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Favorsky Rearrangements

XIV.* Competitive Rearrangement and Deuteration of Polyhalo Ketones

CHRISTOFFER RAPPE and LEIF KNUTSSON

Institute of Chemistry, University of Uppsala, Box 531, S-751 21 Uppsala 1, Sweden

The sodium carbonate induced rearrangement of 1,3-dibromo-2-butanone, 1,1,3-tribromoacetone, 1,1,3,3-tetrabromoacetone, and 1,1,3,3-tetrachloroacetone was studied in deuterium oxide. In all cases the product was deuterated, indicating a pre-equilibrium in the reaction. An increasing number of halogen atoms resulted in increased deuterium-incorporation in the product. No pronounced difference was found in the deuterium content between the products from tetrachloro and tetrabromo ketone.

In 1951 Loftfield proposed that the Favorsky rearrangement of α-halo ketones proceeds by a symmetric mechanism *via* a cyclopropanone, and that the rate determining step was the removal of the α′-proton.[1] If the halo ketone contains no α′-protons, the reaction proceeds *via* an unsymmetric semibenzilic-acid mechanism.[2] Recently it could be established by the present authors by NMR-measurements on the product from the rearrangement of bromocyclobutanone in deuterium oxide, that although this ketone holds α′-protons, it rearranges *via* an unsymmetric mechanism,[3] which was previously suggested by Conia and Salaün.[4]

By mass spectrometry and by NMR it has now been possible to study Loftfields initial postulate, *i.e.* proton removal is the rate determining step in the Favorsky rearrangement. Investigations by House and Thompson,[5] Olsen,[6] and Deghenghi *et al.*[7] concerning halogenated decalone and steroids supported Loftfield's postulate; no or very little hydrogen exchange was found in these experiments.

On the other hand Charpentier-Morize *et al.*[8] and Ginsburg [9] postulated a rapid pre-equilibrium from analyses of recovered haloketone. The present authors' investigation of bromocyclobutanone cited above [3] seems to be the first example where rearranged product (as well as starting ketone) was shown to be deuterated during a Favorsky rearrangement. From this investigation it is also clear that there is a pre-equilibrium in the α- as well as in the α′-position. Later, Bordwell *et al.*[10] obtained similar results from the rearrange-

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ment of diverse halocyclohexanones. In these reactions the rearrangement proceeds *via* a cyclopropanone. Bordwell *et al.* also found that the hydrogen exchange is more pronounced in the rearrangement of chloro ketones than in the rearrangement of the bromo isomers. This is in harmony with the known higher efficiency of bromide as a leaving group compared with chloride.[10]

Previously it has been found that the Favorsky rearrangement of 1,3-dibromo-2-butanone using aqueous solutions of bicarbonates or carbonates yields isocrotonic acid in good yield.[11] 1,1,3-Tribromoacetone yields *cis*-3-bromoacrylic acid,[12] 1,1,3,3-tetrabromoacetone yields 3,3-dibromoacrylic acid,[13] and 1,1,3,3-tetrachloroacetone yields 3,3-dichloroacrylic acid [14] under these conditions. In the present investigation we have studied these reactions in deuterium oxide using sodium carbonate. The isolated products were purified in the usual way, distillation, repeated recrystallizations, or thin layer chromatography,[11-14] prior to analyses by mass spectroscopy. In some cases the product was also analyzed by NMR. The results are collected in Table 1.

In the mass spectral analyses we have used the parent peaks and the peaks at M−17, to avoid errors due to the ease of deuterium exchange from the COOD-group. As NMR analyses are carried out under milder conditions, this method is perhaps more reliable than mass spectral analysis. However, in the case of halogenated acrylic acids the NMR-method cannot give any absolute values for the amount of deuteration due to the absence of reference peaks. In the case of *cis*-3-bromoacrylic acid the relative abundance of protium (or deuterium) at the α- and β-carbon could be estimated by NMR.

