JOC Article

Density Functional Study on the Mechanism of Bicyclic Guanidine-Catalyzed Strecker Reaction

Jing Li, Wan-Yi Jiang, Ke-Li Han,* Guo-Zhong He, and Can Li

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, P. R. China 116023

klhan@dicp.ac.cn

Received June 24, 2003

As a direct and viable synthesis of amino acids, the small organic molecule catalyzed asymmetric Strecker reactions have been explored successfully in recent years. For these catalysts, the active sites may be a guanidine group or similarly a urea group. In an effort to elucidate the reaction mechanism, we have investigated the bicyclic guanidine-catalyzed Strecker reaction of HCN and methanimine using density functional theory with the B3LYP method. Assisted by guanidine, two competitive pathways to aminoacetonitrile were rationalized. The aminoisoacetonitrile may not form due to the instability of the product.

Introduction

For more than 150 years, the Strecker reaction[1] (Scheme 1) has been important as a de novo method of α-amino acid synthesis, which involves the reaction of aldehydes with ammonia and hydrogen cyanide and the subsequent hydrolysis of the resulting α-aminonitriles. As interest in the nonproteinogenic α-amino acids is increasing, a variety of methods of synthesizing chiral amino acids have been developed.[2] And the catalytic asymmetric Strecker synthesis is one of the most direct and practical methods.[3]

Although as early as 1981 Inoue et al.[4] disclosed the asymmetric addition of HCN to benzaldehyde catalyzed by cyclodipeptide **1a** (Figure 1), the similar reaction, the catalytic asymmetric Strecker reaction, was first reported by Lipton et al.[5] 15 years later, using catalyst **1b**, which is analogous to **1a.** The only difference between **1a** and **1b** is that **1a** bears an imidazole group while **1b** has a guanidine. Interestingly, Corey et al. found that bicyclic guanidine **1c** itself could catalyze this reaction efficiently with high yield and good enantioselectivity.[6] Recently urea catalyst **1d** was found to be an excellent catalyst for the asymmetric Strecker reaction.[7,8] Although great successes have been achieved in these asymmetric Strecker reactions catalyzed by small organic molecules, theoretical study[7e,8l] on their mechanism is rather scarce.

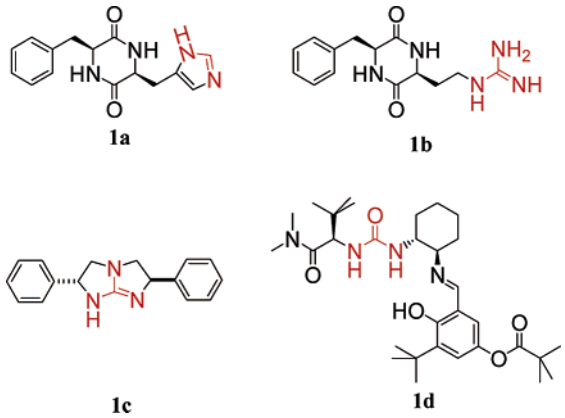
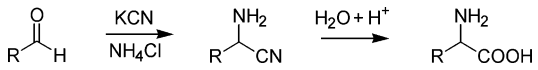


FIGURE 1. Chiral catalysts for asymmetric hydrocyanation reaction.

SCHEME 1. The Strecker Reaction for the Synthesis of α-Amino Acids



Recently, B3LYP methods have been widely used for theoretical prediction of organocatalytic reactions[9] and in some cases results are in excellent accordance with experiments.[10] Herein we chose the reaction of HCN and methanimine catalyzed by bicyclic guanidine (Scheme 2) as a model reaction to study with B3LYP/6-31G(d) methods.

Concerning the prebiotic Strecker synthesis of amino acids,[11,12] the addition of HCN to methanimine has been extensively studied.[13,14] Our results may also give hints on additional pathways of prebiotic amino acids synthesis.[15, 21]

* Corresponding author.

(1) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27.

(2) Reviews: (a) Williams, R. M.; *Synthesis of Optically Active α-amino acids*; Pergamon: Oxford, 1989. (b) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889. (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (d) Arend, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2873. (e) Yet, L. *Agew. Chem. Int. Ed.* **2001**, *40*, 875.

