Reactions of Cyclohexane Derivatives in Superacids

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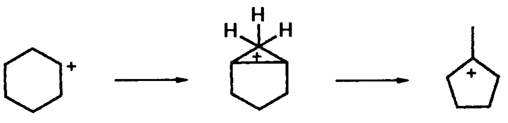
The reactions of menthol with FSO_3H–SO_2 and neomenthyl chloride with SbF_5–SO_2ClF follow different routes. The first yields a substituted cyclopentyl cation and the second a substituted cyclohexyl cation. Experiments on substituted cyclohexyl chlorides show that replacement of all the hydrogen atoms on the next but one carbon atom to the reaction centre blocks formation of a carbocation. It is suggested that ionisation of an equatorial chlorine atom takes place with assistance from an intramolecular electronic interaction, forming the methyl cyclopentyl carbocation in a synchronous process, rather than stepwise *via* the cyclohexyl carbocation. Reasons for contrasting behaviour in solvolytic reactions are discussed.

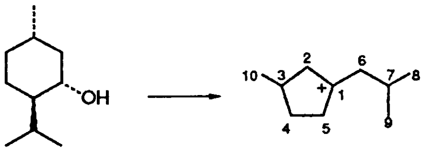
Attempts to generate the secondary cyclohexyl carbocation **1** in superacidic media at temperatures down to −110 °C have all failed.[1,2] In all cases, the ion obtained was the tertiary methyl cyclopentyl carbocation **2**, formation of which is believed to occur[3] *via* a protonated cyclopropane intermediate **3**. The work of Arnett and Petro[2] on the measurement of heats of formation of carbocations in superacidic media showed that the heat of formation of the ion **2** from cyclohexyl chloride in superacidic media was 22.5 ± 0.6 kcal mol^{-1}. However, the free energy of activation for the solvolysis of cyclohexyl chloride to **1** is 16.1 kcal mol^{-1}, and in most examples studied this figure is close to the heat of formation of the carbocation in the corresponding reaction in superacid.[4] This leaves only 6.4 kcal mol^{-1} available for the isomerisation of **1** to **2** in superacid, which is exceptionally low, compared to the normal figure[5] of *ca.* 16 kcal mol^{-1} for secondary to tertiary ion transitions. It has been suggested[2] that this low figure may result from strain in the methyl cyclopentyl cation. However, an investigation[6] of the methyl cyclohexyl cation suggested that this ion existed as a equilibrium of two distorted chairs, with no signs of a particularly strained system. Such evidence as is available[6] on the methyl cyclopentyl ion suggests that it is similar in energy to the methyl cyclohexyl ion.



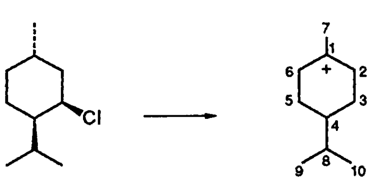
1 **3** **2**

Results and Discussion

In the course of our investigations of the rearrangements of terpenoids in superacidic media,[7] we dissolved menthol (**4**) in FSO_3H–SO_2 at −78 °C. No reaction occurred. On warming to −40 °C reaction took place to give the 1-(2-methylpropyl)-3-methylcyclopentenium ion (**5**), which was identified by ^{13}C NMR spectroscopy. The ion is similar to that reported earlier[8] from reaction of menthol with concentrated sulphuric acid. We then reacted neomenthyl chloride (**6**) with SbF_5–SO_2ClF at −78 °C and obtained the 1-menthyl cation **7**. Clearly, **5** and **7** do not both arise from the same substituted secondary cyclohexyl carbocation. It could be argued that they arose from ions which differed only in the position of the counter ion, but we know of no other examples of this behaviour in superacids. A more likely explanation is that the formation of either **5** from **4** or **7** from **6**, or possibly both, takes place by direct displacement of the leaving group by bonding electrons from within the molecule, so that the secondary carbocation is not formed. This would probably occur by a 1,3-shift involving a cyclopropyl ring. We therefore investigated the possibility that the formation of such an intermediate during the reaction of the cyclohexyl system occurs synchronously with the departure of the leaving group, and that the ion **1** is not involved in the formation of **2** from such a system. We tried to block the shift by substituting the hydrogens on the carbon atoms next but one to the reaction centre.

