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A STEREOSELECTIVE BIOCATALYTIC DIELS-ALDER REACTION[†]

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Abstract: *Baker's yeast catalyzes the stereoselective Diels-Alder reaction of cyclopentadiene 1 with dienophiles 2, 4 and 6. A predominant formation of exo isomer is observed in some cases.*

The ability to control the course of Diels-Alder reaction by the use of aqueous solvents[1] and by the added catalysts such as cyclodextrins[2] is currently attracting considerable attention. But, the utility of enzymes for studying this versatile cycloaddition reaction has not yet been explored.

Further to our studies on enzyme catalyzed cycloaddition reactions[3], herein, we report for the first time that Baker's yeast catalyzes the Diels-Alder cycloaddition of cyclopentadiene 1 with dienophiles 2, 4 and 6 with appreciable stereoselectivity[4]. To Baker's yeast[5] (0.8 g) taken in pH 7.2 buffer (20.8 ml) is added dienophile 2, 4 or 6 (2.5 mmol) in 30% ethanol (16 ml) followed by cyclopentadiene 1 (2.5 mmol) in 30% ethanol (16 ml). It is incubated at 37°C for 48 h. The mixture is then extracted with ethylacetate (2x30 ml), dried and evaporated under reduced pressure to get the product (Table). In the absence of biocatalyst, these Diels-Alder reactions give mixture of isomers with preponderance of the **endo** in most cases (Table). Hence, a noteworthy feature in these enzyme catalyzed cycloadditions is the predominant formation of the **exo** isomer (3a-b and 8b) against the Alder's endo rule[9] in the case of maleic (2a-b) and cinnamic acids (6b) respectively.

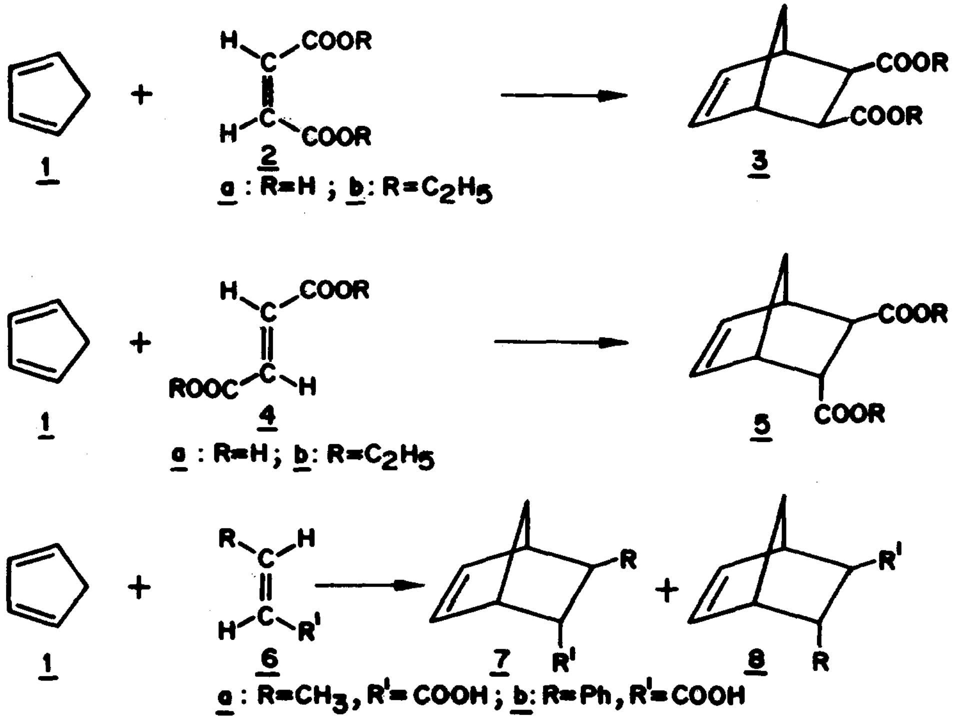
Thus, the ability of biocatalysts to alter the stereoselectivity of Diels-Alder reactions hold promise for future applications.

Table Stereoselectivities in Diels-Alder reactions with cyclopentadiene 1 under various conditions

Dienophile[a]	Organic medium (I) endo:exo	Aqueous medium (II) endo:exo	Aqueous medium in presence of biocatalyst (present studies) (III) endo : exo	Yield (%)
2a	80:20[b]	98:2[2a]	0 : 100	74
2b	73:27[6]	93:7[b]	0 : 100	78
6a	70:30[7]	C	90 : 10	72
6b	50:50[7]	C	3 : 97	76

a) With fumaric acid derivatives (4a-b) only cycloadduct 5[8] is obtained under all the conditions (I,II &III). b) The ratio was determined experimentally by ^{1}H NMR. c) These reactions proceed only to the extent of 5% giving endo isomer.

Scheme



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4 Stereoisomer ratio was determined by ^{1}H NMR spectroscopy as given in a) Kamezawa,K.; Sakashita,K. and Hayamizn,K.,Org.Magn.Reson.,1969,1,405. b) Fraser,R.R.,Can.J.Chem.,1962,78 and by HPLC analysis. HPLC analysis was carried out on a ODS column using acetonitrile as solvent.

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