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Priority Communication

# Zwitterion formation: a feasible mechanism for the Pt-catalyzed enantioselective hydrogenation of ketones?

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**Abstract**

Recently a new mechanism for the enantioselective hydrogenation of (activated) ketones has been suggested, involving a zwitterionic intermediate between the tertiary amine function of the chiral modifier and the keto–carbonyl group of the reactant. The present NMR study indicates that the mechanistic model is probably based on erroneous interpretation of the experimental data; the NMR spectra that have been reported for zwitterion formation may arise from an aldol addition product between the ketone and solvent acetone. Steric effects and the regioselectivity of the hydrogenolysis of the hypothetic zwitterionic intermediate also exclude this mechanism for ketone hydrogenation on Pt.



*Keywords:* Zwitterionic intermediate; NMR, Trifluoroacetophenone; Dabco; Acetone; Aldol-reaction; Cinchonidine; Platinum; Asymmetric hydrogenation; Mechanism

## 1. Introduction

The enantioselective hydrogenation of activated ketones was discovered more than 25 years ago [1], but there is still no agreement on the possible mechanism(s) of these reactions [2]. Excluding the early "template" model [3], all other models assume a 1:1 interaction between the chiral amine or amino alcohol-type modifier and the reactant. The numerous mechanistic models may be divided into two major groups, depending on the chemical nature of the crucial attractive interaction between the amino group and the ketone. One possibility is the formation of an N–H–O-type hydrogen bond, representing the interaction of the protonated amine with the keto O (in acidic medium [4–7]) or the interaction between the amine and the half-hydrogenated state of various ketones [8–12]. An analogous model assumes an N–H–O-type H-bond involving the ester carbonyl O atom of methyl pyruvate [13]. Some other ideas are based on the interaction of the chiral amine as a nucleophile with the keto C atom [14–16]. Recently, even the formation of a covalent C–N bond leading to a zwitterionic intermediate has been suggested [17–20].

Only two of the above-mentioned mechanisms are supported by direct experimental evidence. The N–H–O-type interaction between CD and ketopantolactone was observed by in situ ATR-IR spectroscopy on $Pt/Al_2O_3$ [21], including high-pressure conditions [22]. The model assuming zwitterionic intermediates has been justified by an early [23] and two recent [18,19] NMR studies on the interaction between tertiary amines and 2,2,2-trifluoroacetophenone derivatives. In the past we have studied intensively the interaction of tertiary amine-type modifiers with various activated ketones (including fluorinated ketones) by spectroscopic methods but never found any indication of a covalently bound adduct. Intrigued by this experience, we reinvestigate the phenomenon here by NMR spectroscopy.

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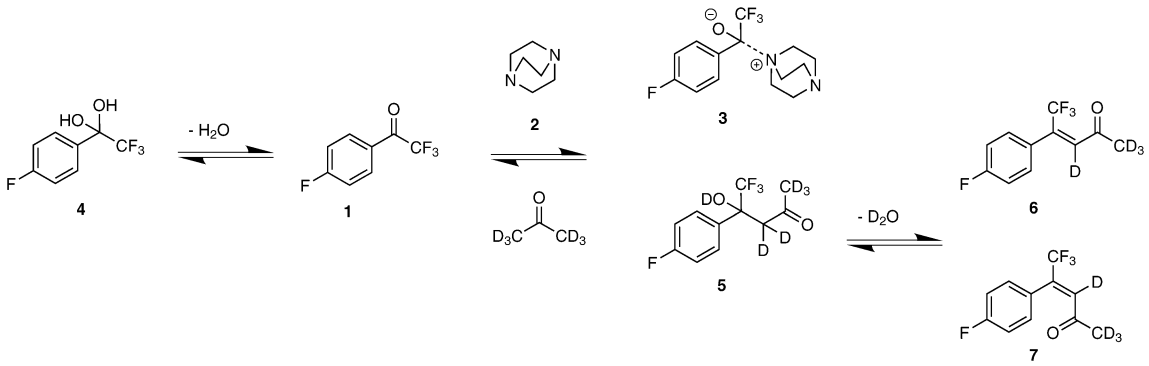


Scheme 1. Possible reactions of 2,2,2-trifluoroacetophenone **1** in the presence of water, Dabco **2**, and acetone.

## 2. Experimental

1,1,1,3,3-Pentadeutero-5,5,5-trifluoro-4-(4′-fluoro-phenyl)-4-hydroxy-2-pentanone **5** was synthesized in analogy to ketol **2** in Ref. [24] (see supporting information). Dabco (1,4-diazabicyclo[2,2,2]octane, **2**, Lancaster, 0.68 mass% water as determined by Karl Fischer titration) was used as received.

