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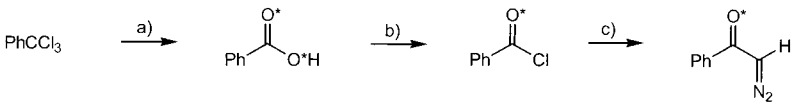
Oxygen Labeling and Exchange

Loss of Isotope Labeling in the Conversion of [$^{18}O_2$]Benzoic Acid into [^{18}O]Benzoyl Chloride with Oxalyl Chloride**

*Peter Haiss and Klaus-Peter Zeller**

In the course of a study on reaction mechanisms, we needed [^{18}O]2-phenyl-2-oxodiazoethane (**4***), which was prepared following the reactions given in Scheme 1. [^{18}O]Water with an enrichment of 95% ^{18}O was used as labeling source in the reactions. Based on this, benzoic acid (**2***) formed by the hydrolysis of benzotrichloride (**1**) should have a composition of 90.25% $^{18}O_2$, 9.5% $^{16}O^{18}O$, and 0.25% $^{16}O_2$. The experimental verification with the help of EI- (positive mode) and ESI-mass spectrometry (negative mode) confirms this isotope distribution (90% $^{18}O_2$, 10% $^{16}O^{18}O$, <1% $^{16}O_2$). Dissolution of the labeled benzoic acid in water/acetonitrile does not result in any decrease in the ^{18}O content.



Scheme 1. Synthesis of α-diazoketone **4***, $*=^{18}O$: a) $H_2{}^{18}O$/110°C/48 h, ampoule; b) 3 equivalents of $(COCl)_2$/77°C/1 h; c) CH_2N_2/Et_2O/0°C.

For the derivatization of the marked benzoic acid (**2***) to [^{18}O]benzoyl chloride (**3***), we chose oxalyl chloride on account of its preparative advantage, a decision which led to unexpected consequences. The reaction of benzoyl chloride (**3***) with diazomethane gives the diazoketone **4***, the carbonyl group of which unexpectedly shows two resonance signals with marginally different shifts ($\Delta\delta = 0.03$ ppm) in the ^{13}C NMR spectrum (Figure 1a).

Risley and Van Etten have also reported a similar isotope effect for the ^{13}C resonances of [^{16}O]- and [^{18}O]-carbonyl groups, in approximately the same range as ours,[2] in which the signal at a somewhat higher field strength can be assigned to the ^{18}O isotopomer. It can be seen from the intensities of the resonance signals of **4*** that the required ^{18}O-isotopomer is formed in only 40%.

At first we thought that a hydration–dehydration sequence involving the formed α diazoketone **4***, because of adventitious moisture present in ethereal diazomethane, could be responsible for the drastic loss of ^{18}O. This inference

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[**] We thank Prof. Dr. H.-J. Machulla, Sektion für Radiopharmazie, Universitätsklinikum Tübingen, for a generous gift of [^{18}O]water.

proved to be unfounded as reexamination revealed that **3*** had also been affected by loss of isotope labeling.

The ^{13}C carbonyl resonance of **3*** is split into two signals, exactly as in the subsequent product (Figure 1b). Mass spectrometry shows the hydrolysis of the intermediate **3*** (ca. 1 mg **3***, few drops of water, ultrasound bath) affords benzoic acid containing an ^{18}O content of 39.8%, and not expected 95%. Oxalyl chloride, used as a reagent in the step **2***→**3***, is thus the source for the considerable incorporation of ^{16}O observed.

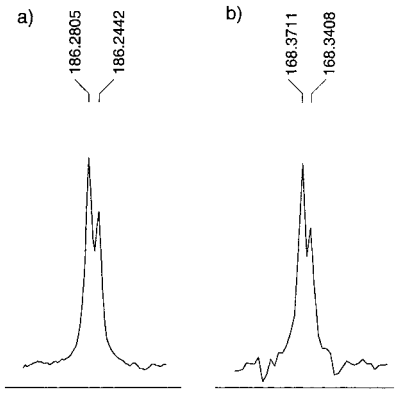
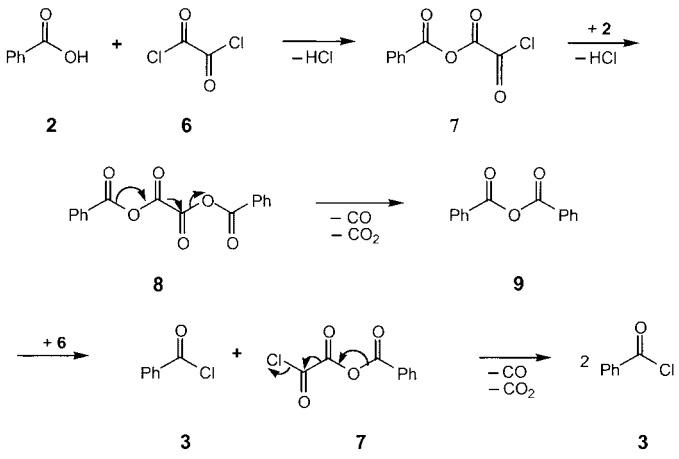


Figure 1. Carbonyl region of the ^{13}C NMR spectra of a) [^{18}O]2-phenyl-2-oxodiazoethane (**4***) and b) [^{18}O]benzoyl chloride (**3***).