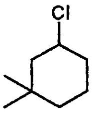


4 **5**



6 **7**

First of all, we treated 3,3-dimethylcyclohexyl chloride (**8**) with SbF_5–SO_2ClF at −78 °C, and obtained the 1,3,3-trimethylcyclopentenium ion (**9**) as the sole ion. We then added 3,3,5,5-tetramethylcyclohexyl chloride (**10**) to SbF_5–SO_2ClF at −120 °C. The spectrum of the solution at −80 °C was mainly polymeric, with a small amount of an alkene. We then tried treating the corresponding alcohol, 3,3,5,5-tetramethylcyclohexanol, with FSO_3H–SbF_5–SO_2ClF (magic acid), but obtained only the spectrum of the protonated alcohol. The spectrum was unchanged over the temperature range up to −20 °C. In similar conditions, Olah[1] found cyclohexanol to react rapidly at −60 °C.



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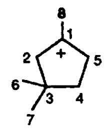

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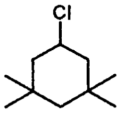

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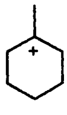

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The cyclohexyl chlorides **8** and **10** are both conformationally mobile so that the chlorine atom will be equatorial. The first reacts readily to yield the corresponding trimethyl cyclopentyl

Table 1 ^{13}C NMR chemical shifts (ppm from Me_4Si) of carbocations

Ion	Solvent	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
5	SO_2	339	47	37	33	45	39	36	21	21	22
7	SO_2ClF	320	44	34	42	34	44	26	36	23	23
9	SO_2ClF	327	66	44	29	59	32	32	22	—	—
11	SO_2ClF	338	57	25	22	25	57	43	—	—	—

carbocation but the second does not react. We suggest that the replacement of all four hydrogens on the next but one carbon atom to the reaction centre is significant in stopping the reaction, favouring the idea that formation of the methyl cyclohexyl cation from cyclohexyl chloride is a synchronous reaction.

Our evidence does not apply to removal of an axial chloride from the cyclohexane ring. Experiments with isomeric methyl cyclohexyl chlorides in which axial or equatorial chlorine atoms could interconvert rapidly all yielded the methyl cyclohexyl carbocation **11**, but interpretation of these data is uncertain, since reaction could take place *via* either the axial or equatorial isomers. A sample of 3,3,5-trimethylcyclohexyl chloride, again a mobile system in which the chlorine could be axial or equatorial, reacted in SbF_5–SO_2ClF at −78 °C to give a mixture of three ions which we were unable to identify. The evidence of isomenthol does, however, suggest a different mechanism for reaction of an axial chlorine, and we cannot exclude the possibility that reaction may occur through the cation **1**. Indeed, our only evidence slightly favours this, since the C-4 hydrogen atom of isomenthol is ideally placed to assist ionisation, but does not do so, as the charge ends up on C-1 rather than C-4.

This type of rearrangement is not important in the solvolysis of cyclohexyl esters in solvents such as aqueous ethanol.[9] A clue to a possible reason for this difference comes from the work on nucleophilic assistance to unimolecular solvolyses,[10] which has shown that most unimolecular solvolyses obtain some assistance from the approach of solvent from the rear. This is only absent in cases such as adamantyl esters, where approach to the rear of the carbon carrying the ester group is sterically difficult. We suggest that in our systems only SbF_5 could similarly assist ionisation, and it is much too large. In the absence of any nucleophilic assistance, an internal bond shift assists departure of the leaving group.

Experimental

Analyses.—^1H NMR spectra were recorded on a Perkin-Elmer R34 (220 MHz) spectrometer using $CDCl_3$ as solvent and tetramethylsilane (Me_4Si) as internal standard. ^{13}C NMR spectra were recorded on a Varian XL 100 (25.2 MHz) spectrometer with $CDCl_3$ as solvent and Me_4Si as internal standard for neutral solutions, and sulphur dioxide or sulphuryl chloride fluoride as solvent for superacidic solutions with an external deuterium lock of [$^2H_6$]acetone or [$^2H_4$]methanol and external standard of Me_4Si enclosed within a 5 mm NMR tube. ^{13}C NMR data is presented in Table 1.

IR spectra were recorded on a Perkin-Elmer 157 G spectrophotometer as liquid film or Nujol mull. Mass spectra were recorded on an A.E.I. MS 12 spectrometer.

Gas chromatographic analyses were carried out on a Perkin-Elmer F21 instrument using nitrogen as the carrier gas and a flame ionisation detector. A 1.5 m long stainless steel column of 2 mm internal diameter, packed with 60–80 mesh Celite coated with 10% Reoplex 100, was used analytically.

