Chinese Chemical Letters Vol. 11, No. 6, pp. 485–488, 2000

Functioned Calix[4]arenes as Artificial Enzymes Catalyze Aldol Condensation

Li LIU, Zu Xing YANG, Yu Liang WANG, Shu Hua CHEN*

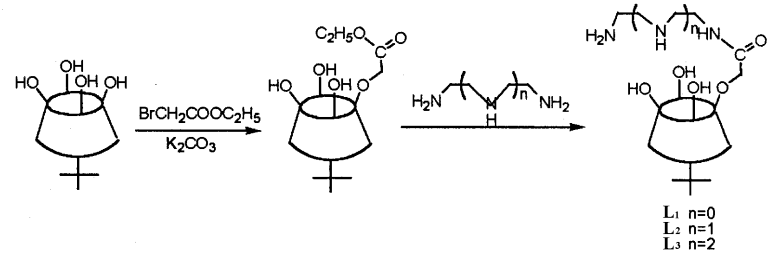
Faculty of Chemistry, Sichuan University, Chengdu 610064

Abstract: Aldolase models derived from calix[4]arene were designed and synthesized. The aldol condensation of *p*-nitrobenzaldehyde with acetone was catalyzed by the synthetic enzymes proceeded under mild conditions to offer chiefly aldol-type product in good yield.

Keywords: Calixarene, artificial enzyme, aldol condensation, catalysis.

Aldol condensation can be generally catalyzed by means of bases or acids. Usually, it is easy to obtain α, β-unsaturated ketones derived from the dehydration of the aldol-type products (β-hydroxy ketones). Watanabe *et al*[1] successfully developed the method to depress the dehydration by using metal(II) complexes of α-amino acid esters with cyclodextrin. Later, Zhao Hua-ming *et al.*[2, 3] studied the functioned cyclodextrins as aldolase to mimic the condensation of *p*-nitrobenzaldehyde with acetone and obtained the aldol-type product in good yield.

Recent years, studies on calixarene-based enzyme models attracted more and more attention and some models are very successful [4-7]. Gutche [8] suggested in 1983 that calixarene could be used to mimic aldolase, but up to now no one has been able to design effective aldolase model based on calixarene. According to the mechanism of class I aldolase. We designed and synthesized a type of aldolase models $\mathbf{L_{1\text{-}3}}$ to catalyze the condensation of *p*-nitrobenzaldehyde and acetone.



Model catalyst $\mathbf{L_2}$ and *p*-nitrobenzaldehyde can form 1:1 supramolecular complexes (Ka=497.4M-1). This result indicated that calixarene moiety in the model was binding

site for *p*-nitrobenzaldehyde. And the polyamine component in the model acted as the catalytic center, the catalytic mechanism may be shown as follows:

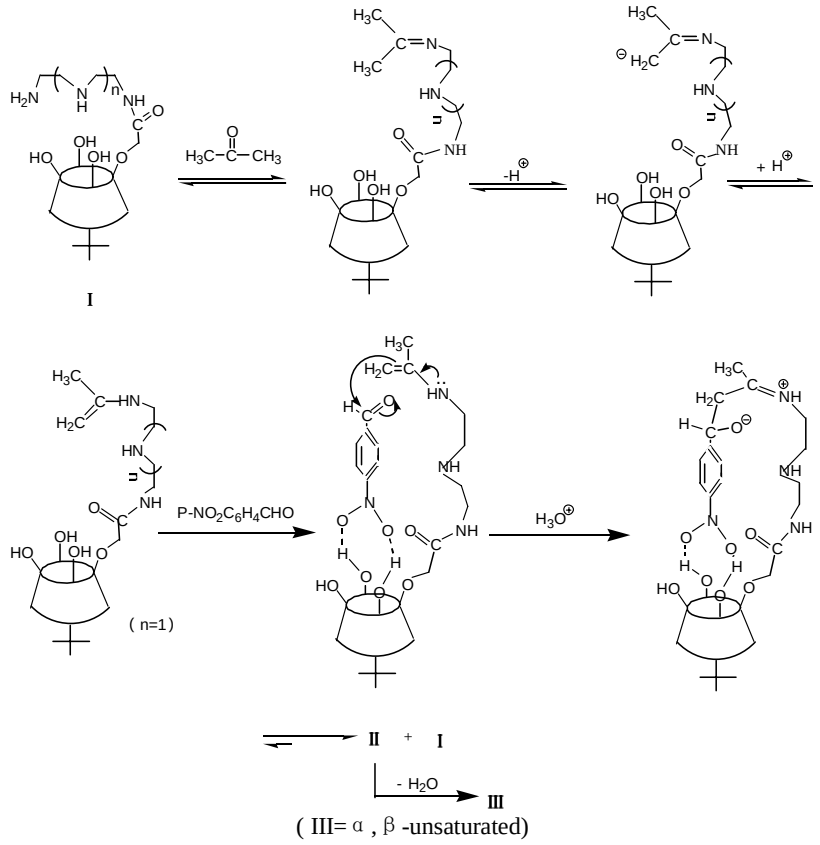


Table 1. Aldol condensation of *p*-nitrobenzaldehyde with acetone

Catalyst	Reaction time (hours)	Isolated yield of β-hydroxy-ketone(%)
No	15	0
Tetra(p-t-butyl)calix[4]arene(TCA)	15	0
TCA + Diethyltriamine (1:1)	15	4.7
	72	13.2
L_1	15	9.5
L_2	15	90.7
L_3	15	Trace

Conditions: [cat.], 8.18×10^{-5}mol/L; Tempt., 50^0C; Others are as general procedure.

Three catalysts were synthesized but only the model **L_2** is the most effective one. Under the selected conditions, the aldol-type product (II) was obtained in 90% yield. (**Table 1**)

Experimental

General considerations

IR spectra were recorded on a Nicolet 5MX-S infrared spectrometer; ^{1}HNMR data were recorded on a Varian Mecury 200 spectrometer, using TMS as an internal standard; MS data were obtained using a VG FAB-HS instrument; K_2CO_3 was dried at 500^{0}C before use; Acetonitrile was refluxed with P_2O_5 and distilled; Polyamine were distilled before use.

5,11,17,23-Tetra(t-butyl)-25-ethoxycarbonylmethoxy-26,27,28-trihydroxy-calix[4]-arene

The mixture of 2.0 g (3.08 mmol) of tetra (t-butyl)-calix[4]arene, 0.233 g (1.69 mmol) of K_2CO_3, 0.333 mL (3.08 mmol) of ethyl bromoacetate and 50 mL of acetonitrile was refluxed at 82^{0}C for 15hrs. Filtration, distillation under reduced pressure gave white solid. The solid was dissolved in CH_2Cl_2, washed with water three times, dried over Na_2SO_4 and chromatographied on silica gel (eluent, CH_2Cl_2) to give 1.42g of 5, 11, 17, 23-tetra (t-butyl)-25-ethoxycarbonylmethoxy-26, 27, 28-trihydroxy-calix[4]-arene (yield:63%). ^{1}HNMR[δ (ppm), $CDCl_3$]: 10.23 (1H, s, OH); 9.26 (2H, s, OH); 7.04 (8H, m Ar-H); 4.88 (2H, s, OCH_2CO); 4.47 (2H, d, *J*=13.32Hz, Ar-CH_2-Ar); 4.45 (2H, m, $COCH_2Me$); 4.30 (2H, d, *J*=13.66Hz, Ar-CH_2-Ar); 3.45 (2H, d, *J*=13.32Hz, Ar-CH_2-Ar); 3.39 (2H, d, *J*=13.66Hz, Ar-CH_2-Ar); 1 .40 (3H, t, CH_3); 1.19 (36H, m, CH_3). FAB-MS *m*/*z*(%)]: 735 (M^++1,100).

