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Thermal Reactions of *erythro*- and *threo*-1-(1-Acetoxyethyl)-indene.[1] Competing Epimerisation, Rearrangement and Acetic Acid Elimination

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Thermally induced hydrogen migrations competing with 1,2-elimination of acetic acid have been studied. Thus, when one of the diastereomeric 1-(1-acetoxyethyl)indenes (*1*) was pyrolysed (neat) at 182 °C, not only the olefin *trans*-1-ethylideneindene (*4a*) was produced, but even the epimer (*2*) and the rearranged ester 3-(1-acetoxyethyl)indene (*3*) were obtained along with starting material. The other diasteromer (*2*) gave both *trans*- and *cis*-olefin (*4a* and *4b*) together with the three isomeric acetates. Compound *3* also produced the olefins and the epimers, but the rearrangement of this compound was slow. By deuterium-labeling experiments, a common dipolar intermediate for the reactions can be ruled out. The results indicate that the epimerisations and the 1,3-proton transfer rearrangements proceed with suprafacial [1,5]-sigmatropic shifts. The kinetic deuterium isotope effect of the disappearance of *1* was determined to be 2.8 ± 0.6.

Thermal suprafacial [1,5]-sigmatropic shifts of hydrogen have been shown in the indene system by deuterium-labeling experiments,[2,3] by isolation of the indene-maleic anhydride adduct,[3,4] and by studying isomerisation and racemisation of an optically active indene derivative.[5] These experiments strongly support the intervention of an isoindene intermediate in the hydrogen migrations. Studies have also been made of other migrating groups. Thus, hydrogen has been shown to migrate much faster than phenyl which in turn migrates faster than methyl.[6]

Pyrolysis of alkyl acetates has been reviewed by Saunders and Cockerill.[7] The elimination of acetic acid proceeds *syn*-stereospecificially *via* a cyclic six-membered transition state.

Bordwell and Landis [8] have explained the non-stereospecific Chugaev reactions of *erythro*- and *threo*-3-*p*-tolylsulfonyl-2-butyl-*S*-methyl xanthate which produce the *trans*- and *cis*-olefins in different proportions by a mechanism involving a dipolar ion intermediate. Internal rotation leads to an interconversion of the *cis*- and *trans*-form of the dipolar intermediate and formation of the more stable olefin as the main product.

Taylor *et al.*[9] have shown that some charge separation occurs in the transition state of acetate pyrolysis. They studied the elimination of acetic acid from 1-arylethyl acetates in the gas phase at 600 K.

Rearrangement seldom accompanies elimination in acetate pyrolysis. However, when the substrate lacks a β-hydrogen rearrangement has been observed.[7] Isomerisation prior to elimination has been proposed to explain that the same product mixture of 1,3- and 2,4-heptadiene was obtained from 2-acetoxy-3-heptene and 4-acetoxy-2-heptene.[10]

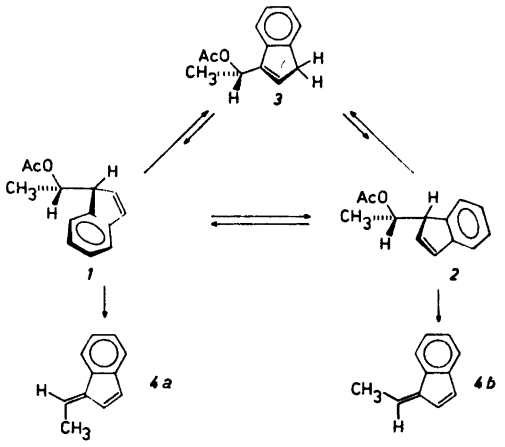
Few isotope effects of pyrolysis of esters have been reported.[11–13] Depuy, King and Froemsdorf [11] found a kinetic deuterium isotope effect of 1.9 at 400 °C and 1.7 at 500 °C for the pyrolysis of 2,2,4,4-d_4-1-methylcyclohexyl acetate.