(3) (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795.

(4) (a) Oku, J. I.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1981**, 229. (b) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181. (c) Kogut, E. F.; Thoen, J. C.; Lipton, M. A. *J. Org. Chem.* **1998**, *63*, 4604.

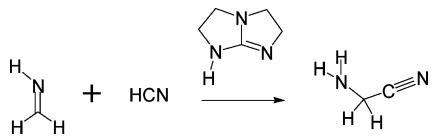
(5) (a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910. (b) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *Amino Acids* **1996**, *11*, 259.

(6) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.

(7) (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279. (c) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (d) Su, J. T.; Vachal, P.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 197. (e) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012. (f) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.

10.1021/jo034891f CCC: $25.00
Published on Web 10/17/2003

SCHEME 2. The Bicyclic Guanidine-Catalyzed Strecker Reaction of HCN and Methanimine



Computational Methods

All the calculations were carried out using B3LYP[16] hydrid density functional theory and the 6-31G(d) basis set as implemented in Gaussion 98W.[17] The effect of solvent on the mechanism was investigated using the Onsager mode.[18] Search for transition states was carried out by the QST2 procedure. The stationary point geometries were fully optimized and characterized as minima (no imaginary frequencies) or first-order saddle points (one imaginary frequency) by calculations of vibration frequencies. Intrinsic reaction coordinate (IRC) calculations were performed for all the transition states with step sizes in the range of 10−13 (in units of 0.01 amu$^{-1/2}$ bohr). All the bond lengths are in angstroms (Å) and energies in kJ/mol.

Results and Discussion

Reaction of HCN with Methanimine To Give Aminoisoacetonitrile without Catalyst. Experimentally, Corey et al.[6] reported that HCN does not react with *N*-benzhydrylbenzaldimine in toluene at 10 °C or below. Barone et al.[13] studied the reaction of HCN and methanimine in vacuo comprehensively and their calculated free energy of the highest transition state is as high as 180.7 kJ/mol with the B3LYP method. Similarly, Basiuk[14a] located three consecutive high-energy transition states for the addition in gas phase. Walch et al.[14b] considered the addition of HNC and protonated methanimine in the addition, and low-energy pathways were found. In our calculations, we found the energy barrier for the addition of HNC to methanimine to produce aminoacetonitrile in toluene is 134.7 kJ/mol. However, the isomerization of HCN to HNC has very high energy barriers.[19]

Addition of HCN to Methanimine To Give Aminoisoacetonitrile with the Bicyclic Guanidine. HCN, methanimine, and guanidine may form a three-component complex **I1a** (Figure 2). In **I1a**, the bond length of H11−C12 in HCN was only 1.110 Å, remaining covalent bonding, and the methanimine is protruding outward. In the transition structure **TS1**, the C12−N13 is almost parallel to the plane of methanimine and the distances of C12 and N13 to C10 of methanimine are almost the same, 2.680 and 2.540 Å, respectively.

Addition of HNC to Methanimine To Give Aminoacetonitrile with the Bicyclic Guanidine. Our preliminary calculations show that the bicyclic guanidine could catalyze the isomerization between HCN and HNC.[19] Though HNC is much less stable than HCN,[20] it is more reactive.[14b] Hence, the complex **I1b** with an isocyanide moiety may be involved in the reaction. In complex **I1b**, methanimine binds to the amino hydrogen, forming a H14···N9 bond 1.820 Å long, and the H14···N9−H23 angle is 125.7°. The complexation with methanimine may add the basicity of the guanidine. Thus, the nitrogen in guanidine attaching to the HNC attracts the hydrogen in HNC so strongly that the distance of H11···N13 is 1.570 Å. In the transition structure **TS2**, the N13−C12 bends toward the C10 in methanimine and the distance of C10 and C12 is 2.090 Å. There is an almost planar nine-member cycle except of the slight N13−C12 tilt.

Isomerization between Aminoisoacetonitrile and Aminoacetonitrile with the Bicyclic Guanidine. Also, a transition structure **TS3** between **I2a** and **I2b** is located. **TS3** bears close resemblance to **TS2**, but the angle of H11···C12−N13 in **TS3** is 174.5°, higher than that in **TS2**, 163.5°. And in **TS3**, C12 is closer to C10 than N13, and the distance of C12 and N13 to C10 of methanimine is 2.360 and 2.750, respectively.