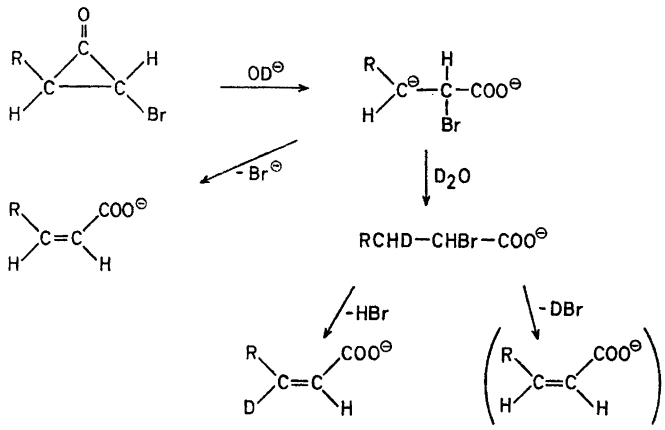
From Table 1 it can be seen that an increasing number of halogen atoms in the starting ketone increases the degree of deuteration. Since an increasing number of halogen atoms increases the acidity of the protons,[15] this observation is in harmony with the general considerations of a pre-equilibrium.

The observation of 20−70 % of d_0-acid in the products and the assumption of an ordinary isotope effect ($k_H/k_D=6-7$) exclude the possibility that saturated acids are intermediates in the formation of the unsaturated acids, see Scheme 1. As a result of the direct way for the formation of the unsaturated acids, it follows that these acids are deuterated to a lower extent than the reacting halo ketone; *e.g.* a d_3-ketone yields a d_2-acid. This is opposite to rearrangements in which saturated acids are formed where one deuterium is incorporated in the fission of the cyclopropanone.

Table 1. Results from the mass spectra and NMR-analyses.

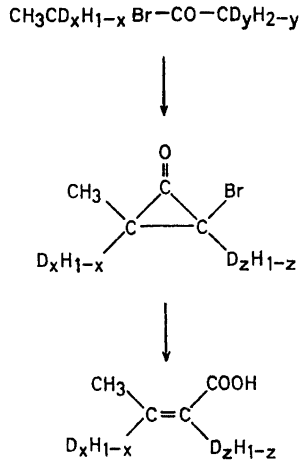
Acid	Mass spectral analyses M				M−17			NMR-analyses α-D	β-D	α-H/
	d_0 %	d_1 %	d_2 %	d_3 %	d_0 %	d_1 %	d_2 %	equiv.	equiv.	β-H
Isocrotonic	68	28	4	0.3	[a]	[a]	[a]	0.18	0.06	—
cis-3-Bromoacrylic	35	38	22	5	48	39	13	—	—	0.86
3,3-Dibromoacrylic	17	82	1	—	17	83	—	—	—	—
3,3-Dichloroacrylic	35	65	—	—	35	65	—	—	—	—

[a] Determinations are not possible due to other peaks.



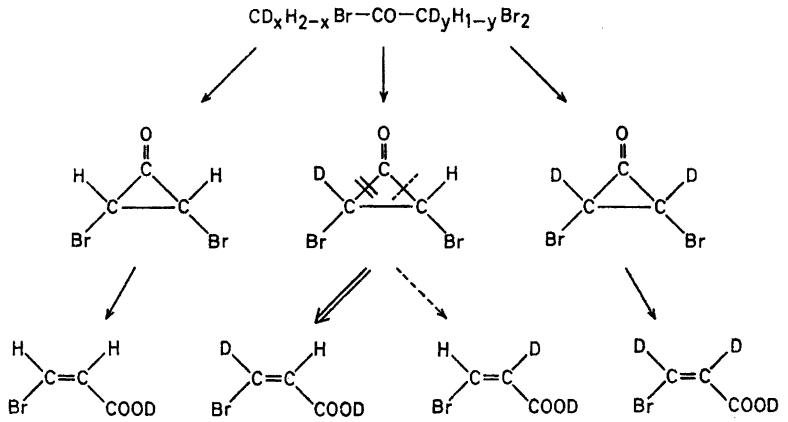
Scheme 1

The NMR-analyses of the isolated isocrotonic acids reveal that the α-carbon incorporates about three times as much deuterium as the β-carbon, $z/x=3$, see Scheme 2. Since some deuterium is lost in the proton removal in an 1-deuterated ketone, $y>z$, see Scheme 2, it follows that 1-deuteration is favoured over 3-deuteration by more than a factor of three in the starting dihalo ketone, $y/x>3$. Here it should be pointed out that very little is known about rates and rate ratios for the proton removal of halo ketones; the first step in the Favorsky rearrangement. An investigation of this topic is being planned.



