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Heptakis-6-Amino-6-Deoxy-ß-Cyclodextrin as a Catalyst for H/D Exchange

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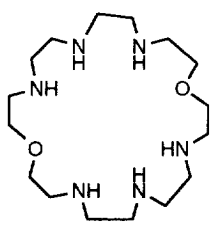
Abstract: Heptakis-6-amino-6-deoxy-ß-cyclodextrin **2** at pD = 6.50, 20°C catalyzes CH/CD exchange in malonic acid, pyruvic acid and acetaldehyde. Accelerations as large as 3800 were observed.

The abstraction of a proton from the alpha position of carbonyl compounds is a physiologically and synthetically important reaction.[1] There are a variety of enzymes[2] which catalyze this proton abstraction under neutral, aqueous conditions using functional groups having pKa-values of up to 15 units below those of the carbon acid substrate. Intramolecular[3a, b] as well as acid-base catalysis[3c, d] have been shown to contribute to the remarkable ability of biocatalysts.

Inspired by the work of Lehn et al.,[4] who used polyaminomacrocycle **1** as an enzyme-like catalyst for the enolization of malonic acid, we decided to investigate heptakis-6-amino-6-deoxy-ß-cyclodextrin **2**[5] as a potential catalyst for H/D exchange. All seven primary amino groups of **2** are positioned at the periphery of the smaller opening of this host molecule, thus creating a possible site for both substrate binding and cooperative proton transfer. Catalyst **2** (0.4 mM) and a substrate **3-14** (5.0 mM, see Table 1) were mixed in



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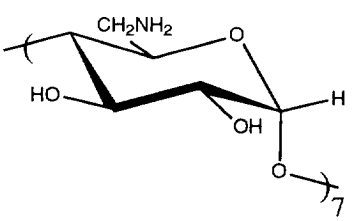


heptakis-6-amino-6-deoxy-β-cyclodextrin **2**

D_2O, the pD[6] was adjusted by the addition of small quantities of diluted NaOD or DCl, and the progress of the reaction was followed by NMR-spectroscopy while observing the disappearance of the protons alpha to

the carbonyl moiety.[7] Despite a 13-fold excess of substrate, the reactions went to completion, demonstrating that a true catalysis was being observed.

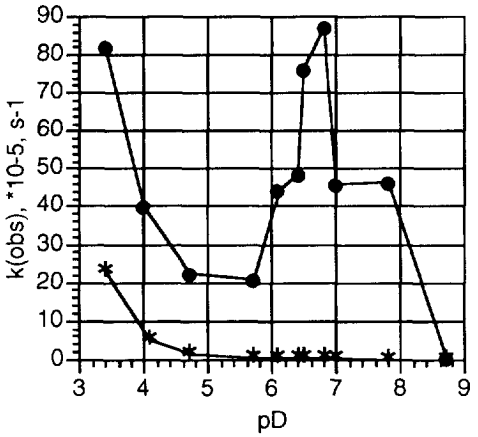
Malonic acid proved to be a good substrate for this reaction: The rate of hydrogen exchange was accelerated by a factor of 150 at pD = 6.50 relative to the uncatalyzed reaction (Table 1). This is somewhat greater than the catalytic effect exerted by polyaminomacrocycle **1** on the same substrate[4] ($k_{(obs,\ cat)}/k_{(obs,\ uncat)}$ ~ 100). The effect of the pD on this reaction (Fig. 1) shows a pronounced maximum at pD = 6.50 - 7.00. This presumably indicates a concerted involvement of both free amino and ammonium groups on the cyclodextrin **2** during catalysis. Addition of a 50 fold excess of NaCl, NaBr and NaI relative to the catalyst did not effect the H/D exchange rate, whereas the addition of 50 equivalents of Na_2SO_4 completely suppressed the catalytic behavior of **2** (data not shown).[8] No complex between malonic acid and **2** was detected by a Job-plot analysis[9] or by a search for saturation behavior.

Table 1. Rate of H/D Exchange catalysed by **2**.