The Possible Reaction Pathways. The relative energy profile and free energy profile of all transition

(8) Selected examples of catalytic asymmetric Strecker-type reaction using metal complex catalysts: for Zr complexes: (a) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3186. (b) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762. (c) Kobayashi, S. Ishitani, H. *Chirality* **2000**, *12*, 540. For Al complexes: (c) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315. (d) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibashaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650. (e) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327. (f) Nogami, H.; Matsunaga, S.; Kanai, M.; Shibashaki, M. *Tetrahedron: Asymmetry* **2001**, *42*, 279. (g) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 6801. (h) Funabashi, K.; Kanai, M.; Shibashaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 10784. (i) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442. For Ti complexes: (j) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284. (k) Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657. (l) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594. (m) Byrne, J. J.; Chavarot, M.; Chavant, P. Y.; Valle Y. *Tetrohedron Lett.* **2000**, *41*, 873. Others: (n) Chavarot, M.; Byrne, J. J.; Chavant, P. Y.; Vallee, Y. *Tetrohedron: Asymmetry* **2001**, *12*, 1147. (o) Liu, B.; Feng, X.; Chen, F.; Zhang, G.; Cui, X.; Jiang, Y. *Synlett* **2001**, *10*, 1551.

(9) Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904.

(10) (a) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475. (b) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911. (c) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273. (d) Rankin, K. N.; Gauld, J. W.; Boyd, R. J. *J. Phys. Chem. A* **2002**, *106*, 5155.

(11) Miller, S. L. *Science* **1953**, *117*, 528.

(12) Woon, D. E. *Icarus* **1999**, *142*, 550.

(13) Arnaud, R.; Adamo, C.; Cossi, M.; Milet, A.; Vallée, Y.; Barone, V. *J. Am. Chem. Soc.* **2000**, *122*, 324.

(14) (a) Basiuk, V. A.*J. Phys. Chem A* **2001**, *105*, 4252. (b) Walch, S. P.; Bakes, E. L. O. *Chem. Phys. Lett.* **2001**, *346*, 267.

(15) (a) Irvine, W. M. *Origins Life Evol. Biosphere* **1998**, *28*, 365. (b) Winnewisser, G.; Krammer, C. *Space Sci. Rev.* **1999**, *90*, 181.

(16) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(17) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.8; Gaussian, Inc.; Pittsburgh, PA, 1998.

(18) Onsager, L. *J. Am. Chem. Soc.* **1936**, *58*, 1486.

(19) The energy difference between the binary complexes of HCN and HNC with the guanidine is 45.0 kJ/mol, lower than 70.7 kJ/mol, the energy difference between HCN and HNC. See Supporting Information for details.

(20) (a) Loew, G. H.; Chang, S. *Tetrahedron* **1971**, *27*, 3069. (b) Loew, G. H. *Theor. Chim. Acta* **1971**, *20*, 203. The isomerization of HCN to HNC has been extensively studied. A selected recent study: (c) Szalay, V. *J. Chem. Phys.* **1990**, *92*, 3633. (d) Shah, P. S.; Rice, S. A. *J. Chem. Phys.* **2000**, *113*, 6536.