Recently, Bock has shown that thermal 1,4-elimination of acetic acid from some 3-acetoxy-1,4-cyclohexadien derivatives proceeds stereochemically *syn*.[14] However, multistep reactions could not be excluded.

The present study was initiated in order to establish the correlation between the two diastereomeric 1-(1-acetoxyethyl)indenes and the structures *1* and *2* in Scheme 1. However, we found that thermally induced hydrogen migrations to epimerised and rearranged material compete with elimination of acetic acid. Therefore we decided to test the hypothesis that the reactions proceed *via* a common (dipolar) intermediate.

RESULTS AND DISCUSSION

When one of the diastereomeric 1-(1-acetoxyethyl)indenes (*1*) was pyrolysed (neat) at 182 °C, the olefin *trans*-1-ethylideneindene (*4a*) was formed. Along with the olefin and starting material, the epimer (*2*) and the rearranged ester 3-(1-acetoxyethyl)indene (*3*) were also obtained. The other diastereomer (*2*) gave both *trans*- and *cis*-olefin (*4a* and *4b*) together with the two isomeric acetates (Table 1). Compound *3* was also shown to produce a mixture of the diastereomers and the olefins.



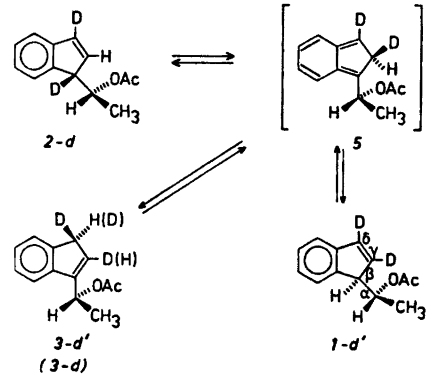
Scheme 1.

The above experiments made it possible to assign the structure *1* in Scheme 1 to the diastereomer *1* and the structure *2* to diastereomer *2*. These assignments were also suggested by studies of methoxide-promoted eliminations, because *anti*-elimination from *2* was favoured over *syn*-elimination (92 % *anti* and 8 % *syn*).[15]

By using specifically deuterated substrate (*2-d*) in the reactions, we found that the epimerisation reaction does not proceed *via* an intermediate internal ion pair. Instead, the results indicate that the epimerised material is formed mainly by suprafacial [1,5]-sigmatropic shifts *via* the isoindene intermediate *5* (Scheme 2). This was established by isolating the *1-d'* (by HPLC) formed from *2-d* after about 50 % reaction and determining the content of protium in the β-, γ- and δ-positions of *1-d'*. The result was (as determined by ^{1}H NMR spectroscopy with the α-proton as a reference): 91 ± 10 atom-% H in the β-position and 0 ± 10 atom-% H in the γ- and δ-positions, respectively. The corresponding result for isolated starting material *2-d* was 0 ± 10 atom-% H in the β-position. This experiment indicates that the hydrogen migrations have a common intermediate of isoindene-type formed by [1,5]-sigmatropic shifts.

Table 1. Product compositions obtained from thermal reactions with *1*, *2* and *3* at 181.6 ± 0.4 °C (^{1}H NMR).

Run No.	Substrate	Time/min	Result/mol-% *1*	*2*	*3*	*4a*	*4b*
1	*1*	75	80.1	2.4	14.5	2.9	–
2	*1*	93	77.1	3.3	16.4	3.2	–
3	*1*	185	60.6	5.8	30.1	3.5	–
4	*1*	226	50.4	10.5	34.9	4.2	–
5	*2*	226	10.2	41.2	45.4	1.6	1.6
6	*2*	226	8.6	43.6	44.0	1.6	2.2
7	*3*	125	2.1	2.2	95.0	0.3	0.3
8	*3*	226	3.0	3.4	92.8	0.5	0.3
9	*3*	375	4.8	5.3	89.1	0.5	0.3
10	*1-d*	216	79.8	2.7	14.8	2.7	–
11	*1-d*	228	79.1	3.1	14.6	3.2	–
12	*2-d*	420	8.8	51.5	37.7	1.0	1.0
13	*2-d*	462	9.5	49.9	39.0	0.8	0.8



Scheme 2.

