Reversible Regulation of a Benzamidine-catalyzed Aldol Reaction by CO₂

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Dedicated to Professor Gerhard Maas on the occasion of his 60th birthday

The catalytic activity of benzamidine during an aldol reaction was reversibly switched on and off with CO₂ as an orthogonal signal without affecting the converted substrate or products.

Key words: Aldol Reaction, Carbon Dioxide, Benzamidine, Regulated Catalysis

Introduction

Regulation of function on the molecular level by external signals is essential for the design of smart devices and materials [1]. The modulation of reactivity is also a common feature of biological receptors and enzymes, and these natural models inspired chemists to develop chemical analogs of reduced complexity [2]. Apart from physical stimuli like light, magnetic and electric signals, chemical triggers namely pH value, radicals, ions, or gases have been applied for the regulation of chemical functions [3], reactivity [4] or catalytic activity [5]. Gases are particularly advantageous because of their ease of application by gas pressure and removal by other gases or vacuum degassing. During the past decade especially carbon dioxide has attracted interest as a signal, since it can bind reversibly to amines and amidines to form carbamates. These carbamates can easily be decomposed by bubbling N₂ or Ar through the solution and/or by heating. CO₂-controlled molecular switches were used in applications like switchable surfactants [6], sequestering and consecutive separation [7], recovery of a homogeneous catalyst [8] and reversible fixation and release systems for temporary storage [9].

Aldol reactions typically require catalysis, and amidines such as DBU (diazabicyclo[5.4.0]undecane) and TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) are widely used as basic catalysts [10]. The related benzamidine has been described as catalyst for different reactions, but to the best of our knowledge it has never been used as catalyst in aldol reactions [11]. However, benzamidine is particularly suitable to reversibly interact with carbon dioxide. We describe here the reversible deactivation of a benzamidine catalyst during an aldol reaction using CO₂/N₂ cycles and report optimized reaction conditions to quantitatively control the reaction progress at atmospheric pressure.

Results and Discussion

The aldol reaction is a well studied C–C bond-forming reaction with miscellaneous applications [12]. The reaction is catalyzed by bases [13] or acids [14], metal- [15] or organocatalysts [16]. Amines and amidines are widely used as basic catalysts, and they are known to react with CO₂ to be either protonated by H₂CO₃ or carbamoylated depending on the basicity, steric hindrance, conjugation and induction effects, and the solvent. This step can be inverted by briefly bubbling nitrogen, argon or simply air through the solution. Increasing the temperature to 40 – 60 °C typically accelerates the release of CO₂. We have investigated the effect of carbon dioxide on the reaction progress of the aldol addition of 4-nitrobenzaldehyde to cyclohexanone in different solvents using several amine bases (Scheme 1).

DBU is reversibly protonated upon CO₂ saturation [6,8], and 10 mol-% of the base were used to catalyze the above aldol reaction in different solvent systems. For the formation of a protonated base, the presence of water, an alcohol or an amine is required. “Wet” DMSO (> 700 ppm water), water, acetonitrile, methanol and ethanol were tested as solvents for the
aldol reaction and the reversible protection of the amidine base. The aldol reaction proceeded cleanly in wet DMSO and stopped after CO2 saturation of the solution. However, the formation of the CO2/amidine adduct could not be reversed by the addition of N2 gas in order to reawaken the conversion of the aldol addition. Alcohols (MeOH, EtOH) as solvent showed very good reversibility of the base inactivation, but led to the formation of hemiacetals which hamper kinetic monitoring of the reaction. In water and acetonitrile (ACN) the reaction either did not proceed, or the reversibility of the base inactivation by CO2 was limited. A solvent mixture of ACN:H2O, 1:1 (v:v), gave a clean conversion for the aldol reaction and allowed reversible inactivation of the amidine base by CO2. Unfortunately, phase separation occurred during the course of the reaction, making the spectroscopic monitoring of the conversion difficult. A stable homogeneous solvent system was obtained after reducing the water content to ACN:H2O = 9:1 (v:v).

Next, different bases were tested since DBU-catalyzed reactions lead to undesired side products, such as aldol condensation and twofold addition to cyclohexanone. Piperidine and the amidine bases mono-, di-, and tri-Boc guanidine, as well as benzamidine were used. Piperidine and benzamidine catalyzed the reaction at a convenient rate and could be reversibly inactivated by carbon dioxide. Benzamidine was chosen for a kinetic study due to the faster completion of the aldol addition.