Scheme 2

The situation for the rearrangement of deuterated 1,1,3-tribromoacetone to deuterated *cis*-3-bromoacrylic acid is given in Scheme 3. Partly deuterated halo ketone can give d_0-, d_1-, and d_2-dibromocyclopropanones, whose fission



Scheme 3

results in d_0-, d_1-, d_2, and d_3-3-bromoacrylic acid. Neglecting a secondary isotope effect, one would predict equal probability for fission at the C—H and C—D carbon in the d_1-cyclopropanone, resulting in an equal amount of deuterium at the α- and β-carbon in the combined (d_0-, d_1-, d_2-, and d_3-) acids. However, the mean value from eight determinations of recrystallized acid gave α-H/β-H=0.86 (Table 1); the individual values ranging from 0.80—0.90. This can be taken as either an indication of the influence of an α secondary isotope effect in the fission of the cyclopropanone ring,[16,17] or as the presence of an unsymmetric mechanism for rearrangement. Work is in progress to distinguish between these two possibilities. It can be pointed out that the value α-H/β-H=0.86 originates from only about 40 % d_1-dibromocyclopropanone (Table 1). If this value is caused only by an α secondary isotope effect (k_H/k_D), the calculated value for this effect is about 1.6—1.7, which seems to be higher than values previously reported for other reactions with only one deuterium in the molecule.[16,17]

The results from the rearrangement of the tetrachloro and tetrabromo ketone indicate no pronounced difference in the deuterium content of the dichloro and dibromo acids. Contrary to the ketones studied by Bordwell *et al.*,[10] we found in our ketones a higher value for the deuterium content in the bromo acid.

EXPERIMENTAL

The NMR-spectra were recorded on a Varian model A-60 spectrometer and the mass spectra on an LKB 9000 using the direct inlet. The mass spectra were corrected for the natural abundance of heavier isotopes, in some cases they are compared with those from non-deuterated samples.

Isocrotonic acid.[11] To a solution of 18.3 g (0.173 moles) of sodium carbonate in 150 ml of deuterium oxide, 23.0 g (0.10 moles) of 1,3-dibromo-2-butanone was added dropwise. The solution was stirred for 3 h and thereafter extracted with dry ether (2×25 ml), acidified with deuterium chloride in deuterium oxide and extracted with dry ether (6×25 ml). Without prior drying, the acidic ether extract was evaporated *in vacuo*. The last traces of ether and deuterium oxide were removed by an oil pump at room temperature during 30 min. The crude product was distilled (no isomerization), b.p. 42°C/1 mm. The NMR-spectrum was recorded on a 50 % carbon tetrachloride solution at +5°C (no isomerization), see Table 1. The mass spectrum was recorded on the acid adsorbed on Al_2O_3.

cis-*3-Bromoacrylic acid.*[12] To a solution of 0.245 g (2.31 mmoles) of sodium carbonate in 2.0 ml of deuterium oxide was added 0.391 g (1.34 mmoles) of 1,1,3-tribromoacetone. After 10 min the solution was extracted with dry ether, acidified (DCl/D_2O) and re-extracted with dry ether. The extract was evaporated and the residual crystalline acid recrystallized once from heptane, m.p. 61°C. The NMR-spectrum was recorded on a carbon tetrachloride solution.

3,3-Dibromoacrylic acid.[13] This acid was prepared from 0.501 g (1.34 mmoles) of 1,1,3,3-tetrabromoacetone and 0.245 g (2.31 mmoles) of sodium carbonate in 2.0 ml of deuterium oxide. The same procedure was followed as in the preparation of *cis*-3-bromoacrylic acid, m.p. 88°C.

3,3-Dichloroacrylic acid.[14] This acid was prepared from 2.62 g (13.4 mmoles) of 1,1,3,3-tetrachloroacetone and 2.45 g (23.1 mmoles) of sodium carbonate in 20 ml of deuterium oxide. The acid was isolated as described for *cis*-3-bromoacrylic acid and purified by treatment with carbon tetrachloride and thin layer chromatography as described in Ref. 14. The mass spectrum was taken on a sample directly from the TLC-plate.

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