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A STUDY OF THE REVERSIBILITY OF FRIEDEL–CRAFTS C-ACETYLATIONS BY MEANS OF ^{14}C-LABELLING

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Abstract—The exchange of acetyl groups between acetyl chloride and carbonyl-labelled mesityl oxide or 4-chloro-4-methyl-2-pentanone in the presence of aluminium chloride has shown the reversibility of aliphatic C-acetylations. No such exchange was found with carbonyl-labelled acetophenone. The significance of these results for the Friedel–Crafts acylation and for the conjugation between the acyl group and the aliphatic or aromatic residues is discussed.

In a previous paper[1] we have shown the reversibility of the Friedel–Crafts acetylation of olefins by studying the specific activity of the pyrylium salts obtained from ^{14}C-labelled acetyl chloride and 4-chloro-3,4-dimethyl-2-pentanone. The present paper brings more direct evidence bearing on this problem.

A literature survey on the reversibility of C-acylations[2] showed that protodeacylations and transacylations occur in mild conditions in the presence of Lewis or Brønsted acids with β-halo- or -hydroxyketones, with α,β-unsaturated ketones especially when steric hindrance to conjugation is present, and with aromatic ketones only when steric strain interferes with the conjugation between the carbonyl group and the aromatic nucleus. Deacylations are not possible or proceed in very drastic conditions when there is an appreciable conjugation energy to be overcome, as in non-hindered, coplanar aromatic or unsaturated ketones, and pyrylium salts.

For determining the extent of deacylation of aliphatic or aromatic ketones, the following procedure was adopted. Carbonyl-labelled 4-chloro-4-methyl-2-pentanone I (a β-chloroketone), mesityl oxide II (an unsaturated ketone), and acetophenone III (an aromatic ketone) were synthesized from acetyl chloride-1-^{14}C and t-butyl chloride or from acetic anhydride 1-^{14}C and benzene, respectively. The starting materials and the specific activities of these compounds are presented in Table 1. The labelled ketones are introduced into a Friedel–Crafts acetylating mixture prepared from inactive acetyl chloride and aluminium chloride. If an exchange of acetyl groups takes place owing to the reversibility of the acylation, then the acetyl chloride becomes radioactive. The reaction mixture is quenched by pouring into an excess of cold aniline. The resulting acetanilide is then recrystallized to constant activity (5 to 6 recrystallizations from water), dried and converted into carbon dioxide in a specially devised apparatus, which allowed the radioactivity measurements to be performed in the same installation in two length-compensated Geiger–Müller counters.[3]

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[1] M. Frangopol, A. Genunche, P. T. Frangopol and A. T. Balaban, *Tetrahedron* **20**, 1881 (1964).

[2] A. T. Balaban, "Deacylations of non-conjugated ketones and the reversibility of C-acylations", in *Omagia Acad. Prof. Raluca Ripan* (Edited by C. Drăgulescu). Ed. Academiei R.S.R., București (1966), p. 103, 68 refs. Cf. also C. D. Nenitzescu and A. T. Balaban, "Aliphatic acylation" in *Friedel–Crafts and Related Reactions* (Edited by G. A. Olah), vol. 3, p. 1068. Interscience, New York (1964).

[3] C. Mânttescu and A. Genunche, *Studii si Cercetări Chim. Acad. R.S.R.* **13**, 1101 (1965).

TABLE 1. ^{14}C-LABELLED COMPOUNDS AND STARTING MATERIALS FOR THEIR PREPARATION

Compound	Starting materials	Specific activity A_i mCi/mole
AcCl-1-^{14}C	AcOH-1-^{14}C and BzCl^{3}	15·0 ± 0·2^{a}
Ac_2O-bis-1-^{14}C	AcOH-1-^{14}C and Ac_2O^{3}	8·8 ± 0·29^{b}
4-Chloro-4-methyl-2-pentanone-2-^{14}C (I)	AcCl-1-^{14}C and t-BuCl in the presence of $AlCl_3$ at 0°, followed by hydrolysis and fractionation	15·4 ± 0·2^{b}
4-Methyl-3-penten-2-one-2-^{14}C (mesityl oxide (II))		14·9 ± 0·2^{b}
Acetophenone-1-^{14}C (III)	Ac_2O-bis-1-^{14}C and benzene in the presence of $AlCl_3$^{4}	4·73 ± 0·06^{b}

Radioactivity measurements were performed: ^{a} by converting the AcCl into acetanilide, combustion of acetanilide, and radioactivity measurement of $^{14}CO_2$; ^{b} by combustion and radioactivity measurement of $^{14}CO_2$.

Before employing this procedure, various other methods for measuring the activity of the acetyl chloride after the reaction were tested: (i) rapid distillation from the reaction flask followed by radioactivity measurements of the acetyl chloride; the reproducibility was poor and the counters became soon useless owing to the halogen content; (ii) conversion of the distilled acetyl chloride into carbon dioxide, and its determination; the measurements then became satisfactory but distillation was not suitable for removing the acetyl chloride, because its activity varied during the distillation, no matter how rapid this was, the variation being due to the presence of dissolved hydrogen chloride, as shown by the increasing activities of the fractions obtained on redistilling the acetyl chloride. These procedures were therefore replaced by that described above.

A blank showed that labelled I and II with acetyl chloride do not yield active acetanilide in the absence of aluminium chloride.

The labelled ketone (1 mole) was introduced into a mixture of acetyl chloride (8·5 moles) and aluminium chloride (2 moles) cooled at 10°, and the results obtained for the radioactivity measurements of the acetyl chloride after reaction are presented in Table 2.