	Substrate	pD	$k_{(obs)}$, s^{-1} in presence [a] of **2**	$k_{(obs)}$, s^{-1} control [b]
3	Malonic acid	6.50 [c]	$7.6 \cdot 10^{-4}$	$5.1 \cdot 10^{-6}$ ($5.0 \cdot 10^{-6}$) [e]
4	Pyruvic acid	4.11	$8.6 \cdot 10^{-5}$	~ 10^{-7} [d]
		6.50	$2.8 \cdot 10^{-4}$	~ 10^{-7} - 10^{-8} [d] ($3.0 \cdot 10^{-7}$) [e]
		8.50	$4.3 \cdot 10^{-4}$	~ 10^{-7} - 10^{-8} [d] ($2.5 \cdot 10^{-6}$) [e]
5	2-Oxo-1-butanoic acid	6.50	$2.5 \cdot 10^{-4}$	~ 10^{-7} - 10^{-8} [d]
6	2-Oxo-1-pentanoic acid	6.50	$1.6 \cdot 10^{-4}$	~ 10^{-7} - 10^{-8} [d]
7	2-Oxo-1-hexanoic acid	6.50	$3.1 \cdot 10^{-4}$	~ 10^{-7} - 10^{-8} [d]
8	3-Methyl-2-oxo-1-butanoic acid	6.50	$3.8 \cdot 10^{-5}$	~ 10^{-7} - 10^{-8} [d]
9	Cyclopropylglyoxylic acid	6.50	≤ 10^{-8} [d]	≤ 10^{-8} [d]
10	Acetaldehyde	6.50	$1.7 \cdot 10^{-4}$	($1.6 \cdot 10^{-6}$) [e]
11	Acetone	6.50	$7.3 \cdot 10^{-7}$	≤ 10^{-7} [d]
12	2-Hexanone	6.50	$1.0 \cdot 10^{-6}$	≤ 10^{-7} [d]
13	Glycolic acid	6.50	--------	--------
14	Phenylacetic acid	6.50	--------	--------

(a) [substrate] = 5.0 mM, [catalyst **2**] = 0.4 mM (b) Dioxane used as internal standard (c) [malonic acid] = 2.5 mM (d) The reaction was followed one month which gave a rough rate estimation of this slow exchange (e) Values in brackets refer to the use of methyl-O-6-amino-6-deoxy-α-D-glucopyranoside **15** (2.8 mM) as catalyst.

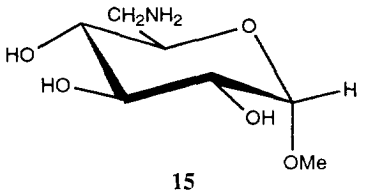
Figure 1. pD Profile for the H/D Exchange of Malonic Acid Catalyzed by **2**.



(•) 2.5 mM malonic acid, 0.4 mM **2**; (*) 2.5 mM malonic acid, 0.23mM dioxane

Various derivatives of 2-oxo-1-carboxylic acids (**4-9**) were also investigated with **2** as a catalyst in this proton exchange reaction (Table 1). The exchange of pyruvic acid **4** and its n-alkyl derivatives **5-7** was accelerated by a factor of 1600- 3800 relative to the uncatalyzed reaction at pD = 6.50, whereas the catalytic effect became less pronounced at more acidic pD values. We also compared the exchange rates of 2-oxo-3-methyl-1-butanoic acid **8** and cyclopropylglyoxylic acid **9**[10] in the presence of **2**. Whereas **8** showed a rate acceleration of more than 300 relative to the uncatalyzed reaction, no H/D exchange was observed in the case of the cyclopropylderivative **9** even after several weeks. Retarded enolization in **9** presumably arises from unfavorable angle strain in an sp^2-hybridized cyclopropyl carbon.