General procedure for the synthesis of enzyme model L

0.5g (0.68mmol) of 5, 11, 17, 23-tetra(t-butyl)-25-ethoxycarbonylmethoxy-26, 27, 28-tri-hydroxy-calix[4]arene was dissolved in 8 mL of toluene, then 0.2 mL (1.85 mmol) of diethylenetriamine in 8 mL of methanol was added and the mixture was refluxed for 5 hrs. The solvents were removed under reduced pressure to give white solid. The crude product was chromatographied on silica gel (eluent, ethanol:acetone=2:1[v/v]) to give 0.3g of enzyme model $\mathbf{L_2}$ (yield: 55.7%). IR[*v*max (cm^{-1}), KBr]: 3367 (OH); 3337 (NH); 1662 (C=O); 1462 (C=C); 1204 (C-O-C). ^{1}HNMR[δ (ppm), $CDCl_3$]: 9.73 (1H, s, CONH); 7.09-6.97 (8H, m, Ar-H); 5.87 (3H, s, OH); 4.46 (2H, s, OCH_2CO); 4.24-4.21 (4H, m, Ar-CH_2-Ar); 3.56 (2H, m, $CONHCH_2$-); 3.31 (2H, d, *J*=12.6Hz, Ar-CH_2-Ar); 3.28 (2H, d, *J*=13.4Hz, Ar-CH_2-Ar); 2.95 (6H, m, CH_2N); 1.19-1.10 (36H, m, CH_3).

General procedure for the catalytic aldol condensation

87mg (0.11mmol) of model catalyst $\mathbf{L_2}$ was dissolved in 7 mL of $CHCl_3$, then 100 mg (0.66mmol) of *p*-nitrobenzaldehyde and 2 mL of acetone were added. The mixture was stirred at 50^{0}C for 15 hrs, then 20 mL of water was added and the $CHCl_3$ was removed under reduced pressure. The obtained mixture was extracted with ethyl acetate. Dried over $MgSO_4$, removed the solvent to give yellow oil. The crude product was chromatographied on silica gel (eluent, cyclohexane: ethyl acetate=2:1[v/v]) to give yellowish solid (yield: 90.7%). mp: 59-59.5^{0}C (lit [9]60-62^{0}C). FAB-MS [*m*/*z* (%)]: 191 (M^+-18, 30); 176 (20); 151(35); 43 (100). ^{1}HNMR[δ (ppm), $CDCl_3$]: 8.23, 8.21 (2H, d, J=8.8Hz, Ar-H); 7.59, 7.49 (2H, d, J=8.8Hz, Ar-H); 5.27 (1H, t, C-H); 3.45 (1H, s, OH); 2.90 (2H, d, J=6Hz, CH_2); 2.23 (3H, s, CH_3).

Acknowledgment

We are grateful for the support of the National Natural Sciences Fundation of China. (Project No: 2977024)

References

1. K. I. Watanabe, Y. Yamada, K. Coto, *Bull. Chem. Soc. Jpn.*, **1985,** *58***,** 1401.
2. H. M. Zhao, Y. Wang, D. Q. Yuan, S. H. Chen, *'Excerpt of TOC@MUN' Conference* (world Assoc. Theo. Org. Chem.), **1989,** P-25.
3. D. Q. Yuan, R. G. Xie, H. M. Zhao, *Chinese Chem. Lett.*, **1991,** *2*(*8*), 617.
4. C.Loeber, D. J.Matt, *Organometallic Chem.*, **1994,** *475***,** 297.
5. L. H. Yuan, S. H. Chen, H. M. Zhao, *Acta Chimia Sinica*, **1994,** *52*, 1035.
6. P. Molenveld, S. Kapsabelis, F. John, J. Engbersen, D. N. Reinhoudt, *J. Am. Chem. Soc.*, **1997,** *119***,** 2948.
7. D. H. Li, S. H. Chen, H. M. Zhao, *Acta Chimia Sinica*, **1999,** *57***,** 869.
8. C. D. Gutsche; *Acc. Chem. Res.*, **1983,** *16***,** 161.
9. D. S. Noyce, W. L. Reed, *J. Am. Chem. Soc.*, **1958**, *80* (20), 5539.

Received 6 December 1999
Revised 31 March 2000