Ion-neutral complexes formation and 1,3-proton transfer in the chemical ionization of alkylcyclohexyl benzoates

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CI, CID, labelling experiments and DFT calculations are used for the elucidation of the mechanism for the decomposition of cyclohexyl benzoates, which proceeds through 1,3-H shift and two equilibrating ion-neutral complexes.

Benzoic acid derivatives have been studied extensively in solution. These studies form some of the fundamentals of physical organic chemistry.[1] Reactive intermediates (*e.g.* cations) in solution chemistry are stabilized by the solvent. The analogous 'self stabilization' of isolated fragmenting ions, in the gas phase, is achieved by the formation of ion-neutral complexes.

We studied the decomposition of protonated alkyl benzoates under chemical ionization conditions. Protonated alkyl benzoates dissociate to afford protonated benzoic acid and the respective cyclohexyl (or its isomeric) product ions (Scheme 1). The formation of an alkyl cation from protonated alkyl benzoate may occur through a simple bond cleavage. However, the formation of protonated benzoic acid must involve hydrogen migration from the alkyl moiety that is likely to occur *via* a stepwise mechanism. Audier and coworkers studied the fragmentation pathways of various alkyl benzoates,[2] and proposed the formation of an ion-neutral complex (INC) during the fragmentation process. We present here a detailed mechanistic study of the fragmentation of protonated alkyl benzoates using chemical ionization (CI),[3] collision induced dissociation (CID), deuterium labeling and theoretical calculations.[4]
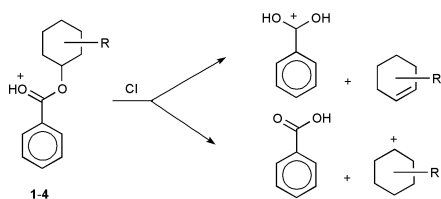
Scheme 1 Principle products of protonated cyclohexyl benzoates under CI conditions. **1**; R-4-*t*-Bu. **2**: R = 2-Me. **3**: R = 3-Me. **4**: R = 4-Me.

A few possible decomposition pathways of **5** (which serves as a model for the experimentally studied compounds)[5] were theoretically investigated (Scheme 2). No transition state was found on the potential energy surface that leads to direct dissociation of **5** to 2-propyl cation and propenoic acid (ΔE =
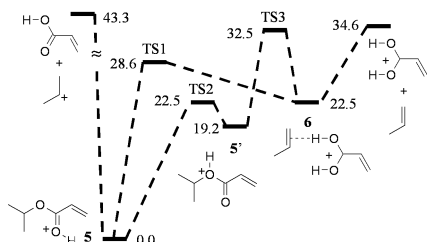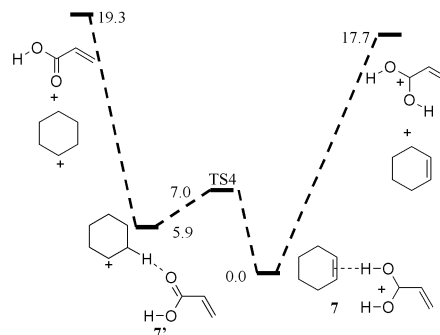
43.3 kcal mol^{-1}).[6] Two 1,3-H shifts have also been considered. One is a shift of a terminal hydrogen atom of the *i*-Pr group to the alkoxylic oxygen, in tandem with breaking the O–C bond. This leads to the formation of an ion-neutral complex between propene and protonated propenoic acid (**6**), which is 22.5 kcal mol^{-1} less stable than **5**. The barrier for this process (TS1) is 28.6 kcal mol^{-1}. Alternatively, a 1,3-proton shift from the carbonyl oxygen to the alkoxy oxygen was considered. Surprisingly, the activation energy for this process (TS2) is only 22.5 kcal mol^{-1}, and **5′** is less stable than **5** by 19.2 kcal mol^{-1} (Scheme 2). It is known that the barrier for 1,3-hydrogen shifts in molecular radical cations is relatively high, and the process is not likely to occur.[7] This argument has been used in order to explain the fragmentation behavior of protonated diesters.[8] However, it has also been shown that the barrier for 1,3-hydrogen transfer can be lower in the case of closed shell MH$^+$ ions.[9] The alkoxy-protonated ester **5′** can then rearrange to the INC **6** through a transition state (TS3) that is 13.3 kcal mol^{-1} above **5′**.

