

# Correction to “Reactivity of (Vicinal) Carbonyl Compounds with Urea”

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In the original paper, triformylmethane (TFM) was one of the compounds with the seemingly highest reactivity with urea at neutral pH. Unfortunately, after having a closer look at the molar buffer capacity of the solvent (phosphate buffered saline, PBS) used in the kinetic experiments involving TFM, we concluded that the pH was not well controlled when this specific compound was allowed to react with urea. In fact, the total amount of (highly acidic) TFM ( $pK_a$  2<sup>1,2</sup>) in the reaction mixture far exceeded the buffer capacity of the solution, meaning that the reaction took place at low pH.

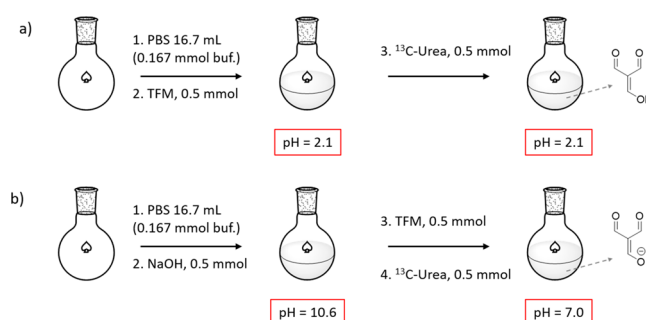
To verify whether the acidic nature of TFM indeed has had an effect on the reaction with urea, the kinetic study involving TFM was repeated while experimentally measuring the pH at all stages of the reaction. Additionally, a second experiment was conducted, in which the pH was corrected by adding an equimolar amount of NaOH prior to reaction to neutralize the acidic TFM. Reinvestigation was not necessary for the other (poly)carbonyl compounds reported in this study, as either the pH was already confirmed experimentally (Table 3, entries 11 and 12), or did not play a role as the carbonyl compound is not acidic in nature (entries 10, 13–17).

In procedure A, the kinetic study originally reported (see for details: “General Procedure for the Kinetic Analysis of the Carbonyl Compounds with Urea” in the original paper) was exactly repeated using TFM as the carbonyl compound, while measuring the pH of the reaction mixture before and after the addition of each reagent. In procedure B, the same experiment was repeated with the addition of 0.5 mmol of NaOH (1 equiv) prior to the addition of TFM.

The order of addition of reagents and measured pH values are summarized in Figure 1 for both experiments. Notably, it can be seen that the final pH of the reaction mixture of urea and TFM in PBS (Figure 1a) was 2.1, due to the acidic nature of TFM. This means that the  $k_2$  value of  $18.4 \pm 5.2 \text{ M}^{-1} \text{ h}^{-1}$  originally reported for TFM at pH 7.4 was actually determined at a pH of 2 and was therefore erroneously reported in Table 3 of the original paper.

When an equimolar amount of NaOH was added prior to the reaction, the pH of the final reaction mixture was 7.0 (Figure 1b). It should be noted that under these conditions TFM is almost exclusively present in its sodium enolate form.

The kinetics of the reaction between TFM (enolate) and  $^{13}\text{C}$ -urea were analyzed by means of  $^{13}\text{C}$  NMR using  $\text{Me}_2\text{SO}_2$



**Figure 1.** Experimental conditions and order of addition of reactants in two kinetic studies between triformylmethane and  $^{13}\text{C}$ -urea. (a) Exact repetition of previous work. The final pH of the reaction mixture was 2.1. (b) Repetition of previous work with pH adjustment (i.e., an equimolar amount of NaOH was added in advance to neutralize the acidic TFM). The final pH of the reaction mixture was 7.0.

as an internal standard, as described.<sup>1</sup> At pH 2 a rapid reaction took place between TFM and urea (Figure 2a,  $k_2$  value  $18.4 \pm 5.2 \text{ M}^{-1} \text{ h}^{-1}$ ). However, at pH 7.0 no reaction was observed within the first hour between TFM (enolate) and urea (Figure 2b).

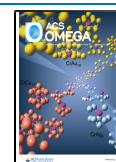
## DETAILS OF THE CORRECTION

We added P. J. Driest as a first author of this correction because the discovery of the mistake, repetition of the experiment, and drafting of this correction were done by him.

Based on these new results described above, we corrected the table that showed the  $k_2$  values of aliphatic (poly)carbonyl compounds (i.e., Table 3, corrected version shown below). As seen, the general trends regarding urea reactivity within this class of compounds are more in line with expectation now. I.e., at pH 7 low urea reactivity is seen for all aliphatic (poly)carbonyl compounds tested. At pH 2, a high urea reactivity is observed for an increasingly optimized chemical structure facilitating

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**Table 3. Corrected. Structural Formulas of Tested Aldehydes and Ketones and the Determined  $k_2$  Values of Their Reaction with Urea in PBS at 323 K**

