Reversible Regulation of a Benzamidine-catalyzed Aldol Reaction by CO_2

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Z. Naturforsch. **2009**, *64b,* 1053 – 1056; received June 1, 2009

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 CO_2 as an orthogonal signal without affecting the converted substrate or products.

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

Introduction

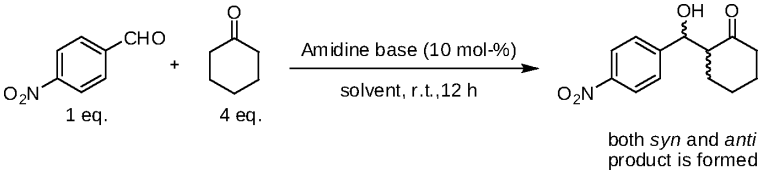
Regulation of function on the molecular level by external signals is essential for the design of smart devices and materials [1]. The modulation of reactivity is also a common feature of biological receptors and enzymes, and these natural models inspired chemists to develop chemical analogs of reduced 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 N_2 or Ar through the solution and/or by heating. CO_2-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 CO_2/N_2 cycles and report optimized reaction conditions to quantitatively control the reaction progress at atmospheric pressure.

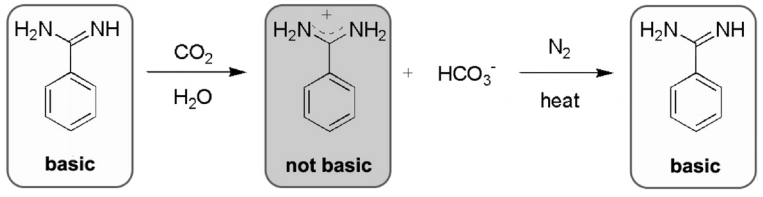
Results and Discussion

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 CO_2 to be either protonated by H_2CO_3 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 CO_2. 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 amidine bases (Scheme 1).

DBU is reversibly protonated upon CO_2 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



Scheme 1. Amidine-catalyzed aldol addition of 4-nitrobenzaldehyde to cyclohexanone.



Scheme 2. Reversible inactivation of a benzamidine base using CO_2 and N_2.

aldol reaction and the reversible protection of the amidine base. The aldol reaction proceeded cleanly in wet DMSO and stoped after CO_2 saturation of the solution. However, the formation of the CO_2 / amidine adduct could not be reversed by the addition of N_2 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 CO_2 was limited. A solvent mixture of ACN:H_2O, 1 : 1 (v : v), gave a clean conversion for the aldol reaction and allowed reversible inactivation of the amidine base by CO_2. 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:H_2O = 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 CO_2 is bubbled into the ACN:H_2O, 9 : 1 (v : v), solution, as confirmed by ^{13}C NMR measurements. The amidine carbon of the free base shows a resonance signal at δ = 166.8 ppm, which is shifted to δ = 167.7 ppm upon introduction of carbon dioxide. In addition a new resonance signal at δ = 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 δ = 167.7 ppm for the amidine carbon, reinforcing the above statement. Pure $NaHCO_3$ in D_2O gives a resonance at δ = 160.5 ppm [17]. When $NaHCO_3$ was added to the proposed protonated/carbamoylated species in D_2O no further signal but an increase of intensity for the signal at δ = 160.4 ppm was detected, supporting the evidence for a protonated species.

Benzamidine as a base is reversibly inactivated by bubbling CO_2 through the solution, while the introduction of N_2 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 CO_2 gas introduced through a long cannula at r. t. for 5 min. Cyclohexanone was added and CO_2 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 N_2 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 proton resonance signals as the sum of the *syn* and the *anti* isomer and the aldehyde proton. Since no side product formation was observed, the ratio of benzylic to aldehyde proton resonance signals was de-