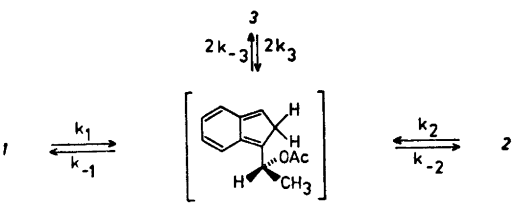
The rate constant of the disappearance of *1* in the thermolysis was determined to be $(4.80 \pm 0.48) \times 10^{-5}$ s^{-1}, and of *1-d* to be $(1.73 \pm 0.17) \times 10^{-5}$ s^{-1} from the data in the table (run Nos. 1, 2, 10, and 11). Accordingly, the kinetic isotope effect is 2.8 ± 0.6, which can be considered to be the isotope effect of the isomerisation of *1*, since elimination is a much slower process. The theoretical maximal isotope effect at 182 °C is ≈ 4.5.[16] An effect smaller than this can be explained with a transition state which is highly asymmetric and/or non-linear with respect to hydrogen migration. A mechanism involving an intermediate which returns to starting material faster than it goes on to product can be ruled out, because analysis of the reaction rates, which can be calculated from the data in Table 1, shows that the isotope effect of the intermediate-forming step is only slightly decreased due to reversibility. The transition states of 1,5-sigmatropic shifts in the indene system must be non-linear due to the rigidity of the ring system. The [1,5]-sigmatropic shift in 1,3-pentadiene has a much larger deuterium isotope effect,[17] 5.4 at 185 °C which includes secondary isotope effects, but in this molecule the transition state has the possibility of being somewhat more linear.

The isotope effect which we have reported above is of similar magnitude to the isotope effect (≈ 3 at 140 °C) determined by Almy and Cram for the rearrangement of 1-methyl-3-*tert*-butylindene.[5] They also found an isotope effect of 2.7 – 2.9 for the reaction of the isoindene intermediate to products by studying the deuterium content of the formed materials.

The equilibrium constants at the reaction temperature were determined to be $[3]_{eq}/[1]_{eq} = 9.6 \pm 2.0$ and $[3]_{eq}/[2]_{eq} = 9.6 \pm 2.0$. These values are considerably lower than those obtained in methanol at 30 °C.[15]

The collapse ratios of the isomerisation reactions could be calculated by assuming a common isoindene intermediate: $k_{-2}/k_{-1} \approx 1$ and $k_{-3}/k_{-1} \approx 2.5$ (Scheme 3). These figures can be compared with Almy and Crams collapse ratio of ≈ 1.[5]

The elimination of acetic acid from *1* is a stereospecific *syn*-elimination (Table 1 and Scheme 1). Only the presumably more stable olefin *4a* is formed. The other epimer *2* produces both of the olefins. Isolated olefin mixture (from run No. 6) was obtained by HPLC and analysed by ^{1}H NMR spectroscopy, which showed about 40 % *4a* and 60 % *4b*. However, at least the main part of the olefin *4a* must have been formed *via* epimerised material, and there is no experimental indication that *2* gives *4a* by a route not involving *1*. This is also supported by an experiment in which *2-d* was reacted about 25 % and the olefins separated from the reaction mixture. Analysis by mass spectroscopy showed a ratio of the mol peaks *m/e* 143 and 144 of 2, *i.e.* about 30 % of the olefins must have been formed from *1-d'*.



Scheme 3.

No interconversion of *4a* and *4b* during the reactions could be detected.

The compound *3* produced the olefins at a low rate (Table 1). Multicenter, 1,4-elimination reactions are thermally allowed.[14] However, the distance between the single-bonded oxygen and the δ-protons in *3* is large, and the rate of a reaction following this mechanism can therefore be expected to be very low. A mechanism in which the acetoxy group picks up a δ-proton and gives a dipolar intermediate is also improbable due to the large distance. The olefins have probably been formed instead *via* the rearranged materials *1* and *2*.