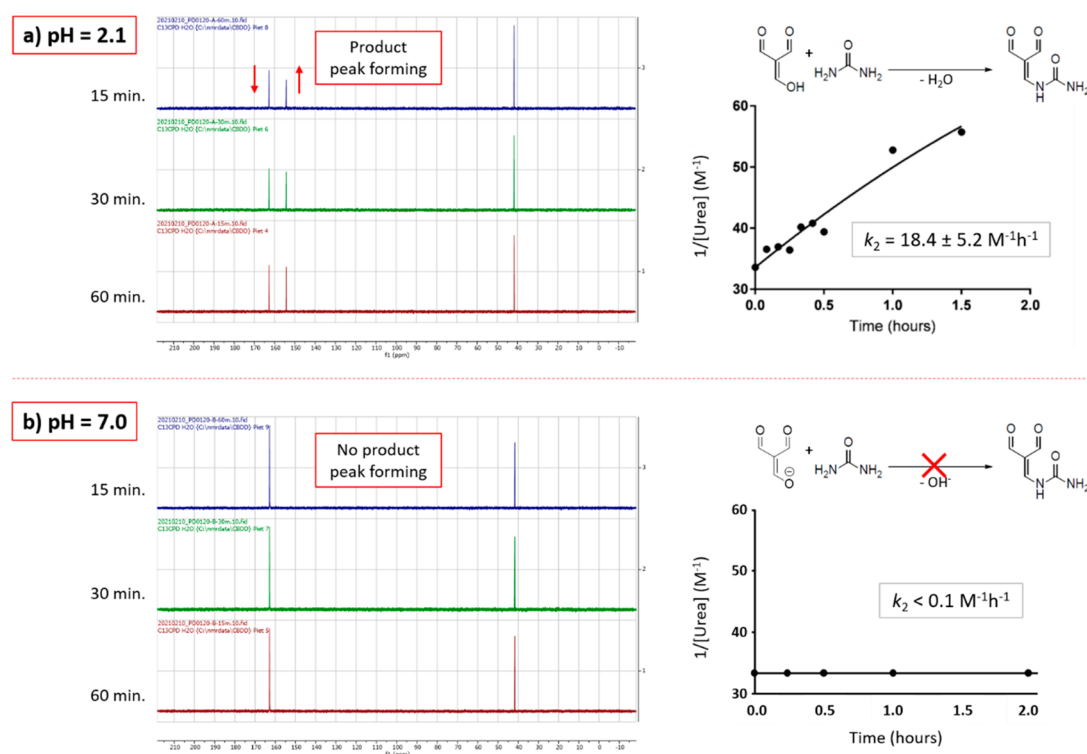
Entry	Structure	$k_2$ [ $M^{-1}h^{-1}$ ] in PBS, pH = 7	$k_2$ [ $M^{-1}h^{-1}$ ] in PBS, pH = 2
9		< 0.1 <sup>a</sup>	18.4 ± 5.2 <sup>a</sup>
11 <sup>b</sup>		< 0.1	18.1 ± 2.3
12 <sup>c</sup>		< 0.1	10.8 ± 0.8
13		< 0.1	1.0 ± 0.1
10		< 0.1	-
14		< 0.1 <sup>d</sup>	-
15		< 0.1 <sup>d</sup>	-
16		< 0.1 <sup>d</sup>	-
17		< 0.1 <sup>d</sup>	-

<sup>a</sup>Measured at 293 K instead of 323 K. <sup>b</sup>1,1,3,3-Tetramethoxypropane in PBS was stirred at pH 2 for 30 min at RT after which the pH was adjusted (to pH 2 or 7.4), and urea was added to the reaction mixture. <sup>c</sup>2,5-Dimethoxytetrahydrofuran was stirred in PBS at pH 2 for 30 min at 293 K after which the pH was adjusted (to pH 2 or 7.4), and urea was added to the reaction mixture. <sup>d</sup>Measured both in PBS and 1:1 PBS/DMSO as solvent at 323 K.

intramolecular ring closure, as presented in Scheme 4B of the original paper. In other words, at low pH the following general order of reactivity toward urea is observed for aliphatic (poly)aldehydes: 1,3,3'-trialdehyde > 1,3-dialdehyde > 1,4-dialdehyde > 1,5-dialdehyde. It should be noted that the  $k_2$  value of TFM at pH 2 was determined at a lower temperature than those of the other aliphatic (poly)carbonyl compounds to lower the reaction rate, signifying that TFM still has a (significantly) higher urea reactivity than e.g. malonaldehyde (entry 11) under these conditions.

It should be noted that  $pK_a$  values were not taken into account in the calculation of the Gibbs free energies for hydration and urea complexation either. The reported numbers for TFM are thus only applicable for undissociated TFM and thus not to the TFM enolate anion. As TFM is predominantly present in its enolate form at pH 7, the calculated numbers for this compound have no physical meaning under physiological conditions.

In conclusion, contrary to what we reported previously, TFM is not urea reactive at a pH of 7 ( $k_2 < 0.1 M^{-1} h^{-1}$ ). At a low pH of 2.1 on the other hand, TFM is highly urea reactive,



**Figure 2.**  $^{13}\text{C}$  NMR spectra of reaction mixtures of TFM and  $^{13}\text{C}$ -urea at different time points. (a) Repetition of previous work (no pH adjustment). A (rapid) reaction takes place between TFM and urea. (b) Repetition of previous work with pH adjustment. No reaction is observed within the first hour.

demonstrating a  $k_2$  value of  $18.4 \pm 5.2 \text{ M}^{-1} \text{h}^{-1}$ , which is the value that was previously (erroneously) reported for pH 7.4. The strong pH dependency in urea reactivity is attributed to TFM's acidic nature, which causes TFM to be present in its (unreactive) enolate form at physiological pH.

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