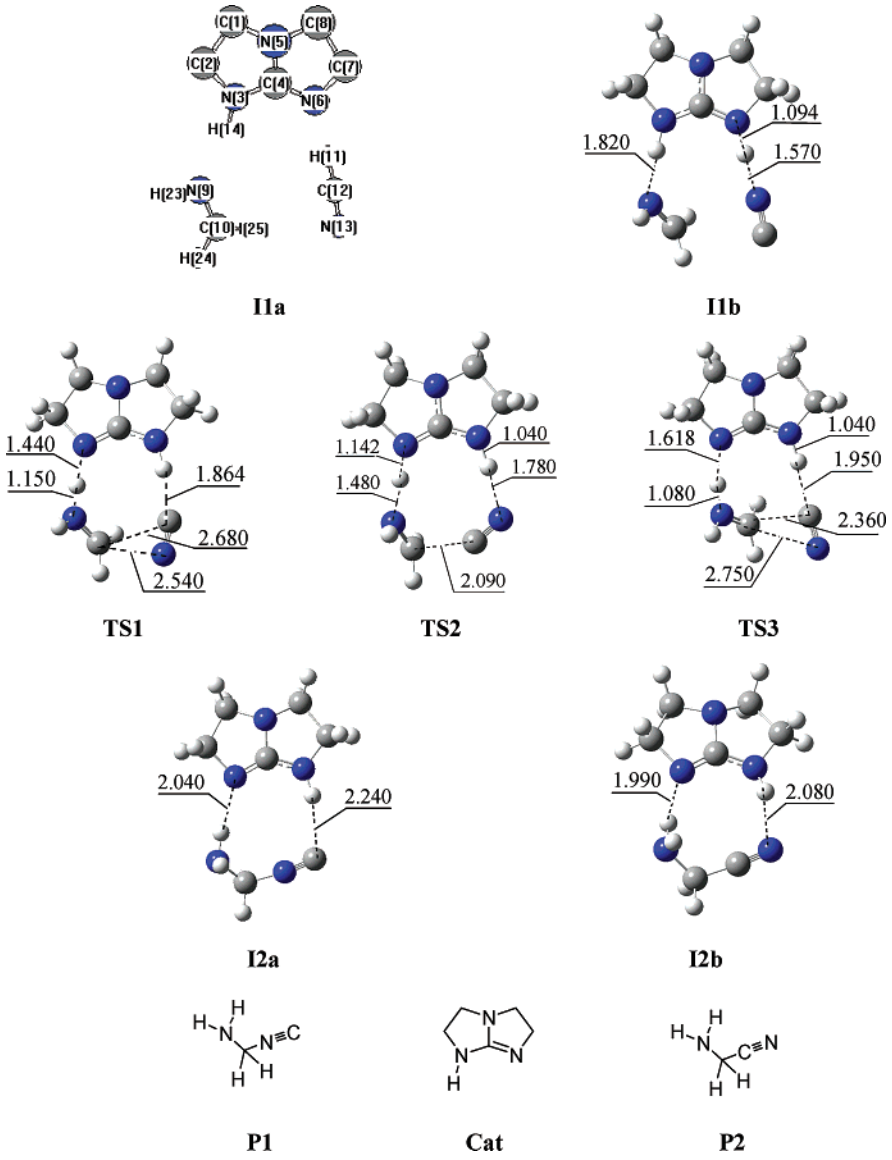


FIGURE 2. Optimized structures of the stationary points.

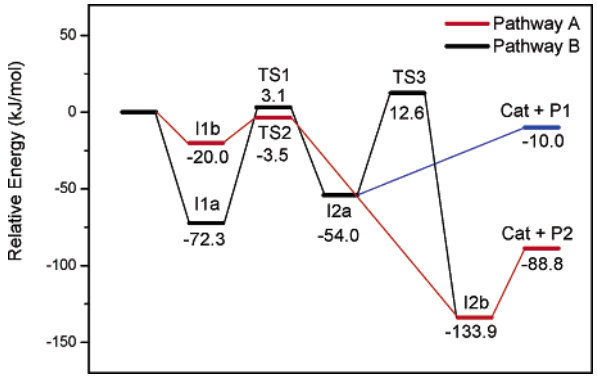


FIGURE 3. Relative energy profile for the reaction of HCN (or HNC) and methanimine with bicyclic guanidine in toluene at 298.15 K computed at the B3LYP/6-31G(d) level of theory.

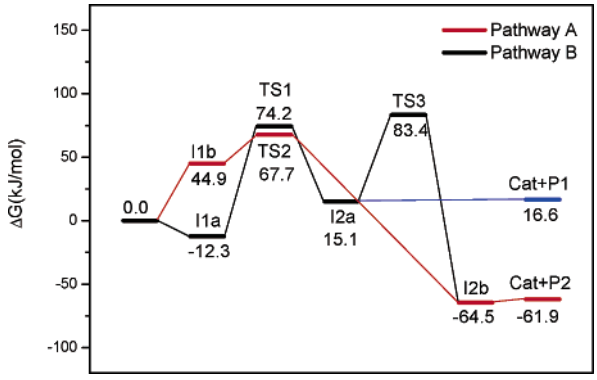


FIGURE 4. Free energy profile for the reaction of HCN (or HNC) and methanimine with bicyclic guanidine in toluene at 298.15 K computed at the B3LYP/6-31G(d) level of theory.