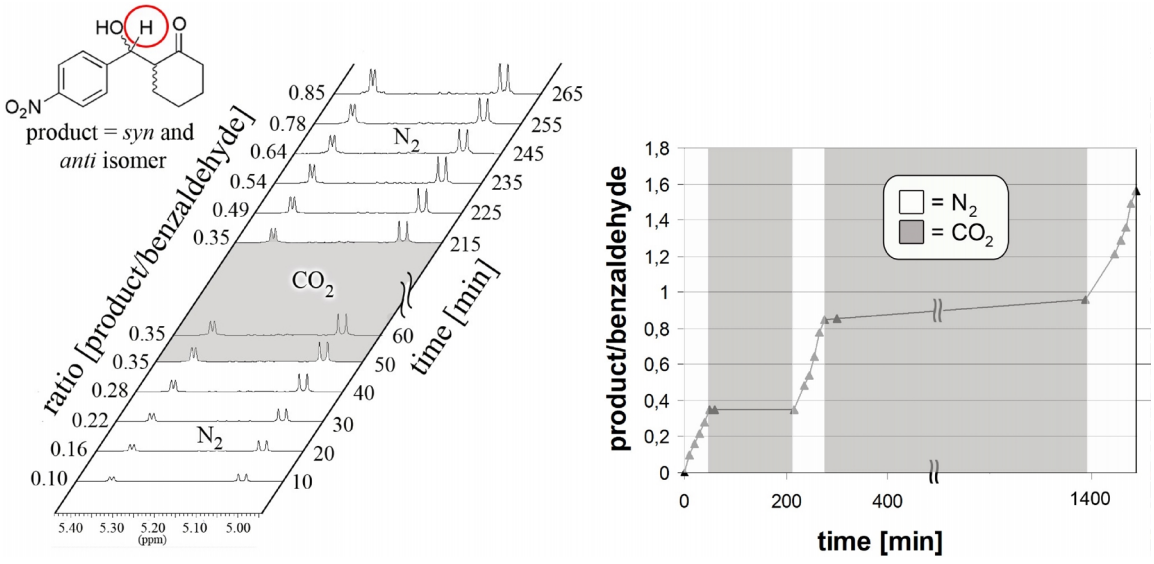


Fig. 1. ^{1}H NMR-monitored CO_2/N_2-regulated aldol reaction. Left: Developing resonance signals of *syn*- and *anti*-benzylic protons during the N_2 and CO_2 cycles between $\delta = 5.00$ and 5.40 ppm. Right: Product to starting material ratio plotted against the overall reaction time. Activation 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.

termined five times every 10 min. Then the reaction was stopped by introducing CO_2 gas, and after another 10 min in the "base-off" state a proton NMR spectrum was recorded which showed that no further conversion occured. When the sample was then stored for 150 min, no additional product formation took place. Another "base-on" state proved that a reversible and repeated switching of the reaction progress by CO_2/N_2 is possible. A very long "base-off" period of 18 h demonstrated the effective silencing of the benzamidine base with little background reaction: An increase of the product/starting material ratio of only 11 %, which corresponds to 0.6 % per h, was observed. Fig. 1 illustrates the developing ratios of product and starting material during indicated "base-on" and "base-off" periods.

In a final activation step the amidine base was deprotonated again to verify the completion of the aldol reaction after several "base-on" and "base-off" cycles. The observed reaction rate after "on" and "off" phases is comparable to that of the unprotected benzamidine. After an overall reaction time of 20 h and 10 min (actual reaction time resulting from subtraction of deactivation phases is 210 min) a product yield of 62 % was reached. The yield of the uninterrupted reaction under otherwise identical reaction conditions (210 min) was determined to be 60 %.

In summary, we have shown that the catalytic activity of a benzamidine base is reversibly switched on and off during an aldol reaction using N_2/CO_2 cycles controlling the reaction progress. During the CO_2 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 H_2O (0.07 mL) and [D_3]ACN (0.63 mL). The solution was transferred into an NMR tube, and the reaction mixture was saturated with CO_2 gas for 10 min using a long cannula. After 5 min, cyclohexanone (0.1 mL, 1.0 mmol) was added to the solution. An ^{1}H NMR spectrum was recorded to analyze the reaction mixture prior

to conversion. To start the reaction, N_2 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 CO_2 flow was applied like described above. NMR spectra of the reaction mixture were recorded after each cycle to monitor the reaction progress [19].

[1] M. V. Peters, R. S. Stoll, A. Kühn, S. Hecht, *Angew. Chem.* **2008**, *120*, 6056 – 6060; *Angew. Chem. Int. Ed.* **2008**, *47*, 5968 – 5972.

[2] N. M. Goodey, S. J. Benkovic, *Nature Chem. Biol.* **2008**, *4*, 474 – 482; L. Zhu, E. V. Anslyn, *Angew. Chem.* **2006**, *118*, 1208 – 1215; *Angew. Chem. Int. Ed.* **2006**, *45*, 1190 – 1196; L. Kovbasyk, H. Pritzkow, R. Krämer, I. O. Fritsky, *Chem. Commun.* **2004**, 880 – 881; Y. Liu, D. Sen, *J. Mol. Biol.* **2004**, *341*, 887 – 892.

[3] T. Yamada, P. J. Lukac, M. Gorge, R. G. Weiss, *Chem. Mater.* **2007**, *19*, 967 – 969; P. G. Jessop, D. J. Heldebrant, X. W. Li, C. A. Eckert, C. L. Liotta, *Nature* **2005**, *436*, 1102.

