Theoretical investigation on isomerization of Et$_2$AlCN to Et$_2$AlNC and cyanation of aldimine

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ABSTRACT

The chemical fixation of diethylaluminum cyanide (Et$_2$AlCN) reacting with N-benzylideneaniline to produce 2-phenyl-2-(phenylamino)acetonitrile has been investigated by using DFT/B3LYP methods. The solvent effect is assessed using the continuum solvent model based on the SCRF/PCM method at the PCM/B3LYP/6-31G* level. Our results reveal that based on isomerization of Et$_2$AlCN to Et$_2$AlNC and their ambidextrous CN groups which will result in C-attack or N-attack to imine center carbon, there are four possible reaction paths to be found. The analysis of activation barriers shows the carbon atom in Et$_2$AlNC firstly attacking the imine C atom in N-benzylideneaniline to afford the five-membered-ring transition state **4′a** is favorable in the gas phase and in solvent toluene. The changing geometries and Wiberg bond indices with NBO analysis indicate the reaction process and the overall reaction is exothermic.

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1. Introduction

Because of the significance of α-amino acids in chemistry and biology, the preparation of various α-amino acids has attracted considerable attention. Recently, the ever-increasing demand for α-amino acids of the non-proteinogen in a variety of scientific disciplines has promoted the development of novel methods for the syntheses of α-amino acids. One of the most important reactions to afford the key α-amino nitrile intermediates for the synthesis of α-amino acids is Strecker reaction of imines and cyanides [1–5].

Metal and non-metal cyanides such as sodium cyanide, potassium cyanide, hydrocyanic acid, trimethylsilyl cyanide (TMSCN), 2-oxopropanenitrile, ethyl cyanoformate and diethyl cyanophosphonate are important and common cyanide sources. Since Toru's group reported the Strecker reaction of diethylaluminum cyanide (Et$_2$AlCN) and aldimine to obtain high yield (up to 99%) in toluene and expected Et$_2$AlCN to behave as a good cyanation reagent [2k], our great consider has been attracted to the character of Et$_2$AlCN and its reaction mechanism in cyanation of aldimine (PG = Protecting Group).
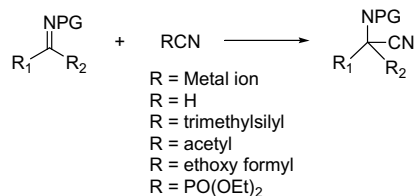
To the best of our knowledge, the theoretical study on the mechanism of the title reaction has not been reported until now. Thus, in this work, our motive is to clearly clarify the mechanism of the reaction of aldimine with diethylaluminum cyanide leading to Strecker reaction product 2-phenyl-2-(phenylamino)acetonitrile. To present the general picture of the mechanism, we have performed the detailed calculations using the B3LYP method [6] to theoretically study this reaction in the gas phase. In addition, the natural bond orbital (NBO) [7] analysis is also carried out to observe the bond order change in the process of the reaction, and the solvent effect is examined by using the continuum solvent model [8] with the density functional theory (DFT). Furthermore, this work might act as an instructional purpose to understand the cyanation mechanism of aldehyde, ketone and ketimine and diethylaluminum cyanide, even different cyanide sources.

2. Computational detail

The geometries of all the species are fully optimized using the hybrid density functional method B3LYP with 6-31G* basis sets. All minimum and transition state structures are verified by vibrational frequency analysis. Zero-point vibrational energies (ZPE) determined at the B3LYP/6-31G* level are not included in the calculation of relative energies for the various species. All electron (AE) calculations are run for various elements. Throughout this paper, all inter-nuclear distances are in angstroms and all angles are in degrees. Relative energies at 298 K for gas phase and solvent are

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all in kJ mol^{-1}. All calculations were performed using GAUSSIAN 03 system of programs [9].

Table 1
Total energies, enthalpies, Gibbs free energies (hartrees) and number of imaginary frequencies (N) for all species

Species	E (298 K)	H (298 K)	G (298 K)	N
1	−556.52826	−556.52731	−556.57493	0
2	−493.60143	−493.60049	−493.64759	0
2-TS	−493.58443	−493.583484	−493.632532	1
2′	−493.60067	−493.59972	−493.65181	0
3	−1050.17090	−1050.16996	−1050.25003	0
3′	−1050.17044	−1050.16949	−1050.24959	0
4a	−1050.10184	−1050.10090	−1050.17723	1
4b	−1050.10843	−1050.10748	−1050.18485	1
4′a	−1050.12327	−1050.12232	−1050.19773	1
4′b	−1050.10196	−1050.10102	−1050.17960	1
5	−1050.14535	−1050.14441	−1050.22418	0
5′	−1050.11619	−1050.11525	−1050.19487	0
6	−649.95293	−649.95199	−650.008126	0
6-TS	−649.88021	−649.87927	−649.93631	1
6	−649.92140	−649.92046	−649.97679	0