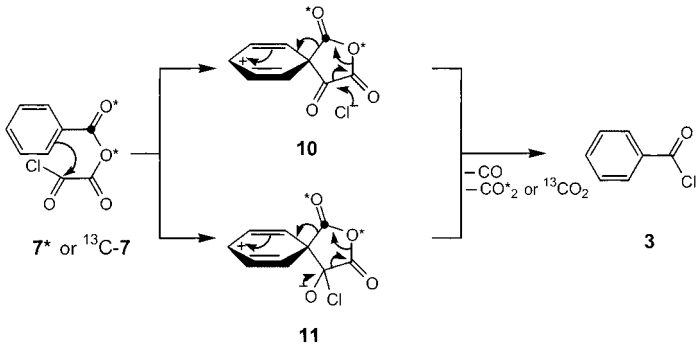
The use of oxalyl chloride (**6**) for the preparation of carboxylic acid chlorides dates back to the classical work of Adams and Ulich.[3] Depending on the amount of **6** used in the reaction with carboxylic acids, either carboxylic acid anhydrides **9** (<1 equiv) or acid chlorides (>2 equiv) are formed. Mixed anhydride **7** and in some cases isolable diacyloxalates **8** have been shown to exist as intermediates in the reaction (Scheme 2).

The carbonyl group of benzoic acid should, in principle, be found intact in benzoyl chloride irrespective of the course of the reaction. Our observation, that the oxygen atom of the carbonyl group undergoes an appreciable oxygen-atom exchange indicates that this view presents only an incomplete picture of the actual processes involved in the formation of benzoyl chloride.



Scheme 2. General reaction of carboxylic acids with oxalyl chloride, with benzoic acid given as a specific example.

An intramolecular Friedel–Crafts attack at the *ipso* position of the intermediate **7*** parallel to the collapse of **7*** to **3*** (following the mechanism postulated by Adams and Ulich[3]) is a plausible explanation for the loss of ^{18}O labeling in **3***. Thus, unlabeled **3** could be formed via a spiro-type σ-complex (either **10** or **11**) with concomitant elimination of CO and labeled CO_2 (Scheme 3). This explanation would demand that all the benzoic acid undergoing a loss of isotope labeling should in fact loose the whole carbonyl group. Thus, a corresponding loss of the ^{13}C isotope labeling should take place when using [carboxy-^{13}C]benzoic acid (^{13}C-**7**).



Scheme 3. Intramolecular *ipso* attack in the intermediate **7*** or ^{13}C-**7**; demands the loss of ^{18}O from **7*** and the loss of ^{13}C from ^{13}C-**7** (not observed), ⋆ = ^{18}O, ● = ^{13}C.

Young and Robinson[4] have converted sodium [carboxy-^{13}C]benzoate into [carbonyl-^{13}C]benzoyl chloride with complete retention of ^{13}C marking, by reaction with oxalyl chloride in the presence of pyridine. In this reaction, ^{13}C-**7** as an isotopomer of **7*** should be formed in the first partial step by elimination of NaCl. The absence of loss of ^{13}C labeling consequently excludes the intramolecular *ipso* attack. However, this could be a result of the presence of pyridine, which catalyzes the collapse to labeled [carbonyl-^{13}C]benzoyl chloride (^{13}C-**3**) and restrains the competing intramolecular Friedel–Crafts acylation (^{13}C-**7**→**3**; Scheme 4).

This consideration made it necessary to treat [carboxy-^{13}C]benzoic acid with oxalyl chloride under the same conditions as for **2*** and to conduct an isotope analysis of the benzoyl chloride thus formed. The hydrolysis of the resulting benzoyl chloride obtained to benzoic acid and the mass spectrometric analysis of the latter shows the complete retention of the ^{13}C enrichment (89.5% ^{13}C).

Our studies lead to the surprising result that in the reaction of benzoic acid with an excess of oxalyl chloride to give benzoyl chloride, the carbonyl oxygen atom is exchanged to an extent of 60%, while at the same time the carbon atom of the carbonyl group retains its identity.