$^{13}C$ and $^{1}H$ NMR spectra were recorded on a Bruker Avance 500 spectrometer with TMS as an internal reference. $^{19}F$ NMR spectra were recorded on a Bruker BZH 200/52 spectrometer. The $CF_3$ signal of 4′-fluoro-2,2,2-trifluoroacetophenone **1** (Scheme 1) was set at +5.9 ppm (relative to trifluoroacetic acid) to be comparable to the data in the early report by Schilling and co-workers [23].

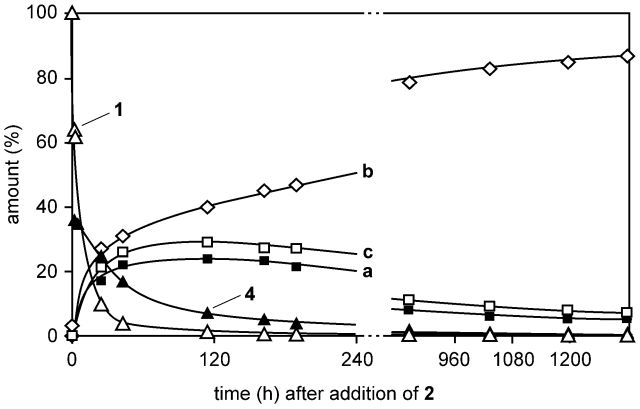


Fig. 1. A sample of 0.1 mmol **1** and 0.5 mmol Dabco **2** dissolved in ca. 0.7 ml *d*-acetone. The evolution of the products was followed by $^{19}F$ NMR during a period of 55 days.

## 3. Results

### 3.1. Solvent effect

In 1980 Schilling et al. [23] published an NMR spectrum as evidence for the equilibrium formation of a zwitterionic adduct **3** from the tertiary amine Dabco **2** and the fluorinated ketone **1** in *d*-acetone (see Scheme 1). Subsequent NMR measurements with other $\alpha,\alpha,\alpha$-trifluoromethyl ketones [19] confirmed the formation of a zwitterionic adduct, though explicitly only in acetone [18]. To clarify the situation, we repeated the original experiment with **1** and Dabco as models for the activated ketone and tertiary amine modifier, respectively (Scheme 1). When Dabco was added to a solution of **1**, the signals of the hydrate **4** appeared immediately. Unfortunately, even a freshly opened bottle of Dabco contained some water (0.68 mass%), and the amine was used in excess relative to the ketone. (This complication was mainly absent when quinuclidine instead of Dabco was applied.) When Dabco was added in fivefold excess to a solution of **1** in *d*-acetone, it took more than 1.5 h until small additional signals could be detected by $^{19}F$ NMR; these signals correspond to those reported by Schilling et al. [23]. Altogether three new sets of fluorine signals could be followed that, in contrast to Schilling's observation [23], did not reach equilibrium even after 55 days at ambient temperature (a, b, and c in Fig. 1). Importantly, the experiments revealed no additional signals that could be traced to the Dabco part of **3**; the interpretation of this fragment is missing in the literature.

Formation of the hydrate was very fast. It is very unlikely that the zwitterion **3** could not be detected simultaneously with the hydrate, because Dabco was present in large excess compared with the amount of water and Dabco is a much stronger nucleophile than water. It was shown that the addition of N-nucleophiles to 2,2,2-trifluoroacetophenone was faster than its hydration [25].

A crucial observation was that formation of the new products (a–c) was highly dependent on the concentration of acetone in the sample. When a 1:5 mixture of acetone:*d*-THF was applied as solvent, the reaction was much slower than in acetone. When the experiment shown in Fig. 1 was repeated in *d*-THF, no new signals in addition to those of hydrate could be detected even after 27 h. Note that *d*-THF is typically used as a solvent when highly polar intermediates have to be stabilized during the reaction [26].

When the interaction of **1** and Dabco was investigated in another weakly polar solvent, $CD_2Cl_2$, a white precipitate dropped out quickly. This compound could be identified as a chloride salt of the N-chloromethyl derivative of Dabco.

The analogous precipitate did not form when quinuclidine was used instead of Dabco, but the zwitterionic adduct could not be detected either. We extended the study in $CD_2Cl_2$ to other fluorinated ketones (2,2,2-trifluoroacetophenone and 1,1,1-trifluoro-2,4-pentanedione) and other strong, cyclic and acyclic N-bases (quinuclidine and triethylamine), but no zwitterionic adduct could be found.