Table 2
Total energies (hartrees) for species in indicated solvent

Species	E_{Ether}	E_{THF}	$E_{toluene}$	E_{DCM}
1	−556.74553	−556.74510	−556.74366	−556.74524
2	−493.75424	−493.75401	−493.75209	−493.75417
2′	−493.75381	−493.75369	−493.75186	−493.75385
3	−1050.54717	−1050.54685	−1050.54345	−1050.54716
3′	−1050.54644	−1050.54633	−1050.54275	−1050.54665
4b	−1050.47981	−1050.47897	−1050.47639	−1050.47923
4′a	−1050.49199	−1050.49164	−1050.49035	−1050.49178
5	−1050.51822	−1050.51778	−1050.51591	−1050.51797
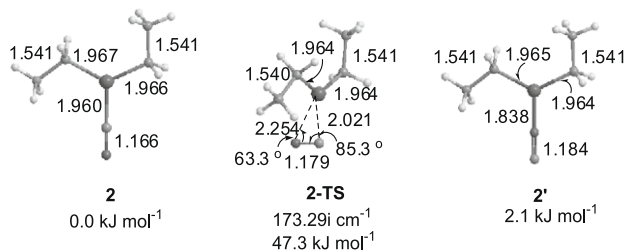
Fig. 1. Isomerization mechanism of Et$_2$AlCN to Et$_2$AlNC.

During investigation on Strecker reaction mechanism of aldimine and Et$_2$AlCN, because chiral additive is not considered and our attention has been paid to different reaction paths resulted from isomerization of Et$_2$AlCN, the chirality of the possible adducts is not studied (Tables 1 and 2).
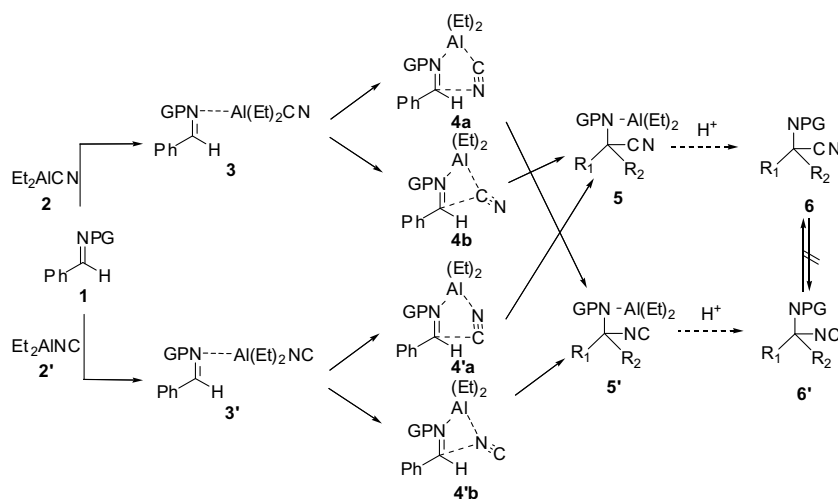
3. Results and discussion

Previous studies with ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and IR spectrum analysis reported that using Ph$_3$PO as an additive in cyanosilylation of aldehydes, TMSCN could be isomerize to TMSNC cyanide donor which expects greater reactivity [10]. Located at B3LYP/6-31G* level, from **2** to **2′**, a transition state **2-TS** is found and corresponding activation energy is 47.3 kJ mol^{-1}. **2′** show a higher energy of only 2.1 kJ mol^{-1} than **2**. The imaginary frequency is 173.29i cm^{-1}, which is associated with the Al(Et)$_2$ moiety swaying motion between C end and N end of cyano group. Of the process from **2** to **2′**, Gibbs free energy is −7.6 kJ mol^{-1}, which suggests that the isomerization is a spontaneous process. According to the Boltzmann equation, it is concluded that species Et$_2$AlCN **2** and Et$_2$AlNC **2′** are concomitant with the molar ratio of 2.3 to 1 (Fig. 1).

The analysis of infrared data shows that in **2**, the strongest peak at 608.37 cm^{-1} corresponds to stretching motion of Al–C bond, 2292.72 cm^{-1} corresponds to stretching motion of C–N bond, and that in **2′** the strongest peak at 2156.55 cm^{-1} corresponds to stretching motion of N–C bond and the peak corresponding to stretching motion of Al–N cannot be found clearly.

Based on the isomerization of Et$_2$AlCN, the title reaction should be considered to include four reaction processes, i.e. (I) **1 + 2 → 3 → 4a → 5′**, (II) **1 + 2 → 3 → 4b → 5**, (III) **1 + 2′ → 3′ → 4′a → 5** and (IV) **1 + 2′ → 3′ → 4′b → 5′**, which contain two reactant complexes (**3** and **3′**), four transition states (**4a**, **4b**, **4′a** and **4′b**) and aluminum-containing intermediates (**5** and **5′**) (Scheme 1). All of the relevant stationary points have been located at the B3LYP/6-31G* level.

As shown in Scheme 1, one can see that each process proceeds via three steps. The first step is to form complex **3** or **3′** via the electrostatic interaction of the imine nitrogen with the aluminum atom in Et$_2$AlCN; the second step is the C-attack or N-attack of CN group to the imine center C atom to form the five-membered ring transition state **4a** or **4′a** or four-membered ring **4b** or **4′b**; the last step is that the CN group breaks away from aluminum atom to afford **5** or **5′**. With the formation of complexes (**3** and **3′**), the lengths of bonds beside the imine nitrogen atom increase, respectively, from 1.276 and 1.406 Å in reactant N-benzylideneaniline (PG = phenyl) to

Scheme 1.