The calculations above (Scheme 2) show that protonated propenoic acid and propene are more stable than propenoic acid and isopropyl cation by 8.7 kcal mol^{-1}. However, the *i*-Bu-CI mass spectra of *cis* and *trans* **1** (not shown) indicate a C$_{10}$H$_{19}^+$/ C$_7$H$_7$O$_2^+$ ion ratio of roughly 1.[10] The proton affinity of 4-*t*-Bu-cyclohexene is significantly higher than that of propene[11,12] and we therefore replaced the *i*-Pr moiety by a cyclohexyl group, as a better model for the experimental system.[12] Scheme 3 illustrates the possible reaction pathways of the INC **7**. It may either dissociate to cyclohexene and protonated propenoic acid (ΔE = 17.7 kcal mol^{-1}), or rearrange, *via* a 7.0 kcal mol^{-1} transition state (TS4), to the 5.9 kcal mol^{-1} less stable INC **7′**, that can further decompose to the cyclohexyl cation and propenoic acid (ΔE = 19.3 kcal mol^{-1}).

Equilibrium between **7** and **7′** may occur if the time scale of the experimental conditions allow it. Thus, exchange between the external proton and the cyclohexyl hydrogen atoms can take place. Furthermore, those rearrangements could result in the formation of a more stable cyclohexyl cation in substituted cyclohexyl residues (*e.g.* **1–4**).

The CD$_3$CN-CI spectrum of **1** (not shown) reveals the formation of an ion at *m/z* 139 (relative abundance 14.0),

Scheme 2 Schematic representation of the theoretically calculated decomposition pathway of **5**. Numbers are energies (kcal mol^{-1}) relative to **5**.

Scheme 3 Schematic representation of the theoretically calculated decomposition pathway of **7**. Numbers are energies (kcal mol^{-1}) relative to **7**.

Table 1 Collision energy during CID of MD$^+$ ions of **1** and the corresponding relative abundances of the ions at m/z 139 and 140 that are *t*-Bu-cyclohexyl cations with and without deuterium

Collision energy (eV)^a	RA (m/z 140 : m/z 139)
^{b}	5.88
5	0.78
20	0.20
30	0.14

^{a} Ar was used as collision gas. ^{b} Without collision gas.

corresponding to 4-*t*-Bu-cyclohexyl cation, followed by an ion at m/z 140 (relative abundance 9.5). This points to the insertion of an external deuteron into the cyclohexyl moiety during the formation of this product ion. Evidently, the formation of a cyclohexyl cation from protonated **1** involves H/D exchange. This is in accordance with the proposed mechanism (Scheme 3) that involves the interconversion between two INC intermediates with the involvement of the hydrogen atoms at the cyclohexyl ring.

CID spectra of CD$_3$CN-CI produced MD$^+$ ions of **1** were recorded at different collision energies. The results (Table 1) show that the extent of H/D exchange depends on the energetic conditions, suggesting that as the lifetimes of the INCs become shorter the less deuterium incorporation is found.

CID spectra were also recorded for CH$_3$CN-CI produced MH$^+$ ions of the deuterium labeled 2,2,6,6-d$_4$-4-*t*-Bu-cyclohexyl benzoate at different energies. These spectra also show the dependence of the H/D exchange on the collision energy. The extent of hydrogen incorporation, however, is low, probably due to a kinetic isotope effect. The CID spectrum of CD$_3$CN-CI produced MD$^+$ ions of 2,2,6,6-d$_4$-4-*t*-Bu-cyclohexyl benzoate exhibits the formation of an ion at m/z 144, corresponding to C$_{10}$H$_{14}$D$_5$$^+$ *t*-Bu-cyclohexyl cation ([m/z 143]/[m/z 144] ion ratio = 2.9). This shows the involvement of other hydrogen atoms other than those at positions 2 and 6 of the cyclohexyl ring in the H/D exchange process.

In substituted cyclohexyl benzoates, an equilibrium analogous to **7** ⇌ **7′** may enable the formation of a more stable cation, and the closer the substituent is to the cyclohexyl–O bond, the faster a tertiary cation is obtained. A support for the existance of this process is obtained from the comparison between the product ions of 2-, 3- and 4-methylcyclohexyl benzoates. Hence, the ratio between C$_7$H$_{13}$$^+$ and protonated benzoic acid is 0.61, 0.055 and 0.018 for **2**, **3** and **4**, respectively, under the same conditions. Deuterium incorporation into the cyclohexyl moiety is also dependent on the substituent position. Thus, the C$_7$H$_{12}$D$^+$/C$_7$H$_{13}$$^+$ ion ratios in the CID spectra of MD$^+$ ions of **2**, **3** and **4** are 0.84, 0.56 and 0.35 respectively.