### 3.2. Identification of the products in acetone

The kinetics of the interaction of **1**, Dabco, and acetone, based on $^{19}F$ NMR analysis, is shown in Fig. 1. The hydrate **4** formed immediately with traces of water in Dabco. Subsequently, both **4** and **1** were consumed and three new species appeared with distinct chemical shifts around −2.9 for the $CF_3$ signal and −37.7 for the aromatic F signal. As mentioned previously, the slow formation of the products a, b, and c was limited to the presence of acetone. The time-dependent changes indicate that of the three adducts, b seems to be the most thermodynamically stable species.

On the basis of earlier studies on the interaction of 2,2,2-trifluoroacetophenone with water and acetone [24], and with various nucleophiles [25], interaction of the activated ketone **1** with acetone in the presence of the sufficiently strong base Dabco should afford the aldol product **5** and, after elimination of water, **6** and **7** (Scheme 1). Self-condensation of acetone in the presence of Dabco was not observed even after 1 month. Despite the steric repulsion between the ring and the carbonyl group in the *cis*-isomer **7**, such compounds are stable and can be synthesized [24].

The proposed Scheme 1 is in line with the NMR analysis: after 6 days, when the concentrations of species a and c in Fig. 1 were close to their maximum, three additional $^{13}C$ carbonyl signals were observed at 205.7 (presumably from **5**), 203.6, and 203.3 ppm. The $^{13}C$ NMR spectrum of the mixture is shown in Fig. 2. The positions of the latter two signals, which were poorly visible again after 50 days, fit well with the carbonyl signals of the aldol condensation products **6** and **7** [24], even though the corresponding unsaturated $^{13}C$ signals of these compounds could not be identified unambiguously. Because of direct coupling with D and long-range coupling with $F_3$ we would expect $2 \times 2$ sets of multiplet structures of low intensity between 130 and 140 ppm, which is the region where the aromatic signals were found. The $^{13}C$ quartets of the $CF_3$ group of **5**, **6**, and **7** are expected at similar frequency around 126 ppm, where indeed three quartets were found.

Let us consider the most characteristic quartet at 75.7 ppm, upon which the identification of the zwitterion was based earlier [23]. After 6 days overlapping quartets of different intensities were found, and after 50 days only the most intense quartet remained. The probable explanation for this is the formation of **5** (quartet) and deuterized **5** (OD instead of OH), which gives a quartet that is further split into a triplet by D via O. The chemical shifts are almost identical and the signals overlap. With time OD was exchanged to OH, and the "simple" quartet remained. The quintet of C(3) of **5** at 46 ppm was almost hidden behind the broad Dabco signal, but part of the fine structure could be seen at higher field. Additional C(1) septets that would correspond to **5**, **6**, and **7** at slightly lower field than the *d*-acetone signal could be clearly seen around 31 ppm. Note that in the literature [23] the signals above 190 and below 65 ppm have been neglected.

From these results we assumed that **5** and b should be identical. To verify this assumption we synthesized **5** and added small amounts (ca. 20–25% relative to b) to the reaction mixture after 55 days. As a result, the characteristic signals of b increased, confirming that the major species is **5**, and not the zwitterion **3**. Moreover, we could never find any signal that could originate from the positively charged Dabco part of **3**. These signals cannot be overlooked, because of their intensity ($3\times$ $CH_2$ next to $N^+$). These data are completely missing from the former reports that suggested zwitterion formation [23]. Note that the signals at 48.5, 61.7, 71.2, and 73.8 ppm were already present when **2** was measured in *d*-acetone in the absence of **1**. Therefore, they cannot be traced to **3**.

To identify species a and c we have to consider the spectral data of **5**, which indicate strong intramolecular hydrogen bridges between the OH group and either the carbonyl or the $CF_3$ group. Different conformers/rotamers that would also have slightly different spectral properties can coexist in solution, but in the presence of Dabco they equilibrate. Moreover, the conformers/rotamers of **5** have identical chemical shifts for the $^{19}F$ signal of the aromatic F and for the aromatic $^{13}C$ signals, which was not the case for a, b, and c. If we consider the different spectral properties for the aromatic part and particularly the two carbonyl signals at 203.6 and 203.3 ppm that formed in the early stage of the reaction (see Fig. 2), the aldol products **6** and **7** are the most probable candidates for species a and c. The slow rehydration of **6** and **7** to **5** is facilitated by the dehydration of **4** to **1** (Scheme 1).

