can also be made on the basis of the intensity of the protonated molecule ion.

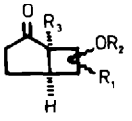
A number of electron and chemical ionization studies have demonstrated that mass spectral behaviour can be correlated with stereochemical features in a molecule.[2-13] Chemical ionization mass spectrometry has been used in this laboratory for the assignment of the configuration in epimeric methyl and TMS-ethers of 3-hydroxycyclopentyl and 3-hydroxycyclohexyl acetic acid esters.[3] These epimers could be distinguished based on the presence of a protonated molecule ion (MH^+), which only occurs in *cis* isomers as a result of stabilization provided by intramolecular proton bridge formation.

In the present study we deal with the problem of identifying $(2\pi+2\pi)$ photocycloaddition reaction products from 2-cyclopentenone or 2-methyl-2-cyclopentenone and various electron-rich alkenes. *cis*-Fused bicyclo[3,2,0]heptanone-2 derivatives are formed, hence four stereoisomers are possible: two pairs of regioisomers, head-to-head (hh) or head-to-tail (ht) isomers, which both may exist as *syn* and *anti* epimers. The four stereoisomers can only be separated by capillary g.c. and can as such be analyzed by g.c.m.s.

A c.i. study on photodimers of cyclic α,β-unsaturated ketones by Ziffer *et al.* has demonstrated that c.i. permits differentiation between regioisomers.[4] Other studies on polyfunctional molecules[3,5-12] have shown that the proton transferred in c.i. can be inserted between two, favourably oriented functions with lone electrons. In our case, this effect can be used for differentiating between *syn* and *anti* epimers in each pair of regiosomers. As our compounds contain a keto and an ether or ester group, we can safely assume that a proton bridge will be formed preferentially in protonated molecule ions of *syn* isomers, where the two functions are in close proximity of each other.

It is also worthwhile mentioning here, that c.i. (isobutane) m.s. has proven its diagnostic value for differentiating between other isomeric bicyclic molecules, e.g. isomeric 7-acetylbicyclo[4.2.0]octenes, where variations are revealed for the intensity of the $[M+1-18]^+$-ions, formed upon loss of water from the protonated ketone.[13]

In this work, only the c.i. (isobutane) spectra are examined, because, in this ionization mode, the exothermicity in the proton transfer reactions is low,[14] offering as such the best chances for stereochemical differences to manifest themselves. The compounds studied are presented below. The isomeric mixtures were characterized by other spectroscopic techniques (IR, UV and ^{1}H NMR) and/or chemical correlations[15,16] but individual distinction only appeared to be possible by c.i.



$I_{1,2,3 \text{ and } 4}$: $R_1 = H; R_2 = C_2H_5; R_3 = H$

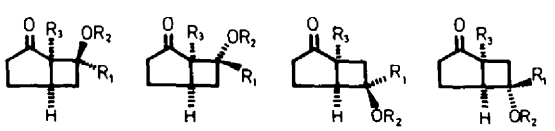
$II_{1,2,3 \text{ and } 4}$: $R_1 = H; R_2 = C_2H_5; R_3 = CH_3$

$III_{1,2,3 \text{ and } 4}$: $R_1 = CH_3; R_2 = CH_3; R_3 = H$

$IV_{1,2 \text{ and } 3}$: $R_1 = H; R_2 = C(=O)CH_3; R_3 = H$

$V_{1,2,3 \text{ and } 4}$: $R_1 = CH_3; R_2 = C(=O)CH_3; R_3 = H$

$VI_{1 \text{ and } 2}$: $R_1 = CH_3; R_2 = C(=O)CH_3; R_3 = CH_3$



hh-*syn* hh-*anti* ht-*syn* ht-*anti*

The indices 1–4 refer to the elution sequence of the compounds in the capillary gas chromatogram.

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§Aangesteld Navorser of the N.F.W.O.

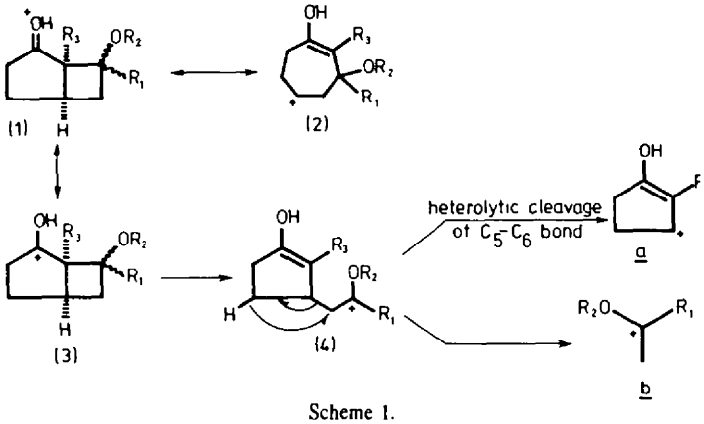
Abbreviations used: c.i., chemical ionization; hh, head-to-head; ht, tead-to-tail; g.c., gas chromatography; m.s., mass spectrometry.

