Chemical Ionization Mass Spectrometry: A Useful Stereochemistry Probe

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The helium charge exchange and the isobutane chemical ionization spectra of 4-methoxy cyclohexanecarboxylic acid ethyl esters (1c and 1t), 2,6-dimethyl-4-hydroxytetrahydropyranes (2c and 2t), 2,4,6-trimethyl-4-hydroxytetrahydropyranes (3c and 3t), and 2,7-dimethoxy-cis-decalins (4c and 4t) have been screened for correlations with the stereochemistry of these molecules. From these data it appears that chemical ionization is especially suited for configurational assignments in epimeric molecules.

Correlations between the spatial arrangement in a molecule and its electron impact (EI) induced mass spectral behaviour have been established on many occasions. Although these data make a convincing case for the utilization of EI mass spectrometry in solving configurational problems, there are many instances in which differentiation of configurational isomers on the basis of EI spectra is difficult, if not impossible.

Studies on the chemical ionization (CI) behaviour of a,a'-dimethoxy-alkanes⁶, a,a'-dilols⁷, a,a'-diamines⁸ and a,a'-dicarboxylic acid esters⁹ have established that the proton transferred to these molecules upon methane or isobutane CI can be coordinated between the two terminal functions in the quasi-molecular ions. This effect of intramolecular coordination has been used¹⁰ for configurational assignment in cyclic systems as it requires a configuration in which the two polar functions can capture the proton between them in a linear hydrogen bridge. From these few studies it follows that chemical ionization mass spectrometry may have great potential for the determination of the relative configuration of polar substituents in cyclic systems. This is especially so as stereochemical differences have the best chances to manifest themselves at low ion internal energies: proton transfer chemical ionization¹³,¹⁴ using methane or isobutane as a reagent gas, is a relatively soft ionization technique producing ions with substantially lower average internal energy than under EI conditions. Moreover, some control of the energy input is possible through the selection of the reagent gas¹³,¹⁴ and through the adequate use of temperature effects¹⁴,¹⁵, thus providing the necessary flexibility to cope with a variety of problems. Methane and/or isobutane chemical ionization should therefore be a very useful stereochemistry probe.

It is the purpose of the present communication to report a few illustrative examples. In all cases presented here, both the helium charge exchange (CE)¹⁶ and the isobutane chemical ionization spectra have been recorded, thus allowing an appreciation of the relative merits of CI to be made.

4-Methoxy cyclohexanecarboxylic acid ethyl esters (1c, 1t)

In extension of earlier results on bifunctional cyclonexanes, the study of the epimeric 4-methoxy-cyclohexane carboxylic acid ethyl esters 1c and 1t is of particular interest. These compounds differ from the methoxy substituted esters investigated earlier (i) in that the substituents are in a 1,4-position (hence necessitating at least a six-membered ring), and (ii) in that the ethoxycarbonyl function...
is directly connected to the ring (without inter- 
mediate methylene unit). The CE(He) spectra of \( I_c \) 
and \( I_t \) (Fig. 1) are sufficiently different to permit 
unequivocal differentiation of both isomers. The 
spectral differences can be correlated with the 
respective structures. In this context the loss of 
methanol from the molecular ions (yielding a 
fragment at \( m/e = 154 \), see Fig. 1) is of particular 
interest. Based on the data\(^1\) for cyclohexyl methyl-
ether (showing 66% of 1,3- and 23% of 1,4-
elimination of methanol) and in the absence of 
activating groups\(^2\), it seems logical to assume that

![Fig. 1. CE and CI spectra of compounds \( I_c \) and \( I_t \).](image)