[4] W. Li, Z. Zhang, B. Han, S. Hu, J. Song, Y. Xie, X. Zhou, *Green Chem.* **2008**, *10*, 1142 – 1145; I. Tokarev, V. Gopishetty, J. Zhou, M. Pita, M. Motornov, E. Katz, S. Minko, *ACS Appl. Mater. Interfaces* **2009**, *1*, 532 – 536.

[5] D. Vomasta, C. Högner, N. R. Branda, B. König, *Angew. Chem.* **2008**, *120*, 7756 – 7759; *Angew. Chem. Int. Ed.* **2008**, *47*, 7644 – 7764; L. Kovbasyuk, R. Krämer, *Chem. Rev.* **2004**, *104*, 3161 – 3187; M. S. Masar, N. C. Gianneschi, C. G. Oliveri, C. L. Stern, S. T. Nguyen, C. A. Mirkin, *J. Am. Chem. Soc.* **2007**, *129*, 10149 – 10158.

[6] Y. Liu, P. G. Jessop, M. Cunningham, C. A. Eckert, C. L. Liotta, *Science* **2006** *313*, 958 – 960.

[7] V. Stastny, D. M. Rudkevich, *J. Am. Chem. Soc.* **2007**, *129*, 1018 – 1019.

[8] S. L. Desset, D. J. Cole-Hamilton, *Angew. Chem.* **2009** *121*, 1500 – 1502; *Angew. Int. Ed.* **2009**, *48*, 1472 – 1474; C. D. Ablan, J. P. Hallet, K. N. West, R. S. Jones, C. A. Eckert, C. L. Liotta, P. G. Jessop, *Chem. Commun.* **2003**, 2972 – 2973.

[9] T. Endo, D. Nagai, T. Monma, H. Yamaguchi, B. Ochiai, *Macromolecules* **2004**, *34*, 2007 – 2009; D. M. Rudkevich, H. Xu, *Chem. Commun.* **2005**, 2651 – 2659; B. Ochiai, K. Yokota, A. Fujii, D. Nagai, T. Endo, *Macromolecules* **2008**, *41*, 1229 – 1236.

[10] W. Ye, J. Xu, C.-T. Tan, C.-H. Tan, *Tetrahedron Lett.* **2005**, *46*, 6875 – 6878.

[11] P. S. Raghavan, V. S. Srinivasan, *Proc. Indian Acad. Sci. (Chem. Sci.)* **1985**, *95*, 375 – 80; A. Marsura, C. Luu Duc, G. Gellon, *Tetrahedron Lett.* **1984**, *25*, 4509 – 10; V. Fiandanese, F. Naso, *J. Chem. Soc., Perkin Trans. 2* **1977**, 1047 – 1051.

[12] J. Mlynarski, J. Paradowska, *Chem. Soc. Rev.* **2008**, *37*, 1502 – 1511; C. H. Heathcock, in *Comprehensive Organic Synthesis*, Vol. 2, (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 133 – 179; R. Mahrwald (Ed.), Modern Aldol Reactions, Vols. 1, 2, Wiley-VCH, Weinheim, **2004**; F. Tanaka, C. F. Barbas, III, in *Enantioselective Organocatalysis*: *Reactions and Experimental Procedures*, (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**, pp. 19.

[13] Y. Orito, S. Hashimoto, T. Ishizuka, M. Nakajima, *Tetrahedron* **2005**, *62*, 390 – 400; M. J. Climent, A. Corma, S. Iborra, A. Velty, *Green Chem.* **2002**, *4*, 474 – 480.

[14] K. Manabea, S. Kobayashi, *Tetrahedron Lett.* **1999**, *40*, 3773 – 3776.

[15] B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003; S. E. Denmark, R. A. Stavenger, *Acc. Chem. Res.* **2000**, *33*, 432 – 440; V. A. Soloshonok, A. D. Kacharov, D. V. Avilov, K. Ishikawa, N. Nagashima, T. Hayashi, *J. Org. Chem.* **1997**, *62*, 3470 – 3479.

[16] P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248 – 5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138 – 5175; P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840 – 3864; *Angew. Chem. Int. Ed.* **2001**, *41*, 3726 – 3748; B. List, *Adv. Synth. Cat.* **2004**, *346*, 1021; B. List, *Chem. Commun.* **2005**, 719 – 722.

[17] $NaHCO_3$ was not soluble enough in an ACN:H_2O (9 : 1) mixture to detect a signal in the ^{13}C NMR spectrum. For this reason the addition of $NaHCO_3$ to the protonated species was done in D_2O where $NaHCO_3$ shows high solubility.

[18] N. J. Green, J. Xiang, J. Chen, L. Chen, A. M. Davies, D. Erbe, S. Tam, J. F. Tobin, *Bioorg. Med. Chem.* **2003**, *11*, 2991 – 3013.

[19] The loss of ACN upon heating/bubbling was compensated by addition of new ACN.