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Journal of Molecular Catalysis A: Chemical 258 (2006) 191–197

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

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Calculation on enantiomeric excess of catalytic asymmetric reactions of diethylzinc addition to aldehydes with topological indices and artificial neural network

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Received 21 January 2006; received in revised form 10 May 2006; accepted 11 May 2006
Available online 30 June 2006

Abstract

The relationships between the enantiomeric excess of products in several types of asymmetric diethylzinc addition reactions and the structures of the catalysts and reagents were studied by using the BP neural network with topological indices. Moderate cross-validated correlation coefficients were yielded by the models generated from the neural network. Then the models were further used to validate reaction mechanisms, determine the proper reaction environment, and predict the activities of new catalysts.

Keywords: Asymmetric catalytic reaction; Enantiomer excess; Topological indices; Artificial neural network; QSAR

1. Introduction

Ever since the initial report of Oguni and Omi on the addition reaction of diethylzinc to benzaldehyde in the presence of a catalytic amount of (*S*)-leucinol with moderate enantioselectivity (49% e.e.) in 1984 [1], researches on asymmetric organozinc additions to carbonyl compounds have grown dramatically as this type of reaction is able to form carbon–carbon bond and asymmetric configuration synchronously as shown in Scheme 1. The first highly enantioselective ligand for the dialkylzinc addition to aldehydes is (−)-3-exo-dimethylaminoisoborneol [(−)-DAIB] discovered by Noyori and his co-workers in 1986 [2]. Over the past decades, a large number of chiral catalysts have been developed and high enantioselectivities have been achieved. In addition, the reaction of diethylzinc with aldehydes has also become a classical test in the design of new ligands for catalytic enantioselective syntheses [3].

As the growing number of the catalysts has been applied in this field, new ligands must be carefully designed and screened to achieve improved enantioselectivities. In this article, QSAR (quantitative structure–activity relationship) calculations were performed on some typical diethylzinc addition reactions with topological indices and artificial neural networks. The calculation results were useful to refine ligand structures, optimize catalysis environment, and validate reaction mechanisms.

2. Method of calculation and experimental data

2.1. Molecular descriptor

Because of the easiness of calculation and the flexibility in varieties of situations, topological descriptors including Randic index [4], Kier and Hall index [5] and Kier shape index [6] were used in our calculations.

The atom partial charge was also introduced as one of the descriptors of certain molecules after structure being optimized by the AM1 method [7] with the lowest energy.

Since the structures of catalysts varied a lot from each other in different types of reactions, a "universal" descriptor set could not be applied. Different descriptors were screened for different reactions to produce the models with acceptable predictive abilities.

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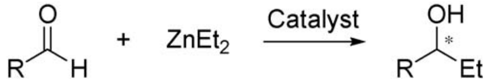
doi:10.1016/j.molcata.2006.05.020



Scheme 1. Diethylzinc addition to aldehyde: the typical type of organozinc additions to carbonyl compounds.

2.2. ANN calculation

The ANN calculations were carried out in ANN-analyser, a generalized program that we have developed. Feed-forward networks with three layers were trained with the back-propagation of errors algorithm [8]. In all calculations, r is the correlation coefficient, and q is the cross-validated correlation coefficient.

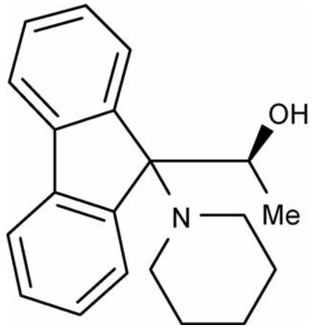
2.3. Experimental data

All experimental data were obtained from papers published [9,10,13] or the work of our laboratory.

3. Results and discussion

3.1. Diethylzinc additions to aldehydes catalyzed by amino alcohols

Amino alcohols have been used as classic ligands for the asymmetric diethylzinc additions since the discovery of the first effective catalyst to this type of reactions by Noyori and his coworkers. Here a set of data from the work done by Pericàs et al. [9] was calculated. Amino alcohol ligand shown in Scheme 2 derived from fluorene was found to be an excellent ligand to a number of aldehydes to produce preponderant *S* configuration products. Topological indices Randic order 2, Kier and Hall order 2 and Kier shape index order 3 were selected to represent the aldehyde structures as the input variables among topological candidates after screening. The enantiomeric excess (e.e.%) was chosen as the dependent variable. A BP network consisted of three input neurons, one output neuron and three hidden neurons was used to produce the model. All 19 entries were divided into five groups to perform cross-validation. Prediction results in each validation group are shown in Table 1 and Fig. 1. Acceptable predictions were generated from the calculation.



Scheme 2. Amino alcohol catalyst derived from fluorene.

3.2. Diethylzinc additions to aldehydes catalyzed by amino thiols

The amino thiols with cyclic and acyclic amino substituents shown in Scheme 3 were used by Kang et al. to catalyze diethylzinc addition reactions with 70–100% e.e. of *R* configuration products [10]. This set of reactions was also inspected by us.

Topological indices Kier and Hall (order 2) were used to represent the aldehydes and the substituent R^2 in different

Table 1
Observed [9] and predicted e.e.% of diethylzinc additions to aldehyde catalyzed by amino alcohols[a]

Entry	Aldehyde	Configuration	e.e.% (experimental)	e.e.% (predicted)
1	Benzaldehyde	*S*	96	96
2	*o*-Chlorobenzaldehyde	*S*	91	94
3	*o*-Methylbenzaldehyde	*S*	96	95
4	*o*-Methoxybenzaldehyde	*S*	82	82
5	*m*-Chlorobenzaldehyde	*S*	97	95
6	*m*-Methylbenzaldehyde	*S*	96	96
7	*m*-Methoxybenzaldehyde	*S*	96	97
8	*p*-Fluorobenzaldehyde	*S*	97	96
9	*p*-Methylbenzaldehyde	*S*	97	95
10	1-Naphthaldehyde	*S*	90	95
11	2-Naphthaldehyde	*S*	96	95
12	Hexanal	*S*	91	91
13	Heptanal	*S*	91	90
14	Nonyl aldehyde	*S*	90	90
15	Isovaleraldehyde	*S*	95	93
16	3-Phenylpropionaldehyde	*S*	91	95
17	Cyclohexanecarboxaldehyde	*S*	98	96
18	2-Ethylbutyraldehyde	*S*	94	94
19	*E*-α-Methylcinnamaldehyde	*S*	94	93
Correlation coefficient (r)				0.8575
Squared cross-validated correlation coefficient (q^2)				0.5245

[a] The reactions were carried out at 0 °C in toluene in the presence of 3 mol% of catalyst and 2.2 equiv. of diethylzinc (1 M in hexane).