Neomenthyl Chloride (3-*Chloro*-4-*isopropyl*-1-*methyl-cyclohexane*) (**6**).—Triphenylphosphine (20 g) in tetrahydrofuran (THF) (50 cm^3) was added to *N*-chlorosuccinimide (13 g) in THF (200 cm^3) cooled in a salt–ice bath. Menthol (12.5 g), obtained from Aldrich, was slowly added to the cooled slurry, then stirred for 4 h. The solvent was then removed under reduced pressure and the products extracted with pentane. Removal of pentane followed by distillation of the resulting oil gave neomenthyl chloride (11 g, 78%); b.p. 54 °C at 0.3 Torr;* (lit.,[11] 101–101.5 °C at 21 Torr); M^+, 176 and 174.

3,3-*Dimethylcyclohexanol.*—Methyl magnesium iodide, generated from 17 g methyl iodide, was cooled to 0 °C and copper(I) iodide (2 g) was added. 3-Methylcyclohex-2-enone (10 g) was then added to the cooled slurry at such a rate that the temperature did not rise above 5 °C. The mixture was stirred for 1 h, then quenched with saturated aqueous ammonium chloride (25 cm^3). Extraction of the aqueous layer with diethyl ether, followed by removal of the solvent gave a yellow oil which was distilled at 54–56 °C at 20 Torr (lit.,[12] 74–76 °C at 8 Torr) to give 3,3-dimethylcyclohexanone (2.7 g, 24%). Reduction of the ketone with lithium aluminium hydride in diethyl ether gave 3,3-dimethylcyclohexanol (2.5 g); *m/z* 128, 110; δ 0.87, 0.92 (both 3 H, s), 1.05 (3 H, m), 1.3 (1 H, m), 1.43 (1 H, m), 1.55 (3 H, m), 1.95 (1 H, m) and 3.73 (1 H, m, C*H*OH); ν_{max}/cm^{-1} 3300, 2910, 1450, 1050, 1060 and 1020.

3,3,5,5-*Tetramethylcyclohexanol.*—The method of Chiurdoglu[13] was used. Isophorone (3,5,5-trimethylcyclohex-2-enone, 20.6 g) was converted into 3,3,5,5-tetramethylcyclohexanone by reaction with methyl magnesium iodide from 30 g methyl iodide, using the above method. The reaction yielded an oil which was distilled at 99–92 °C at 20 Torr; (lit.,[14] 59–61 °C at 5 Torr). Reduction of the ketone with lithium aluminium hydride gave 3,3,5,5-tetramethylcyclohexanol; M^+, 156; δ 1.2 (6 H, s, CH_3 eq.), 1.29 (6 H, s, CH_3 ax.), 1.45–1.65 (3 H, 3 sep. m., H eq.), 2.03 (3 H, br m, H ax.) and 4.22 (1 H, m, C*H*OH); ν_{max}/cm^{-1} 3330, 2900 and 1020.

Cyclohexyl Chlorides.—Cyclohexanols were converted into cyclohexyl chlorides by placing 0.03 mol of the parent alcohol in a 10 cm^3 flask and cooling in ice. Zinc chloride (7 g) and concentrated hydrochloric acid (5 cm^3) were added, and the mixture was warmed to 50 °C with stirring. Aliquots were checked by thin layer chromatography until reaction was complete, when the mixture was quenched and extracted with pentane. Removal of the solvent, followed by distillation, yielded the appropriate chloride.

Generation of Carbocations with FSO_3H.—Sulphur dioxide (1 cm^3) was condensed in a 10 cm^3 round-bottomed flask and FSO_3H (2.5 cm^3) was added. The solution was cooled to −78 °C using a solid CO_2–acetone bath. The substrate (250–500 mg) was dissolved in sulphur dioxide (1 cm^3) and cooled to −78 °C then added dropwise, down the inside of the cooled reaction vessel, to the stirred FSO_3H–SO_2 solution. The reaction mixture was stirred for 10 min and added to a 12 mm bore NMR tube also cooled in a CO_2–acetone bath. The NMR

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* 1 Torr ≈ 133 Pa.

tube was removed from the cooling mixture, quickly cleaned of any residual acetone and placed within the spectrometer. The probe had been previously cooled in a stream of nitrogen passed through a heat-exchanger immersed in liquid nitrogen. The temperatures of the probe and sample were then regulated using a heating coil in the nitrogen stream.

Generation of Carbocations using SbF_5.—Antimony pentafluoride (1 cm^3) was condensed in a 10 cm^3 round-bottomed flask cooled to −78 °C, following evaporation under reduced pressure from a connected vessel. Sulphuryl chloride fluoride (2 cm^3) was then added to the condensed solid and the mixture warmed until dissolution. The solution was then cooled again to −78 °C and the cooled substrate solution (250–500 mg) in 2 cm^3 SO_2 was added dropwise down the side of the reaction vessel. The reaction mixture was then treated as for the FSO_3H reaction mixture.

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