Benzamidine is reversibly protonated, and not carbamoylated, when CO2 is bubbled into the ACN:H2O, 9:1 (v:v), solution, as confirmed by 13C NMR measurements. The amidine carbon of the free base shows a resonance signal at $\delta = 166.8$ ppm, which is shifted to $\delta = 167.7$ ppm upon introduction of carbon dioxide. In addition a new resonance signal at $\delta = 161.5$ ppm is detected which is assigned to bicarbonate and does not match a carbamate resonance. In the same solvent mixture benzamidine hydrochloride showed a signal at $\delta = 167.7$ ppm for the amidine carbon, reinforcing the above statement. Pure NaHCO3 in D2O gives a resonance at $\delta = 160.5$ ppm [17]. When NaHCO3 was added to the proposed protonated/carbamoylated species in D2O no further signal but an increase of intensity for the signal at $\delta = 160.4$ ppm was detected, supporting the evidence for a protonated species.

Benzamidine as a base is reversibly inactivated by bubbling CO2 through the solution, while the introduction of N2 restores its basic character (Scheme 2).

The reaction was monitored by 1H NMR spectroscopy following the resonance signals of the benzylic protons of the addition product. The conversion is described by the ratio of the product integrals in relation to the starting material.

All components except cyclohexanone were dissolved in the acetonitrile:water (9:1, v:v) solvent mixture and the solution placed in an NMR tube. This solution was saturated by CO2 gas introduced through a long cannula at r.t. for 5 min. Cyclohexanone was added and CO2 introduction continued for another 5 min. An 1H NMR spectrum was recorded to analyze the composition of the reaction mixture before conversion. The reaction was then started by initial heating to 60 °C for 20 s and then bubbling N2 through the NMR tube for 10 min. After 10 min in the “base-on” state an 1H NMR spectrum was recorded to monitor the progress of the reaction by integration of the benzylic to aldehyde proton resonance signals. Since no side product formation was observed, the ratio of benzylic to aldehyde proton resonance signals was de-
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Fig. 1. 1H NMR-monitored CO₂/N₂-regulated aldol reaction. Left: Developing resonance signals of syn- and anti-benzylic protons during the N₂ and CO₂ cycles between δ = 5.00 and 5.40 ppm. Right: Product to starting material ratio plotted against the overall reaction time. Activation and inactivation cycles are indicated by white and shaded areas. The slopes (product formed/time) during the on-states are 2.2 × 10⁻¹¹ mol s⁻¹, 2.3 × 10⁻¹¹ mol s⁻¹, and 2.2 × 10⁻¹¹ mol s⁻¹, respectively, indicating no significant loss in catalytic activity.

In summary, we have shown that the catalytic activity of a benzamidine base is reversibly switched on and off during an aldol reaction using N₂/CO₂ cycles controlling the reaction progress. During the CO₂ cycles the base is reversibly protonated and not carbamoylated. The reaction progresses during “base on” periods with the same rate as observed in uninterrupted reactions.

The experiments demonstrate that the application of gases as chemical input signal can control an aldol reaction without affecting the converted compounds. Such an orthogonal chemical control mimics allosteric regulation and may find applications in analytical signal amplification or chemical processing of information.

Experimental Section

Benzamidine was obtained from benzamidine·HCl following the procedure of Tobin [18]. 4-Nitrobenzaldehyde (37.8 mg, 0.25 mmol) and benzamidine (6.0 mg, 0.05 mmol, 25 mol-%) were dissolved in H₂O (0.07 mL) and [D₃]ACN (0.63 mL). The solution was transferred into an NMR tube, and the reaction mixture was saturated with CO₂ gas for 10 min using a long cannula. After 5 min, cyclohexanone (0.1 mL, 1.0 mmol) was added to the solution. An 1H NMR spectrum was recorded to analyze the reaction mixture prior to further activation cycles.
to conversion. To start the reaction, N₂ was bubbled through the solution for 10 min after initially heating the mixture to 60 °C for 20 s. To stop the reaction again a CO₂ flow was applied like described above. NMR spectra of the reaction mixture were recorded after each cycle to monitor the reaction progress [19].

[17] NaHCO₃ was not soluble enough in an ACN:H₂O mixture were recorded after each cycle to monitor the reaction. For this reason the addition of NaHCO₃ to the solution for 10 min after initially heating the mixture to 60 °C for 20 s. To stop the reaction again a CO₂ flow was applied like described above. NMR spectra of the reaction mixture were recorded after each cycle to monitor the reaction progress [19].
[18] The loss of ACN upon heating/bubbling was compensated by addition of new ACN.