![Scheme 1.](image)
both 1,3- and 1,4-elimination of CH$_3$OH will occur in $\text{I}_c$ and $\text{I}_t$, with a preference for the 1,3-mechanism. Apart from loss of CH$_3$OH subsequent to ring opening, it is clear that 1,3-elimination from $\text{I}_t$ can only occur in the unfavourable diaxial conformation (see Scheme 1), whereas 1,4-elimination requires the energetically also less favoured boat conformation. The cis isomer $\text{I}_c$ however can only undergo 1,3-diaxial loss of CH$_3$OH from one of the two nearly equienergetic conformations of the molecular ions. In analogy to the results of Winkler and Robertson $^{22}$ it is assumed that 1,3-diaxial elimination occurs faster than conformational changes $^{23}$ subsequent to ionization. As a result the different degrees of fragmentation of $\text{I}_c$ and $\text{I}_t$ should reflect the preference of the original molecule for a conformation allowing a 1,3-diaxial mechanism. This is indeed so as such a conformation is only important for $\text{I}_c$, thereby causing enhanced loss of CH$_3$OH from this isomer (yielding largest $m/e = 154$ peak) and also producing a larger peak at $m/e = 109$ through subsequent loss of an ethoxy radical.

Confirmation of the above correlation is found in the loss of formaldehyde which occurs in cis molecular ions only. As $\text{I}_c$ is the only isomer where the two functions can approach each other close enough for interaction, some functional group interaction must be at hand. The reaction most probably occurs as depicted in Scheme 2: the mechanism bears resemblance to the well-known formaldehyde loss from cis-dimethoxy substituted cyclohexanes $^{22}$.

A somewhat similar reaction is responsible for the enhanced loss of ethanol ($m/e = 140$, see Fig. 1) from the trans isomer $\text{I}_t$ and is due to the presence of the activated hydrogen on C-4 (see Scheme 3) which can be abstracted by the ethoxy carbonyl function in a boat conformation.

In striking contrast to the CE(He) spectra, the isobutane CI spectra of $\text{I}_c$ and $\text{I}_t$ (Fig. 1) are very simple and exhibit blatant differences, allowing stereochemical inferences to be made even more easily than from the CE spectra. As expected protonation of the cis isomer results in a quasi molecular ion stabilized by proton bridging and undergoing only minor decomposition through loss of either CH$_3$OH or EtOH (see Scheme 4). In the trans isomer no stabilization of the quasi molecular ion occurs. Protonation can occur either on the OCH$_3$ or on the COOEt function $^{24}$ but the former case produces MH$^+$ ions which are much more prone to decomposition because of neighboring group participation $^{25}$: as a result loss of CH$_3$OH is greatly enhanced and is outcompeting loss of EtOH (see
Fig. 1). Note that the loss of C\textsubscript{2}H\textsubscript{4} subsequent to CH\textsubscript{3}OH expulsion yields a \( m/e = 127 \) fragment absent in the spectrum of the cis isomer.

**Substituted Tetrahydropyranes**

Catalytic hydrogenation\textsuperscript{26} of 2,6-dimethyl-4-pyrene (Scheme 5) yields a mixture of two epimeric tetrahydropyranes, \( 2_c \) and \( 2_t \), with very similar CE(He) spectra (Fig. 2). Loss of water (\( m/e = 112 \)) from the molecular ions of these compounds should predominantly occur by 1,3-diaxial elimination\textsuperscript{22a}, especially as the hydrogens on C-2 and C-6 are activated\textsuperscript{19} by the presence of the ring oxygen atom. In analogy to the results of Winkler and Robertson\textsuperscript{22a}, indicating 1,3-diaxial losses to be faster than conformational changes\textsuperscript{23} in the molecular ions, enhanced loss of H\textsubscript{2}O will be found for \( 2_t \) in which
1,3-diaxial elimination is possible in the most stable conformation. This is reflected in the $|m/e = 112|:|m/e = 115|$ ratios of 1.6 and 0.6 for $2_t$ and $2_c$, respectively.

An analysis of the above reaction mixture (Scheme 5) can far more reliably be performed by GC–MS coupling in the CI mode as the isobutane CI spectra (Fig. 2) differ considerably and in a manner that is readily correlated with their stereochemistry. Enhanced decomposition of the quasi molecular ions occurs for the all-cis isomer $2_c$: this is attributed to increased steric hindrance from the two methyl groups in the proton bridged (twist-boat conformation) quasi molecular ions (Scheme 6). Introduction of an additional 4-methyl group, as in $3_c$ and $3_t$ (see Fig. 3) results in enhanced decomposition for both isomers as is readily deduced from the data in Table I: compounds $3_t$ consistently show a reduced quasi molecular ion abundance relative to the corresponding $2_t$ isomer. This behaviour is the result of the 4-methyl group stabilizing the carbenium center produced upon loss of water (Scheme 7).