It is interesting to note that a common intermediate has been found also for other reactions with similar compounds. Thus we have found strong indications for the intermediacy of a common ion pair in base-catalysed 1,3-proton transfer competing with 1,2- and 1,4-elimination reactions in protic solvents with tertiary amines as bases.[18] The substrates were 1- and 3-(2-acetoxy-2-propyl)indene.

EXPERIMENTAL

General

The ^{1}H NMR spectra were obtained with Varian A 60D and JEOL FX 60 NMR spectrometers. The HPLC was performed with a Waters

6000A solvent delivery system and 440 absorbance detector. The purity of the acetates was checked with HPLC using a silica column (Waters μPorasil 0.30 m).

Syntheses

1-(1-Hydroxyethyl)indene. A diastereomeric mixture of the alcohols was prepared according to the method given by Courtot.[19] The alcohol (*1-OH*) corresponding to the acetate *1* was formed predominantly (≈70 % of the mixture). Pure *1-OH* was obtained by recrystallization of the distilled product twice from light petroleum. The other diastereomer (*2-OH*) was separated from the remaining oil (containing 35 % *1-OH* and 65 % *2-OH*) by liquid chromatography on a Sephadex LH-20 column with 80 % 1,2-dichloroethane and 20 % cyclohexane as solvent. The pure *2-OH* crystallized in the refrigerator.

3-(1-Hydroxyethyl)indene. In 110 g of dry pyridine 55.0 g (0.343 mol) of 1-(1-hydroxyethyl)indene (diastereomeric mixture) was dissolved. The reaction mixture was heated under dry nitrogen, and after 20 h at 65 °C, an equilibrium mixture was obtained containing about 4 % of each of the diastereomer along with the rearranged alcohol and traces of eliminated material. The product mixture was poured onto ice, and after addition of 200 ml of water, extraction was performed with 3 × 200 ml of ether. The combined ether extracts were washed, first with 100 ml of water, then with 2 M HCl until acidic, and finally with four further portions of HCl. The organic phase was washed with water until neutral and then with saturated sodium chloride solution. After drying over sodium sulfate the ether was evaporated and the residue flash-distilled in vacuum. The final purification of the rearranged alcohol was performed on a split-tube column (Fischer HMS 300) at 13 Pa. The high-boiling fraction was pure and free from isomers and eliminated material, as shown by ^{1}H NMR spectroscopy.

1-(1-Acetoxyethyl)indene (1). In 23.9 g (0.234 mol) of acetic anhydride 8.26 g (0.0516 mol) of diastereomerically pure 1-(1-hydroxyethyl)-indene (*1-OH*) and 0.25 g of anhydrous zinc(II) chloride were dissolved. The reaction mixture, which was stirred under dry nitrogen, became warm, and after 2 h no trace of unreacted starting material could be detected with ^{1}H NMR spectroscopy. The reaction solution was diluted with 50 ml of benzene, washed with 3 × 5 ml of water and dried over magnesium sulfate. After evaporation of the benzene and unreacted acetic anhydride, the residue was distilled in vacuum through a short Vigreux column. Yield 7.2 g (69 %), b.p. 90.5–91.5 °C/7 Pa, m.p. 31–32.5 °C. ^{1}H NMR spectrum and HPLC showed the compound to be pure and free from isomerised and eliminated material. MS (IP 12 eV): *m/e* 202 (M). ^{1}H NMR (60 MHz, CCl_4): δ 0.87 (3 H, d, *J* 6.2 Hz), 1.97 (3 H, s), 3.67 (1 H, d, *J* 5.7 Hz and further small coupling), 5.23 (1 H, p, *J* 6.2 Hz), 6.33 (1 H, dd, *J* 5.6 Hz and 1.9 Hz), 6.74 (1 H, dd, *J* 5.6 Hz and 1.9 Hz), 6.88–7.35 (4 H, complex).