To further check the catalytic behavior of **2**, the H/D exchange of pyruvate **4** was followed using methyl-O-6-amino-6-deoxy-α-D-glucopyranoside **15**,[11] representing the monomeric equivalent of **2**. Incubation of



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pyruvate **4** (5.0 mM) with **15** (2.8 mM, which refers to the effective concentration of amino groups compared to **2**) resulted in only a slight rate enhancement at pD = 8.50 and virtually no rate acceleration at

pD = 6.50[12] (Table 1). This indicates that, due to total protonation at neutral pH, simple amines are poor catalysts, whereas **2** possesses free amino groups even at a neutral pH because electrostatic repulsion lowers pKa values.[13]

Whereas **2** catalyzes H/D exchange in acetaldehyde **10**, only a minor enhancement was observed in the exchange rate of acetone **11** and 2-hexanone **12**. Likewise no catalytic effect was seen for glycolic acid **13** and phenylacetic acid **14**.

In summary, **2** represents a catalyst for the chemoselective H/D exchange in the alpha position of 2-oxo-1-carboxylic acids, malonic acid and acetaldehyde, whereas simple ketones remain virtually unaffected. If intermediates are formed (a possibility with the substrates other than malonate), they must be transient because exchange goes to completion with a large excess of substrate.

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REFERENCES AND NOTES

1. See for instance : Kresge, A. J.; *Pure & Appl. Chem.* **1991**, Vol. *63*, No 2, 213-221 and references therein.
2. Selected examples : (a) Powers, V. M.; Koo, C. W.; Kenyon, G. L.; Gerlt, J. A.; Kozarich, J. W. *Biochemistry* **1991**, *30*, 9255-9263 (b) Stubbe J.; Abeles, R. H. *Biochemistry* **1980**, *19*, 5505-5512 (c) Neidhart, D. J.; Howell, P. L.; Petsko, G. A. *Biochemistry* **1991**, *30*, 9264-9273 (d) Xue, L.; Talalay, P.; Mildvan, A. S. *Biochemistry* **1990**, *29*, 7491-7500.
3. (a) Hine, J. *Acc. Chem. Res.* **1978**, 11, 1-7. (b) Hine, J.; Sinha, A. *J. Org. Chem.* **1984**, *49*, 2186-2190. (c) Gerlt, J. A.; Kozarich, J. W.; Kenyon, G. L.; Gassman, P. G. *J. Am. Chem. Soc.* **1991**, *113*, 9667-9669. (d) Zeng, B.; Pollack, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 3838-3842.
4. Fenniri, H.; Lehn, J.-M.; Marquis-Rigault, A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, No 3, 337-339.
5. (a) Compound **2** was synthesized according to the following literature : Ashton, P. R.; Koeniger, R.; Stoddart, J. F. *J. Org. Chem.* **1996**, *61*, 903-908. (b) All compounds synthesized were shown to be identical with the corresponding literature data. All other compounds were purchased from Aldrich.
6. The term "pD" used in this article always refers to the pH-meter reading without further correction. Refer to the following literature for further details : Glasoe, P. K; Long, F. A. *J. Phys. Chem.* **1960**, *64*, 188-190.
7. This method yields k(obs) for the H/D exchange.
8. The same effect was observed by Lehn et al. and is attributed to strong ion binding of the polycation to the dianion. See the following literature for further detail : Hosseini, M. W.; Kintzinger, J.-P.; Lehn, J.-M.; Zahidi, A. *Helv. Chim. Acta*, 1989, Vol. *72*, 1078-1083.
9. Job, A. *Ann. Chim.* (10th series) **1928**, *9*, 113-204.
10. Basnak, I.; Farkas, *J. Coll. Czech. Chem. Commun.* **1975**, *40*, 1038-1042.
11. Synthesis : Whistler, R. L. and Anisuzzaman, A. K. M.; in *Methods in Carbohydrate Chemistry*, Vol. VIII, **1980**, Academic Press, (editors : Whistler, R. L. and BeMiller, J. N.); pp 229 and pp 297-299.
12. 1, 4, 7, 10 - Tetraazacyclododecane was also shown to effect only a small rate enhancement on the H/D exchange rate of pyruvate at pD = 6.50 ($k_{(obs)} = 3.0 \cdot 10^{-7}$ s^{-1}).
13. Dietrich, B.; Hosseini, M. W.; Lehn J.-M.; Sessions, R. B. *Helv. Chim. Acta* **1983**, *66*, 1262-1278.

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