The occurrence of subsequent elimination of an acetaldehyde neutral ($m/e = 83$) cannot be compared as the corresponding $m/e = 69$ fragment from compounds $2_t$ was not recorded (interference of reagent gas peaks).

Table I. $|MH^+|-abundances from compounds $2$ and $3$.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$2_c$</th>
<th>$2_t$</th>
<th>$3_c$</th>
<th>$3_t$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$</td>
<td>MH^+</td>
<td>$</td>
<td>1.04</td>
<td>8.34</td>
</tr>
<tr>
<td>$</td>
<td>MH^+ - H_2O</td>
<td>$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Substituted cis-decalins

It has been reported that the three isomeric dimethylethers of cis-decalin-2,7-diols yield virtually identical EI spectra. The absence of steric control in these compounds has been rationalized by the observation that of the three possible isomers $4_a$, $4_b$, and $4_c$, there is only one ($4_a$) where the two functionalities can approach each other sufficiently for interaction to occur: unfortunately this is only achieved in a conformation (a) having one of the rings in a boat conformation (Scheme 8). Apparently the very short ion source residence times of the
molecular ions \((10^{-6} \text{ sec})\) keep the fraction of the molecular ions passing through conformation \textbf{a} very low and thus limit the probability for functional group interaction. As a result no measurable effect of such interaction is found in the EI spectrum of 4\textsubscript{a}.

From an analysis of models it was felt that isobutane chemical ionization mass spectrometry could resolve the spectral ambiguity found in EI spectra. As can be seen in Fig. 4 the spectra of the three isomers permit unequivocal differentiation in mixtures analyzed by GC–MS. Of the three isomers 4\textsubscript{a} is the only one yielding an abundant quasi molecular ion: obviously proton bridging does occur, the additional stabilization thus provided apparently being sufficient to overcome the strain incurred by the necessary boat conformation of one ring (Scheme 9). In the quasi molecular ions of 4\textsubscript{b} and 4\textsubscript{c} no such stabilization is possible as there is no way the two functionalities can capture a proton between them. As a result these quasi molecular ions are much more prone to undergo the loss of methanol also observed in monofunctional ethers\textsuperscript{30}, and have all undergone decomposition prior to mass analysis. Differentiation of 4\textsubscript{b} and 4\textsubscript{c} is however possible on the basis of the \(|m/e = 167|:|m/e = 135|\) ratio (0.71 and 0.22, respectively). This can be rationalized in terms of a SN\textsubscript{1}-type reaction\textsuperscript{25} leading to a stabilized \(m/e = 167\) ion in the case of 4\textsubscript{b} (Scheme 10), whereas no such intermediate is possible for 4\textsubscript{c}.

From the preceding examples it should be clear that isobutane chemical ionization is of great value for the assignment of configuration in epimeric
molecules and offers certain advantages over electron impact or charge exchange ionization. The most important are that (i) CI spectra are far less complex (see Figs. 1–4), (ii) generally exhibit more pronounced differences for epimers, and (iii) are more amenable to analysis as it concerns the behaviour of even electron ions (in contrast to the odd electron species obtained upon EI or CE). These should be sufficient arguments for an increased application of CI as a stereochemistry probe, especially as CI also offers some advantages with respect to GC–MS coupling.13,31

Experimental

All mixtures of epimers were analyzed by GC–MS coupling on a Finnigan 3200 quadrupole mass spectrometer equipped with an all-glass chromatographic inlet system and a Finnigan 6000 data system. Wide bore capillary columns (0.5 mm ID, 100 m), statically coated with SE-30 have been used in all cases. All other normal operating conditions have been reported elsewhere.10d

Compounds 1 were obtained through Raney-Ni catalyzed hydrogenation of ethyl 4-methoxybenzoate.32 An analogous reduction36a,b of 2,6-dimethyl-4-pyrene results in a mixture of 2e and 2i. Their 4-methylated homologs 3c and 3i, are obtained by a Grignard reaction of methylmagnesiumbromide on 2,6-dimethyl-tetrahydropyran-4-one.26 The 2,7-dimethoxy-cis-decalanes are prepared via sodiumborohydride reduction of cis-decalane-2,7-dione.94 All isomers have been separated and were independently identified using spectroscopic methods (UV, IR and 1H NMR).

