Title	Addition Effect of Some Macrocyclic Polyethers on the Asymmetric Reduction with Chiral NADH Model Compounds (Commemoration Issue Dedicated to Professor Yuzo Inouye on the Occasion of his Retirement)
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NOTE

Addition Effect of Some Macrocyclic Polyethers on the Asymmetric Reduction with Chiral NADH Model Compounds

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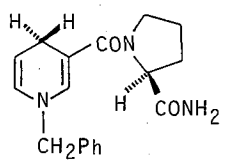
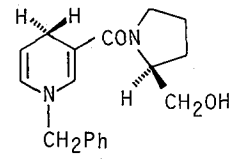
As reported in our previous publications dealing with an NADH model reaction,[1] dependence of enantiomeric excess (e.e.) on the reaction conversion and addition effect of the oxidized form on the product stereochemistry were found to appear notably with the chiral 1, 4-dihydronicotinamide carrying polar functional groups. The phenomenon has been explained in terms of stereochemical participation of oxidized form of the remaining reductant. A later study concerning this problem showed that asymmetric reduction of ethyl benzoylformate with a chiral dihydronicotinamide was significantly affected also by aromatic additives capable of exerting an attractive interaction with dihydropyridine molecules, which was further consolidated by the chelation of the hydroxyl groups with magnesium.[2] This finding and a working-hypotheses suggested that some sterochemically bulky compounds which may not be necessarily aromatics but have chelation site(s) with metals and/or inclusion capability of metals may also render chiral dihydropyridines more stereoselective toward prochiral substrate. So that a series of asymmetric reductions of ethyl benzoylformate were performed with the NADH models **1** and **2** in the presence of additives given below.



1



2

Structure of 1 and 2

Typically, a solution of the model **1** (0.165 g, 0.5 mmol), dry magnesium perchlorate (0.078 g, 0.35 mmol), ethyl benzoylformate (0.089 g, 0.5 mmol) and [2.2.2]-cryptand (0.066 g, 0.175 mmol) in dry acetonitrile (5.0 ml) was stirred at room temperature for 16 h. Usual work-up and isolation afforded pure ethyl mandelate. Chem. yield, 41.4%, $[\alpha]_D^{20}$, $-94.9°$(*R*) (*c* 0.840, EtOH). 90.9%e.e.

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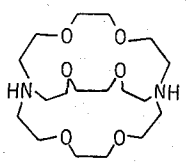
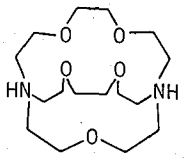
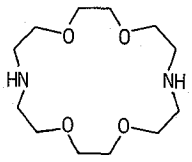


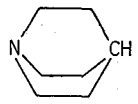
[2.2.2]-cryptand



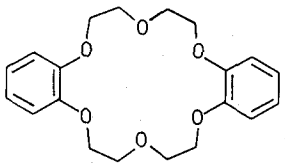
[2.2.1]-cryptand



1,10-diaza-18-crown-6



quinaldine



dibenzo-18-crown-6

Structure of additives

Table. Asymmetric Reduction of Ethyl Benzoylformate with the Models **1** and **2** in the Presence of the Additives

run	NAH (mmol)	$Mg(ClO_4)_2$ (mmol)	Mg/NAH	additive	additive/NAH	subst./NAH	chem. yield	%e.e.
1	1 (0.5)	0.35	0.7	[2.2.2]-cryptand	0.036	1.00	57.5	77.5
2	1 (0.5)	0.35	0.7	[2.2.2]	0.175	1.00	58.6	84.2
3	1 (0.5)	0.35	0.7	[2.2.2]	0.350	1.00	41.4	90.9
4	1 (0.5)	0.35	0.7	[2.2.2]	0.600	1.00	43.1	89.0
5	1 (0.5)	0.35	0.7	[2.2.2]	0.800	1.00	43.1	88.0
6	1 (0.5)	0.35	0.7	[2.2.2]	1.000	1.00	29.1	89.6
7	1 (0.5)	0.35	0.7	none	0	1.00	75.1	72.7
8	1 (0.5)	0.35	0.7	[2.2.2]	0.35	0.20	43.4	90.6
9	1 (1.0)	0.8	0.8	none	0	0.20	100	53.6
10	2 (0.4)	0.28	0.7	[2.2.2]	0.35	1.00	41.9	33.8
11	2 (0.6)	0.48	0.8	none	0	1.00	54.9	54.5
12	1 (0.5)	0.35	0.7	[2.2.1]	0.35	1.00	16.2	61.3
13	1 (0.5)	0.70	1.4	[2.2.1]	0.35	1.00	62.0	58.4
14	1 (0.5)	0.35	0.7	1, 10-diaza-18-crown-6	0.35	1.00	46.5	89.2
15	1 (0.5)	0.70	1.4	1, 10-diaza-18-crown-6	0.35	1.00	70.6	76.5
16	1 (0.5)	0.35	0.7	quinaldine	0.35	1.00	43.2	67.1
17	1 (0.5)	0.70	1.4	quinaldine	0.35	1.00	56.5	41.6
18	1 (0.5)	0.35	0.7	dibenzo-18-crown-6	0.35	1.00	44.9	80.1
19	1 (0.5)	0.70	1.4	dibenzo-18-crown-6	0.35	1.00	44.9	43.6

As can be seen from the experimental data in Table and Figure, the new findings in the present study can be summarized as follows.