1-(1-Acetoxyethyl)indene (2) was prepared from *2-OH* according to the method above. The product, which was a liquid at room temperature, had the same b.p. as its diastereomeric isomer, and was pure and free from isomerised and eliminated material as shown by ^{1}H NMR spectroscopy and HPLC. MS (IP 12 eV): *m/e* 202 (M). ^{1}H NMR (60 MHz, CCl_4): 0.90 (3 H, d, *J* 6.2 Hz), 1.91 (3 H, s), 3.64 (1 H, p, *J* 4.6 Hz and 1.9 Hz), 5.28 (1 H, qd, *J* 6.2 Hz and 4.6 Hz), 6.22 (1 H, dd, *J* 5.5 Hz and 1.9 Hz), 7.49 (1 H, dd, *J* 5.5 Hz and 1.9 Hz), 6.81–7.41 (4 H, complex).

3-(1-Acetoxyethyl)indene (3). In 60 ml of acetic anhydride 36.2 g (0.226 mol) of 3-(1-hydroxyethyl)indene and 0.5 g of anhydrous zinc(II) chloride were dissolved. The reaction mixture was stirred under dry nitrogen for 4 h, 100 ml of benzene was added and the solution washed with 3 × 10 ml of water and finally dried over magnesium sulfate. The benzene and the excess of acetic anhydride were removed in vacuum and the residue distilled through a short Vigreux column. Yield 32.9 g (72 %), b.p. 90–92 °C/13 Pa. ^{1}H NMR showed that the compound was pure and free from isomerised and eliminated material. MS (IP 12 eV): *m/e* 202 (M). ^{1}H NMR (60 MHz, CCl_4): δ 1.51 (3 H, d, *J* 6.5 Hz), 1.92 (3 H, s), 3.19 (2 H, t, *J* very small), 5.84 (1 H, qd, *J* 6.5 Hz and 1.1 Hz), 6.23 (1 H, q, *J* 1.1 Hz), 6.90–7.30 (4 H, complex).

Mixture of trans- *and* cis-*ethylideneindene (4a and 4b).* Synthesis of this compound has been reported previously by Courtot.[20]

In this work the olefins were prepared for calibration purposes from *1* by elimination with potassium *tert*-butoxide in *tert*-butyl alcohol. After one distillation, b.p. 66–67 °C/13 Pa, a pure mixture of the *trans*- and *cis*-olefins was obtained (88 % *4a* and 12 % *4b*). MS (IP 19 eV): *m/e* 142 (M).

1,3-d$_2$-1-(Hydroxyethyl)indene. The preparation of 1,1,3-*d*$_3$-indene has been described previously.[18c]

To 0.36 mol BuLi in hexane/ether 41.0 g (0.344 mol) of 1,1,3-*d*$_3$-indene (containing 98.7 ± 1.0 atom-% D in the 1 and 3 positions) was added dropwise under dry nitrogen. The temperature was kept below −50 °C for 1.5 h, and then 45.0 g (1.02 mol) of acetaldehyde was added dropwise to the cooled solution. After the addition the reaction mixture was stirred for 5 min and then poured slowly into a stirred mixture of 2 M HCl (excess) and ice. The water phase was extracted with 2 × 100 ml of ether. The combined organic phases were washed first with water until neutral and then with saturated sodium chloride solution, and

were finally dried over magnesium sulfate. Evaporation of the ether and distillation of the products through a short Vigreux column gave a viscous liquid containing 56 % of the alcohol corresponding to *1-d* and 44 % of the other diastereomer. The liquid was dissolved in light petroleum, and *1-d-OH* crystallized from the solution. The crystalline product, which was recrystallized once, was pure and free from rearranged, epimerised and eliminated material as shown by ^{1}H NMR spectroscopy.

The other diastereomer (*2-d-OH*) was separated from the remaining oil by LC, and a product free from rearranged, epimerised and eliminated material and any other impurity was obtained. Yield (before separation of the diastereomers) 35.2 g (63 %), b.p. 98 – 102 °C/27 Pa.