In conclusion, it is suggested the gas phase decomposition of protonated cyclohexyl benzoates proceeds *via* 1,3-shifts of hydrogen or proton to yield an INC, which is in equilibrium with an isomeric INC. Each of these complexes decomposes to different product ions. The experimental results are in agreement with the theoretically derived suggested mechanism. Finally, we also found that protonated *para*-substituted 4-*t*-butyl-cyclohexyl benzoates give rise to both [MH-C$_n$H$_{2n-1}$]$^+$ and [MH-ArCO$_2$H]$^+$ product ions and that the ion ratio depends on the substituent. The effect of electron withdrawing and donating substituent on this process is presently under investigation.

Notes and references

1 See, for example, T. H. Lowry and T. H. Richardson, *Mechanism and Theory in Organic Chemistry*, 2nd edn., Harper & Row, New York, N.Y., 1981.
2 E. Audier, A. Milliet, C. Perret, J.-C. Tabet, P. Varenne and A. Horeau, *C. R. Acad. Sci. Paris*, 1979, **288**, 33; E. Audier and A. Milliet, *Bull. Soc. Chim. Fr.*, 1980, **11**, 571.
3 The gas chromatographic-chemical ionization mass spectrometric analysis (CI-GC-MS) and CID measurements were carried out on a Finnigan TSQ-70B triple-stage quadrupole mass spectrometer. The stereoisomeric pairs were introduced as mixtures and separated on the capillary column DB-5 (0.25 μm film thickness, 30 m × 0.25 mm i.d.). The temperature was programmed from 100 to 280 °C at 20 °C min^{-1}. The scan rate was 2 scan s^{-1}. CI measurements were performed at 150 °C ion source temperature, 0.6 Torr (indicated) reagent gas pressure (isobutane) and 0.03 Torr (indicated) reagent gas pressure (CH$_3$CN). CID measurements were performed with argon as the target gas (0.3 mTorr, indicated) at 5–30 eV collision energies (indicated). All the data presented in each figure were obtained on the same day under identical conditions, in order to ensure reliable comparisons. Materials: Cyclohexyl benzoates (**1**–**4**) were prepared from the corresponding cyclohexanols and benzoyl chloride derivatives.
4 Gaussian 98 was used. All the geometries were fully optimized at the B3LYP/6-31G* theoretical level. Stationary points and transition states were characterized by analytical frequency calculations (*i.e.* Nimag = 0 and 1, respectively). ΔE reported here is ΔE_{elect}. Gaussian 98, Revision A.7, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1998.
5 This model was chosen for this purpose as the important features that may affect the process, namely, a secondary carbon at the alkyl and a π system at the acid are present.
6 It is not possible to estimate the experimental temperature in order to assess thermodynamic parameters. ZPE corrections, alone, could be misleading and are therefore left out.
7 M. A. Trikoupis, J. K. Terlouw and P. C. Burgers, *J. Am Chem. Soc.*, 1998, **120**, 12131; M. Sena and J. M. Riveros, *Chem. Eur. J.*, 2000, **6**, 785; D. H. Williams, *Acc. Chem. Res.*, 1977, **10**, 280; P. C. Burgers and J. L. Holmes, *Org. Mass Spectrom.*, 1982, **17**, 123.
8 A. Idina, A. Etinger and A. Mandelbaum, *J. Am. Chem. Soc.*, 1993, **115**, 7397.
9 H. E. Audier and T. B. McMahon, *J. Mass Spectrom.*, 1997, **32**, 201.
10 The CI mass spectra of all *cis* and *trans* isomers that were studied in this work showed minor differences and we therefore refer to them as a mixture. See also C. Denekamp and A. Stanger, *J. Mass Spectrom.*, accepted for publication.
11 Although both 2-propyl cation and cyclohexyl cation are secondary carbenium ions, our calculations show that the latter is stabilized by hyperconjugation to both 2,3-C–C bonds, an interaction that does not exist in 2-propyl cation. See also A. Rauk, T. S. Sorensen, C. Maerker, J. W. de Carneiro, S. Sieber and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1996, **118**, 3761. The proton affinity of any of the isomers of *t*-Bu-cyclohexene is unknown, but it is crtainly at least as large as that of cyclohexene.
12 The experimental proton affinity of cyclohexene is 7.9 kcal mole^{-1} higher than that of propene (NIST Standard Reference Database No. 69, February 2000 Release. http://webbook.nist.gov/chemistry). At the B3LYP/6-31G* level of theory the cyclohexyl cation is found to be 7.2 kcal mol^{-1} more stable than the 2-propyl cation (relative to the respective alkenes).