(i) In the reduction with the model **1**, [2.2.2]-cryptand improved the e.e. with highest extent among the additives under the condition of additive/NAH=0.35 and $Mg(ClO_4)_2$/NAH=0.7 (Compare runs 3, 7, 12, 14, 16 and 18).

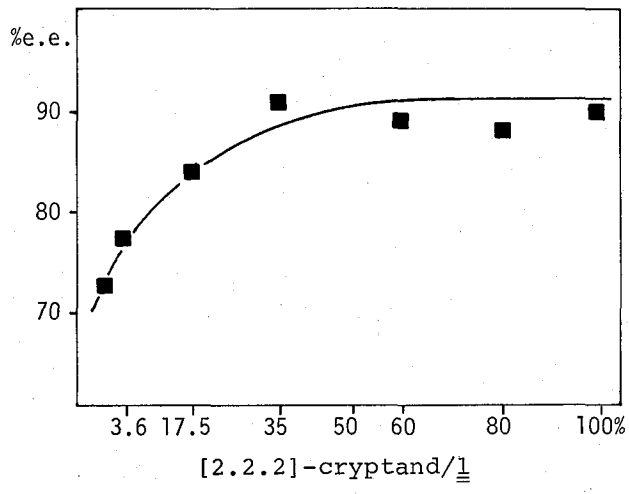


Figure. Change of %e.e. on the Varying Amount of [2.2.2]-cryptand in the Asymmetric Reduction of Ethyl Benzoylformate with the Model **1**.

(ii) 1, 10-Diaza-18-crown-6 was also a good additive (run 14), however, the others were ineffective or rather reduced the e.e. in some cases (runs 12 and 16) comparing with the value obtained in the absence of additives (72.7% in run 7).

(iii) The maximum e.e. was obtained at the concentration of 35 mol % to the NAH **1** and the e.e. was nearly constant thereafter.

(iv) In the asymmetric reduction with the prolinol model **2**, the addition of [2.2.2]-cryptand rather lowered the e.e. (runs 10 and 11) by about 20%.

(v) As already reported, the product stereochemistry in the present asymmetric reduction was found to depend on the initial concentration of the substrate. For example, as run 9 shows, when the substrate concentration was 20 mol% relative to the model **1**, the e.e. was only 54%. However, in the presence of 35 mol% of [2.2.2]-cryptand the e.e. increased up to 90% (run 8).

Thus the effect of [2.2.2]-cryptand for improving the e.e. was unequivocally demonstrated for the first time. From the foregoing, the product stereochemistry seems to be sensitively influenced by the symmetry, molecular size and sort of heteroatoms of the additives. Also included is an interesting result that by the addition of [2.2.2]-cryptand the low e.e. observed at the low concentration of the substrate[3] was strikingly improved indicating that the cause of the low e.e. was successfully eliminated by the additive.

Although the mechanistic explanation for the addition effect presented here is still obscure, the stereochemical outcome suggests much better chiral or achiral additives for NADH model reactions to exist.

MATERIAL AND METHOD

[2.2.1]-, [2.2.2]-Cryptands and 1, 10-diaza-18-crown-6 were purchased from Aldrich Co Ltd. Dibenzo-18-crown-6 was kindly offered by Dr. Nobuharu Ando in

our laboratory. Preparations and physical properties of the NADH models **1** and **2** will be described elsewhere.[4] The general procedure for the asymmetric reductions were just as exemplified typically in preceding. The percent e.e. of the product mandelate were determined from its optical rotation in ethanol which was recorded on Perkin-Elmer 241 polarimeter. Shimadzu gaschromatograph GC-4CM with 5%-polyethylene glycol succinate was used for determination of chemical yield and concentration of the sample solution for the optical measurement.

ACKNOWLEDGMENT

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REFERENCE

(1) T. Makino, T. Nunozawa, N. Baba, J. Oda, and Y. Inouye, *J. Chem. Soc.* Perkin Trans I, 7, **1980**.
(2) T. Makino, T. Nunozawa, N. Baba, J. Oda, and Y. Inouye, *Tetrahedron Lett.*, 1683, **1979**.
(3) N. Baba, J. Oda, and Y. Inouye, *Angew. Chem.*, **94** 465 (1982). Int. Ed. Engl., **21**, 433.
(4) It is being presented in a paper prepared for the dependence of product stereochemistry on the initial concentration of substrate in asymmetric reductions with chiral NADH model compounds.