states and intermediates are illustrated in Figures 3 and 4, and some thermodynamic data are listed in Table 1. The complexation lowers the energy substantially. Thus, the reaction is energetically favorable. However, the contribution of entropies increases the free energies of the transition states relative to the reactants. The reaction pathway may be that the HNC adds to methanimine to yield aminoacetonitrile (pathway A) or the

TABLE 1. Relative Thermodynamic Contributions (kJ/mol) at 298.15 K for the Stationary Points in HCN Addition to Methanimine with Bicyclicguanidine[a]

structure	Δ (ZPE)	ΔE[b]	$-T\Delta S$	ΔH	ΔG
I1a	14.2	−72.3	59.6	−71.9	−12.3
I1b	15.4	−20.0	65.5	−20.6	44.9
TS1	11.3	3.1	75.4	−1.2	74.2
TS2	13.4	−3.5	75.9	−8.2	67.7
TS3	18.0	12.6	75.2	8.3	83.4
I2a	28.0	−54.0	73.2	−58.1	15.1
I2b	28.5	−133.9	73.8	−138.1	−64.5
cat. + P1	23.0	−10.0	32.2	−15.6	16.6
cat. + P2	23.5	−88.8	32.8	−94.7	−61.9

[a] With respect to the reactants: HCN, methanimine, and bicyclicguanidine. [b] Relative energy with respect to the reactants: HCN, methanimine, and bicyclicguanidine.

HCN adds to methanimine to afford aminoisoacetonitrile, which then isomerizes to aminoacetonitrile (pathway B). Pathway A is thermodynamically more favorable. Additionally, we have located a transition structure between **I1a** and **I2a** using a 6-31G basis set; however, this transition structure evolves to **TS3** at the 6-31G(d) level. However, a reaction pathway of direct addition of HCN to methanimine to render aminoacetonitrile is also very likely.

The free energy of **TS2** is 67.7 kJ/mol, much lower than 180.7 kJ/mol, the value reported by Barone et al. for the addition in vacuo without catalyst. And the energy barrier of **TS2** is only 16.5 kJ/mol, substantially lower than 134.7 kJ/mol, the energy barrier of the addition of HNC to methanimine to supply aminoacetonitrile without catalyst. The free energy of aminoisoacetonitrile **P1** is 78.5 kJ/mol higher than that of aminoacetonitrile **P2**. Thus, the guanidine could catalyze the addition of HCN (or HNC) to methanimine, yielding aminoacetonitrile, and the aminoisoacetonitrile is thermodynamically unstable. In **I1b**, the complexation of aminoacetonitrile to bicyclic guanidine lowers the free energy by only 2.6 kJ/mol. Thus the aminoacetonitrile, once formed, will be very easy to dissociate from the complex **I1b**. This is consistent with the catalytic efficiency of Corey et al.'s catalyst.[6]

Conclusions

Two competitive pathways for the bicyclic guanidine-catalyzed reaction of HCN and methanimine to furnish aminoacetonitrile were rationalized. Namely, the HCN isomerizes to HNC and then adds to methanimine to give aminoacetonitrile, or the HCN adds to methanimine to provide aminoisoacetonitrile, which then isomerizes to supply aminoacetonitrile. The formation of aminoisoacetonitrile is unfavorable.

Thus, our calculations confirm that guanidine could efficiently catalyze the Strecker reaction of HCN and methanimine. And the results may be helpful for catalyst design for catalytic Strecker reactions.[21]

Acknowledgment. The authors thank Prof. Zhuo Zheng for help and the NKBRSF, the Knowledge Innovation Program of the Chinese Academy of Sciences (Grant DICP K2001/E3), for financial support of this research.

Supporting Information Available: Cartesian coordinates of all reported structures. This material is available free of charge via the Internet at http:/pubs.acs.org.

JO034891F

(21) A further study on the addition of HCN to methanimine catalyzed by formamidine, formamide, and urea is well underway in our laboratory.