To explain these results, we propose the reversible formation of the 1,3-dioxetanes **12**[5] or alternatively the 1,3,5-trioxanes **13** or **14** from benzoyl chloride and oxalyl chloride (Scheme 5). Such processes and intermediates ex-

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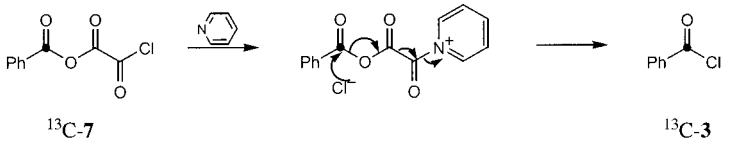
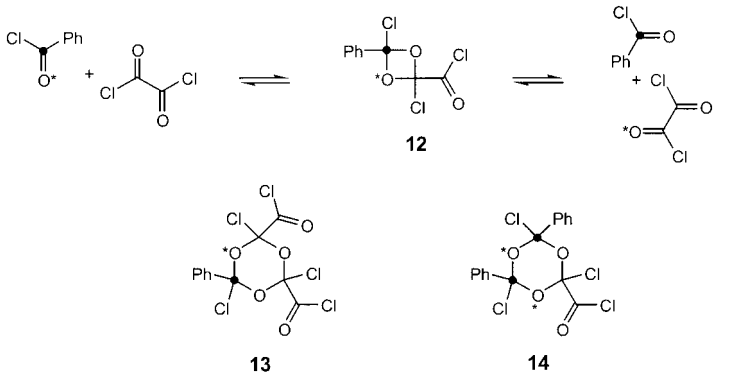


^{13}C-**7** ^{13}C-**3**

Scheme 4. Catalytic acceleration of the breakdown of ^{13}C-**7** to ^{13}C-**3** by pyridine.



12 **13** **14**

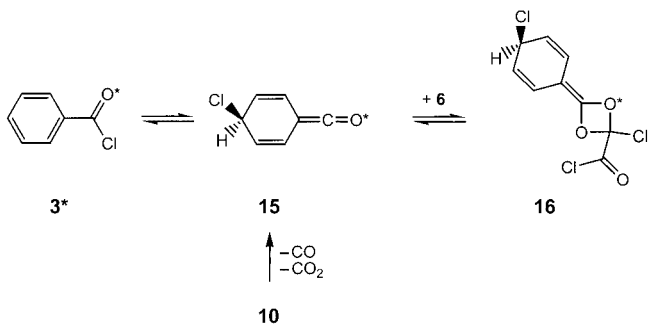
Scheme 5. Oxygen exchange between [^{18}O]benzoyl chloride (**3***) and oxalyl chloride (**6**) via 1,3-dioxetane **12** or the 1,3,5-trioxanes **13** and **14**.

plain the equilibration of the oxygen atoms of benzoyl chloride and oxalyl chloride without an intermolecular exchange of carbonyl carbon atoms in accordance with our experimental observations.

In principle, the same outcome would result from similar equilibria between the starting material benzoic acid (**2**) and the intermediates **7**, **8**, and **9** on one side, and oxalyl chloride (**6**) on the other side, these equilibria would be established simultaneously on the formation of benzoyl chloride (**3**). Because **3** possesses the highest carbonyl reactivity of all the benzoic acid derivatives present in the reaction mixture, we consider it as the most suitable candidate for this role.

Finally, as an especially reactive carbonyl compound, the formation of intermediate cyclohexadienylideneketene **15**[9] through isomerization of benzoyl chloride (**3***) or the decay of the ion pair **10** can be considered (Scheme 6). The intermediate **15** could undergo an oxygen-atom replacement with oxalyl chloride (**6**), for example, via **16** in an analogous manner.

We used exactly three equivalents of oxalyl chloride for the reaction with benzoic acid. Two equivalents from the oxalyl chloride remain after formation of benzoyl chloride (**3**) to set up the equilibrium with **12**, or **13** and **14** as intermediates. Thus, for the distribution of the oxygen atoms the ratio ^{16}O:^{18}O is 4:1. Therefore under complete equilibration, the benzoyl chloride (**3***) resulting from **2*** should contain 20% of the ^{18}O labeling. After a total reaction time of 1 hour, we find an enrichment of 39.8% ^{18}O, which shows that the oxygen-exchange process has not yet reached the equilibration stage. A further loss of ^{18}O marking is to be expected for longer reaction times.



3* **15** **16** **10**

Scheme 6. Oxygen Exchange via ketene intermediate **15**.

Received: June 28, 2002 [Z19636]

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