TABLE 2. RADIOACTIVITIES OF ACETYL CHLORIDE AFTER THE EXCHANGE WITH LABELLED KETONES (CF. TABLE 1).

	Reagents Labelled ketone (A_i, mCi/mole)	(ml)	AcCl (ml)	$AlCl_3$ (g)	Temp. °C	Time min.	Activity of AcCl, A_t mCi/mole	Per cent of exchange P
I	15·4 ± 0·2	1·0	4·0	2·0	10	1	1·64 ± 0·02	100 ± 1
						5	1·63 ± 0·02	
II	14·9 ± 0·2	1·0	5·3	2·3	10	1	0·47 ± 0·01	29 ± 0·5
						5	0·46 ± 0·01	
						60	0·47 ± 0·01	
III	4·73 ± 0·06	1·0	5·3	2·3	50	120	0	0
						1440	0	

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[4] E. M. Shantz and D. Rittenberg, *J. Amer. Chem. Soc.* **68**, 2109 (1946).

The percent of exchange P from the theoretically possible exchange, in which the acetyl groups in the ketone (labelled) and the acetyl chloride (non-labelled) become equivalent leading to the scrambling of the label, was calculated as follows. After complete equilibration (100% exchange), the initial activity, A_i, of the ketone (1 mole) becomes scrambled over $1 + 8{\cdot}5 = 9{\cdot}5$ moles, therefore the specific activity per mole of acetyl group is $A_i/9{\cdot}5$. A final specific activity A_f of the acetanilide, hence of the acetyl chloride, then corresponds to a percent of exchange $P = 950\ A_f/A_i$.

The results presented in Table 2 show conclusively that the β-chloroketone I is totally equilibrated with the acetyl chloride, while the unsaturated ketone II is partly (29%) equilibrated. Interestingly, the process is instantaneous, as shown by the fact that the activities do not differ at various reaction times. However, acetophenone shows no exchange when refluxed for 2 or 24 hr with acetyl chloride and aluminium chloride; the activity of the resulting acetanilide lies statistically within the background.

These results are in agreement with our previous findings[1,2,5,6] and with literature data[8] for aliphatic or aromatic ketones.

The explanation of the incomplete (29%) equilibration between mesityl oxide (1 mole) and acetyl chloride (8·5 moles) in the presence of 2 moles aluminium chloride is not readily apparent. Partial resinification (by polymerization or condensation) of the ketone, or the increased conjugation in the unsaturated ketone relatively to the chloroketone, can account for this fact.

The results also show that under the reaction conditions, the β-chloroketone I is not dehydrochlorinated to mesityl oxide II, nor does the latter add hydrogen chloride. This lack of interconversion between I and II also explains why only β-haloketones can be reduced by hydride donors such as cyclohexane,[7] unlike unsaturated ketones. This difference between β-halo- and unsaturated ketones also provides an explanation for the formation of different pyrylium salts, depending on the nature of the catalyst, in the diacetylation of olefins $Me_2C{=}CHR$ (R = Me[1,2,5,6,8] or Ph[9]).

EXPERIMENTAL

The conversion of AcOH-1-^{14}C into carbonyl-labelled AcCl and Ac_2O was described previously.[5] The ketones I and II were prepared by introducing powdered $AlCl_3$ (1 mole) into a stirred and ice-cooled mixture of AcCl-1-^{14}C and t-BuCl (1 mole each). After 3-hr stirring under protection from atmospheric moisture, the mixture was poured into ice-water, extracted with ether, dried ($MgSO_4$), and fractionated under red. press., yielding carbonyl-labelled mesityl oxide and 4-chloro-4-methyl-2-pentanone in approximately equal amounts. The chloroketone with dimethylaniline smoothly affords mesityl oxide.

The exchange reactions were carried out in double-walled Erlenmeyer flasks connected through ground-glass joints to a dropping funnel containing the labelled ketone and to a reflux condenser protected from atmospheric moisture by a $CaCl_2$ tube. After introducing with microburettes the liquid reagents (the ketone I or II in the dropping funnel, the acetyl chloride in the flask), the weighed $AlCl_3$ was introduced in flask with cooling. After stirring magnetically at 10° ± 0·1 (with thermostatted water in the cooling jacket) for some time, the labelled ketone was added. After stirring at 10° for a

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[5] A. T. Balaban, M. Mărculescu-Frangopol and P. T. Frangopol, *Isotopentechnik* **2**, 235 (1962).

[6] A. T. Balaban and C. D. Nenitzescu, *J. Chem. Soc*. 3523 (1961); D. Fărcaşiu, M. Fărcaşiu and A. T. Balaban, *Rev. Roumaine Chim*. **9**, 137 (1964); D. Fărcaşiu, A. T. Balaban and M. Gutman, *Ibid*. **9**, 727 (1964).

[7] C. D. Nenitzescu and I. P. Cantuniari, *Liebigs Ann*. **510**, 269 (1934).

[8] G. Baddeley and M. A. R. Khayat, *Proc. Chem. Soc*. 382 (1961).

[9] A. T. Balaban, *Tetrahedron Letters* 91 (1963).

certain period (cf. Table 2), the mixture was poured on to excess solidified aniline, the crystalline acetanilide was recrystallized from water in the presence of charcoal 5 to 6 times, and the radioactivity was measured as described previously.[3] Supplementary recrystallizations of acetanilide did not affect the radioactivity.

Acetophenone-1-^{14}C, prepared from benzene and Ac_2O,[4] was refluxed in similar conditions for 2 or 24 hr with AcCl + $AlCl_3$, without showing any exchange of the acetyl group.

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