RESULTS and DISCUSSION

The c.i. (isobutane) mass spectra of all the compounds examined and their structural assignment on the basis of these data are given in Table 1.

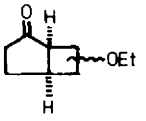
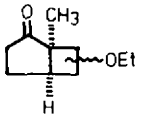
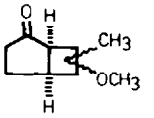
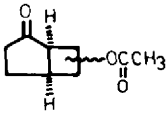
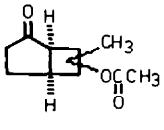
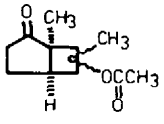
From these data it is apparent that the bicyclo[3,2,0]heptanone-2 derivatives give rise to two types of mass spectral patterns from which the regioisomerism may be deduced. The hh-isomers exhibit a prominent fragment ion **a**, which is absent or of minor importance in the spectra of the corresponding ht-isomers (Table 1). Rationalization is given in Scheme 1; protonation upon c.i. yields a MH^+-ion, which can have four protonated molecular ion forms (**1–4**). Form **4** can readily undergo fragmentation by heterolytic cleavage of the C_5–C_6 bond, resulting in ion **a**; a competitive cleavage with hydrogen migration (most probably from the 4-position) yields ion **b**. In the series of the bicyclo[3,2,0]heptanone-2 esters (IV, V and VI; Table 1) no ions **b** are formed, probably as a result of their decreased stabilization, induced by the electron withdrawing acetate group.

For ht-regioisomers, the fragmentations given in Scheme 1, have lower probability because the contribution of form **4** (= a primary carbenium ion) is decreased, resulting in a more stable MH^+-ion.



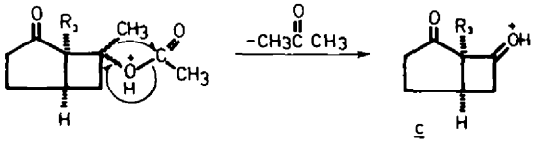
Scheme 1.

Table 1. Mass spectral data for the most relevant ions of compounds I–VI and their structural assignment[a]

Compound		MH^+	a	b	c	d	e	Assignment
	*m/e*	155	83	73	n.p.	109	n.p.	
	I_1	3.9(2.0)	100(50.1)	73.6(36.9)	—	4.7(2.4)	—	hh
	I_2	1.9(1.0)	100(52.8)	64.0(33.8)	—	4.0(2.1)	—	hh
	I_3	100(85.2)	—	1.3(1.1)	—	3.5(2.0)	—	ht-*syn*
	I_4	42.4(25.0)	—	—	—	100(58.9)	—	ht-*anti*
	*m/e*	169	97	73	n.p.	123	95	
	II_1	—	100(46.2)	96.3(44.5)	—	—	—	hh
	II_2	5.1(2.4)	26.1(12.2)	48.4(22.7)	—	9.1(4.3)	100(46.9)	ht
	II_3	—	100(53.2)	64.1(34.1)	—	—	—	hh
	II_4	9.2(4.0)	33.0(14.4)	33.7(14.7)	—	26.4(11.5)	100(43.5)	ht
	*m/e*	155	83	73	n.p.	123	n.p.	
	III_1	53.0(19.6)	30.6(11.3)	100(37.0)	—	46.0(17.0)	—	hh-*syn*
	III_2	13.6(7.0)	46.3(23.8)	100(51.4)	—	12.7(6.5)	—	hh-*anti*
	III_3	100(35.1)	5.4(1.9)	36.5(12.8)	—	89.3(31.4)	—	ht-*anti*
	III_4	100(68.7)	2.6(1.8)	8.5(5.8)	—	4.0(2.8)	—	ht-*syn*
	*m/e*	169	83	n.p.	n.p.	109	n.p.	
	IV_1	42.6(19.3)	47.1(21.4)	—	—	100(45.4)	—	hh-*syn*
	IV_2	3.8(3.4)	—	—	—	100(88.9)	—	ht
	IV_3	4.8(4.1)	100(86.3)	—	—	—	—	hh-*anti*
	*m/e*	183	83	n.p.	125	123	95	
	V_1	46.8(22.2)	11.4(5.4)	—	17.2(8.2)	100(47.4)	2.4(1.)	hh
	V_2	80.3(33.9)	4.7(2.0)	—	6.9(2.9)	100(42.2)	2.9(1.2)	ht
	V_3	90.5(26.4)	46.4(13.5)	—	41.9(12.2)	100(29.2)	5.0(1.5)	hh
	V_4	56.7(30.9)	—	—	—	100(54.4)	2.2(1.2)	ht
	*m/e*	197	97	n.p.	139	137	n.p.	
	VI_1	17.2(10.7)	6.8(4.2)	—	2.4(1.5)	100(62.3)	—	ht
	VI_2	7.5(3.6)	100(48.5)	—	18.9(9.2)	54.6(26.5)	—	hh