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Scheme 10.

2 Aangesteld Navorser of the Belgian “National Fonds voor Wetenschappelijk Onderzoek” (NFVO).
3 Bursary of the “Instituut tot aanmoediging van het Wetenschappelijk Onderzoek in Nijverheid en Landbouw” (IWONL).
4 Aspirant of the NFVO.
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   b R. Yamaguchi and P. Kelarle, ibid. 95, 3504 [1973].
10 a P. Longevialle, G. W. A. Milne, and H. M. Fales, J. Amer. Chem. Soc. 92, 1597 [1970];
   b J. Winkler and F. W. McLafferty, Tetrahedron 30, 2971 [1974];
   d F. Van Gaever, J. Monstrey, and C. C. Van de Sande, ibid., accepted for publication.
15 a M. S. B. Munson and F. H. Field, J. Amer. Chem. Soc. 88, 4337 [1966];
   b D. P. Weeks and F. H. Field, ibid. 92, 1600 [1970];
   c I. Dzidic, ibid. 94, 3333 [1972];
   d M. Meot-Ner and F. H. Field, ibid. 95, 7207 [1973].
16 These are obtained using helium as a reagent gas in CI conditions: a plasma of He+ ions results in which molecules are ionized by charge exchange.13 Odd electron molecular ions are produced (as in EI), the
fragments of which follow the general rules established in EI. The major incentives for the use of CE(He) as a substitute for EI are (i) that it allows both CI and CE (= EI) measurements to be carried out in the same CI source, and (ii) that the CE(He) spectra are virtually identical to EI spectra in all cases so far examined by us. This observation is in apparent disagreement to earlier recommendations\(^{13}\) for the use of nitrogen or argon in CE measurements and implies that the rather high initial energy imparted to a molecule upon CE(He) is partially dissipated (collisional deactivation) prior to mass analysis.

The subscripts c and t refer to the relative configuration of the two substituents on the ring.


\(^{19}\) These are groups which reduce the C-H bond dissociation energy when attached to the carbon atom. Methoxy substituents for instance have this effect as the dissociation energy for a C-H bond in a carbinol is approximately 20 kcal \(\cdot\) mole\(^{-1}\) less than the normal C-H bond dissociation energy\(^{20}\). Aryl substituents have a similar effect\(^{21}\). The presence of such groups in 3- or 4-position with respect to a RO substituent on specific sites has been found to be a valid formalism for the understanding of CI induced fragmentation of polyfunctional compounds.

\(^{25}\) A few selected examples in CI-MS:

- a T. A. WHITNEY, L. P. KLEMM, and F. H. FIELD, Anal. Chem. 43, 1048 [1971];
- b G. W. A. MILNE, T. AXENROD, and H. M. FALES, J. Amer. Chem. Soc. 92, 5170 [1970];


b R. SCHROOTEN, B. S.-thesis, State University of Gent, Gent, Belgium 1976;


\(^{27}\) Loss of a methyl radical by cleavage a to the ring oxygen atom should be independent from the stereochemistry and therefore serves as an internal standard \((m/e = 115)\).

\(^{28}\) As contrasted to cis-decalin-1,4-diol\(^{29a}\) and cis-decalin-1,5-diol\(^{29b}\) dimethyl ethers. Similarly CE(He) spectra (not shown) of 4\(_a\), 4\(_b\), and 4\(_c\) are also virtually identical.


b H.-F. GRÜTZMACHER and K.-H. FECHNER, ibid. 9, 152 [1974].

\(^{30}\) Own unpublished observations on a variety of ethers. See also:


\(^{33}\) F. ARNDT, B. EISTERT, H. SCHOLZ, and E. ARON, Chem. Ber. 69, 2373 [1936].