1,1-d_2*-3-(1-Hydroxyethyl)indene* was prepared from the previous compound and purified according to the method for the corresponding protium compound, but the reaction time was increased to 120 h at 60 °C. The isomeric purity of the distilled product was > 99.5 %, and the compound was free from other impurities detectable with ^{1}H NMR.

1,3-d_2*-1-(1-Acetoxyethyl)indene (*1-d*)*. In 25 ml acetic anhydride 7.0 g (0.0432 mol) of diastereomerically pure 1,3-d_2-1-(hydroxyethyl)-indene (*1-d-OH*) was dissolved and 0.25 g of anhydrous zinc(II) chloride was added. The mixture was stirred under dry nitrogen for 3 h and then 50 ml of benzene was added. The solution was washed with 3 × 5 ml of water and dried over magnesium sulfate. The benzene and unreacted acetic anhydride were removed in vacuum and the residue was distilled through a short Vigreux column. Yield 6.4 g (73 %), b.p. 83 – 84 °C/9 Pa. The deuterium content was 98.2 ± 1.0 atom-% (in the 1 and 3 positions, ^{1}H NMR). HPLC and ^{1}H NMR showed the compound to be pure and free from isomerised and eliminated material.

1,3-d_2*-1-(1-Acetoxyethyl)indene (*2-d*)* was prepared from *2-d-OH* according to the method above. Also this acetate was pure and free from isomerised and eliminated material as shown by ^{1}H NMR spectroscopy and HPLC. The deuterium content was the same as in *1-d*.

1,1-d_2*-3-(1-Acetoxyethyl)indene (*3-d*)*. In 20 ml of acetic anhydride 5.0 g (0.0308 mol) of 1,1-d_2-3-(1-hydroxyethyl)indene was dissolved, and 0.20 g of anhydrous zinc(II) chloride was added. The mixture was stirred under dry nitrogen for 12 h, and then 50 ml of benzene was added. The solution was washed with 3 × 5 ml of water and dried over magnesium sulfate. The benzene and the unreacted acetic anhydride were removed in vacuum and the residue was distilled through a short Vigreux column. Yield 4.5 g (71 %), b.p. 90 – 92 °C/13 Pa. The deuterium content was 98.2 ± 1.0 atom-% in the 1 position (^{1}H NMR). No trace of isomerised or eliminated material or any other impurity could be detected.

Thermal reactions

Base-catalysed 1,3-proton transfer rearrangements of the substrates together with base-promoted elimination of acetic acid occur at much lower temperatures.[15] Therefore, the equipment was thoroughly washed to remove traces of base.[5] Furthermore, the acetic acid formed in the thermal eliminations suppresses the base concentration. Polymer was formed after long reaction times. However, when the reaction from *1* was stopped after about 50 % reaction, less than 3 mol-% of the material had been polymerised.

Pyrex tubes (3 mm i.d.) were sealed at one end, cleaned with chromic acid, and then rinsed with water, dilute ammonium hydroxide, distilled water, dilute acetic acid and again with distilled water before drying at 130 °C at least over night. The samples were added to the tubes, which were then degassed four times under 13 Pa. Dry nitrogen was introduced between the evacuations. The tubes were sealed under vacuum and placed in a silicone oil bath at 181.6 ± 0.4 °C. After the appropiate time the reactions were quenched by dipping the tubes in light petroleum. The reaction mixtures were dissolved in CCl_4 and analysed by ^{1}H NMR spectroscopy. The temperature was measured with a calibrated mercury thermometer.

The isolation of *1-d'* was performed with reversed phase HPLC (recycling on a Waters 610 × 7 mm C_{18}/Porasil B column, 40 % by weight ethanol-water solution, 280 nm). The purity of the chromatographic fractions was checked on a Waters μBondapak C_{18} analytical column (0.30 m).

The rate constants were obtained by one-point kinetics (run Nos. 1, 2, 10, and 11 in Table 1). The estimated errors are maximal errors including random errors and maximal systematic errors calculated considering the maximal errors in the concentration determinations of *1* and *1-d* to be ± 2 mol-%.

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