[a]Relative intensities are given and $\%\Sigma_{70}^{MH^+}$-values are presented between brackets for ions with $\%\Sigma_{70}^{MH^+} > 1$.
n.p. denotes: not present.

Differentiation between regioisomers of the bicyclo[3,2,0]heptanone-2 esters (IV, V and VI; Table 1) also appears to be possible when R_1 is a Me group. The MH^+-ions of hh-isomers show loss of a molecule of acetone, whereas this fragmentation is absent or much less pronounced in ht-isomers. A possible mechanism for the loss of acetone from MH^+-ions of hh-isomers is advanced in Scheme 2. Upon protonation at the ester site, expulsion of a molecule of acetone can occur, giving rise to ion **c**. In the case of hh-isomers, ion **c** is stabilized and again, this stabilization is absent in the corresponding ht-isomers. The absence of acetaldehyde loss in the homologues where R_1 is an H atom (series IV) cannot be interpreted in a straightforward manner and more work is in progress to illuminate the exact mechanism of this fragmentation.



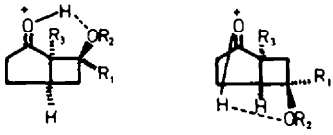
Scheme 2.

Another important fragmentation route is the loss of a neutral molecule R_2OH from the MH^+-ion, resulting in ion **d**. In some cases, ion **d** further fragments through loss of 28 a.m.u. (most probably CO), leading to ion **e** (Scheme 3). Absolute proof however, for this sequence cannot be given, since metastables are not present in

$$MH^+ \xrightarrow{-R_2OH} \text{ion } \mathbf{d} \xrightarrow{-CO} \text{ion } \mathbf{e}$$

Scheme 3.

quadrupole spectra. The abundance of MH^+ and/or ion **d** makes it possible to differentiate between *syn* and *anti* isomers in each pair of regioisomers, provided the two stereoisomers are available. For *syn* isomers, the proton transferred upon c.i., can be coordinated between the CO function in position 2 and the R_2O-group and leads to proton bridge formation. This effect results in extra stabilization, renders MH^+ less prone to expulsion of R_2OH and is reflected in more abundant MH^+-ions. This situation is impossible in *anti* isomers, which more



readily show loss of R_2OH. A favourable alternative may however operate, back side attack (SN_i mechanism) of the oxygen lone pair electrons from the CO group can also result in expulsion of R_2OH. The stabilization effect, due to intramolecular proton bridge formation, is nicely demonstrated in series III, where structural assignment of the four isomers can be made on the basis of c.i. data alone. Since ht-isomers exhibit more abundant MH^+-ions (*vide supra*), in most cases, *syn* and *anti* epimers will only be conveniently discerned in these regioisomers (e.g. series I). In series V, the differences for the abundances of MH^+-ions in each pair of regioisomers, are too low to permit unambiguous identification.

The effect of introducing a Me group at the bridgehead position 1, becomes apparent when comparing series I and V to series II and VI respectively. In series II for instance, the abundances of MH^+-ions in each pair of regioisomers are too low to allow structural assignment and a more extensive fragmentation can be noticed for ht-isomers. The decreased abundances of MH^+-ions and increased formation of ions **a** and **b**, observed upon introduction of a Me group, cannot be explained by steric interference effects of the Me group in the proton bridged MH^+-ion, but may be attributed to facilitated cleavage of the C_1–C_7 bond, required for the formation of ions **a** and **b** (Scheme 1).

More work is in progress to evaluate the utility of c.i. in analogous stereochemical problems.

EXPERIMENTAL

Compounds I–VI were available from ongoing work in this laboratory; their preparation has been described.[15,16]

A 3200c.i. Finnigan gaschromatograph-mass spectrometer, interfaced with a Finnigan 6000 data system and equipped with an all glass chromatographic inlet system have been used for g.c.m.s. analysis. G.c. was performed on a 100 m SE-30 glass capillary column (i.d. = 0.5 mm) with a helium flow of 4 ml/min. The reagent gas, isobutane, was introduced as make-up gas and was added until the source pressure reached 0.6 Torr. The m.s. conditions were: electron energy, 150 eV; emission current, 1 mA; repeller voltage 1 V and ion source temperature, 110°.

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