## 4. Discussions

A major source of difficulties in clarifying the real nature of interactions during the enantio-differentiating step is the numerous side reactions of activated ketones, including the Pt-catalyzed oligomerization and decarbonylation, and the amine-catalyzed aldol reaction and cyclization [27]. As a result, most mechanistic ideas in heterogeneous enantioselective catalysis are based on assumptions and (at best) calculations, and reliable experimental evidence is difficult to provide. A recent proposal for the mechanism of enantioselective hydrogenation of ketones on cinchona-modified Pt is based on the NMR observation of quaternarized (zwitterionic) adducts between cyclic tertiary amines and $\alpha,\alpha,\alpha$-trifluoromethyl ketones [17–20]. However, our detailed NMR analysis, involving several fluorinated ketones, tertiary amines, and apolar or polar solvents, gave no

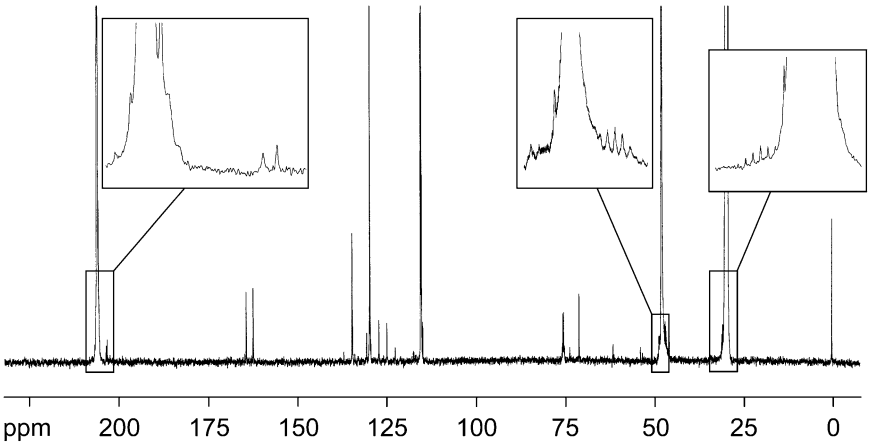


Fig. 2. $^{13}$C NMR spectrum of 0.1 mmol **1** and 0.5 mmol Dabco **2** in *d*-acetone after 144 h. The regions where aldol addition can be observed are enlarged.

hints to the formation of a zwitterionic adduct. Nevertheless, the $\alpha,\alpha,\alpha$-trifluoromethyl ketone **1** was not unreactive: the basic amine catalyzed the hydration and the aldol reaction of the activated ketone with acetone, as depicted in Scheme 1.

In addition to this experimental evidence, the zwitterionic model is not favored also because of steric effects. Nucleophilic attack of the quinuclidine N atom of cinchona alkaloids on the carbonyl C atom of small cyclic ketones and formation of a zwitterionic adduct are improbable, particularly when the bulkiness around the N atom is considered. However, good to high ee's have been achieved with these substrates, including ketopantolactone [28], cyclohexane-1,2-dione [29], cyclic $\alpha$-keto ethers [30], pyrrolidine-2,3,5-triones [12,31], and some isatin derivatives [32].

Another critical point is the rate and regioselectivity of the hydrogenolysis of the zwitterionic C–N$^+$ bond. Hydrogenation of activated ketones is very fast on Pt, but this metal is a poor choice for C–N bond hydrogenolysis, and successful reactions are rare. In both examples cited in the original mechanistic proposal [17], the C–N$^+$ cleavage occurs in the benzylic position [33,34], which is no option for the hydrogenation of aliphatic ketones, for example, pyruvate esters on cinchona-modified Pt. Furthermore, when naphthylethylamine is used as a modifier, cleavage of the analogous zwitterionic C–N$^+$ bond, if it would occur at all, would lead to ethylnaphthalene and a carbinolamine derived from the ketone. The modifier would be consumed rapidly, and the reaction would lead to an (almost) racemic product, in contrast to the observations [7].

## 5. Conclusions

The presented NMR study provides strong experimental evidence against a recent mechanistic model for the Pt-catalyzed enantioselective hydrogenation of ketones that is based on a zwitterionic intermediate between tertiary amines and activated ketones. The NMR spectra that have been used to justify the existence of such an intermediate probably arise from an aldol addition product between the $\alpha,\alpha,\alpha$-trifluoromethyl ketone and the solvent acetone, and the reaction is catalyzed by the tertiary amine used as a model for the chiral amine modifier.

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## Supporting information

The online version of this article contains additional supporting information (synthesis of **5** and detailed NMR spectra).

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