DFT studies on Meisenheimer rearrangement

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ABSTRACT

[1,2]- and [2,3]-Meisenheimer rearrangements have been investigated on the basis of density functional theory. When allylic group is involved in tertiary amine N-oxide, the concerted [2,3]-allylic shift is most favorable. On the other hand, in [1,2]-Meisenheimer rearrangement, calculations indicate that methyl, ethyl, isopropyl, benzyl and 3-homoadamantyl transfer all favor the radical mechanism, which is in good agreement with the experiments; while phenyl transfer prefers the concerted mechanism. Meanwhile, oxidation will facilitate the functional group transfer. Calculations show that density functional theory provides a suitable tool for explaining the Meisenheimer rearrangement mechanisms.

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1. Introduction

Meisenheimer rearrangement, first introduced in 1919, is widely used in the organic synthesis [1–7] of many chemical materials, such as the indole analog isoindolo[2′,1′;1,2]azocino[5,6-b]indole (Fig. 1) [8], 5-alkoxypyrido[4,3-d]-pyrimidin-4(3H)-one derivative [7], and linalool [9], etc. In general, Meisenheimer rearrangement consists of two kinds of transfer: one is the [1,2]-sigmatropic rearrangement of tertiary amine N-oxides to hydroxylamines (Fig. 2a), while the other type is the [2,3]-sigmatropic rearrangement of allylic tertiary amine-N-oxides to produce O-allylhydroxylamines (Fig. 2b). As for [1,2]-Meisenheimer rearrangement, alkyl and benzyl can migrate from nitrogen to oxygen. On the other hand, the existence of allylic or propargyl group in tertiary amine N-oxide is the prerequisite condition for [2,3]-Meisenheimer rearrangement [10–12].

Although the Meisenheimer rearrangement is a classical organic reaction, the mechanism of this reaction has not been formally established. For example, as for [1,2]-Meisenheimer rearrangement, in the literature there have been three probable pathways proposed, as is shown in Fig. 2c: (i) A concerted sigmatropic rearrangement from nitrogen to oxygen to produce hydroxylamine; (ii) the initial homolytic cleavage of a carbon–nitrogen bond to form a radical pair, and then the alkyl radical can recombine the oxygen atom, yielding the hydroxylamine; (iii) an analogous ionic mechanism, which entails formation of the carbanion intermediate originating from the heterolytic cleavage of a carbon–nitrogen bond. Lorand et al. has studied the thermal Meisenheimer rearrangement of N-benzyl-N-methylaniline N-oxide [13]. In their work, oxygen,

as a scavenger of carbon radicals, could reduce the yield of N-benzyloxy-N-methylaniline from 89% (observed under nitrogen) to 33%. The reason was proposed as that oxygen could trap the benzyl radical, which came from the homolytic cleavage of a carbon–nitrogen bond in N-benzyl-N-methylaniline N-oxide. Besides, the other corresponding radical: N-methyl-N-phenylnitroxyl radical, were clearly characterized by ESR measurements on solutions of N-methyl-N-benzylaniline oxide. In addition, Leple et al. studied N-methyl-N-phenylnitroxyl radical by PMR technique [14]. On the basis of Lorand's and Leple's instructive work, it is indicated that the thermal Meisenheimer rearrangement of tertiary amine oxides proceeds via a homolytic dissociation–recombination mechanism, namely pathway (ii) in Fig. 2c rather than the heterolytic cleavage of the carbon–nitrogen bond to form ion pairs (pathway (iii), Fig. 2c). Even so, pathway (i) in Fig. 2c could not be excluded, for the addition of radical scavengers could not completely prevent the formation of the Meisenheimer product.

In this paper, density functional theory (DFT) has been applied to investigating the mechanism of Meisenheimer rearrangement in a series of tertiary amine N-oxides. As reported in the literature, DFT has been widely used to study the mechanism of organic reactions [15,16]. Through the comparison of the dissociation energy (BDE) of the pivotal C-N bond with the activation energy of the corresponding concerted sigmatropic rearrangement, the current study attempts to explore the intrinsical principle of the Meisenheimer rearrangement on the basis of theoretical calculations.

2. Computational methods

All calculations were carried out using the Gamess 09 program package [17,18]. Density functional theory was applied in this

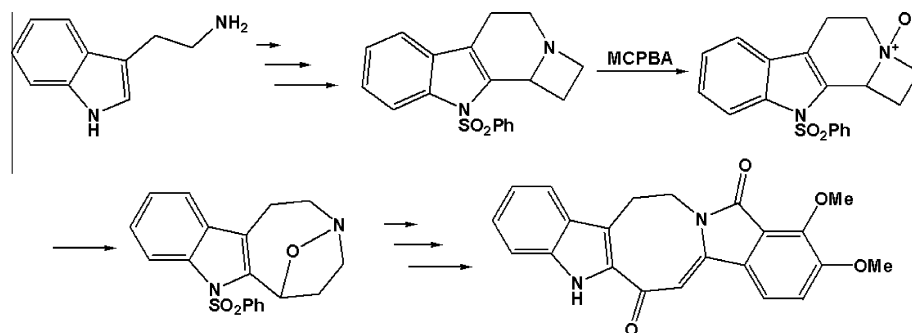*E-mail address:* zhangxiang@mail.zjgsu.edu.cn

Fig. 1. Total synthesis of the indole analog isoindolo[2′,1′;1,2]azocino[5,6-b]indole.

study to determine the optimized geometry, vibrational frequencies, and single-point energy of all stationary points. Single-point energies were obtained at the (U)B3lyp/6-311+G(3df,2p) level with the optimized (U)B3lyp/6-31G(d) geometries [19]. Frequency calculations identify minimum structures with all real frequencies, while transition states with only one imaginary frequency. A scaling factor of 0.9806 was used for the zero-point vibrational energy (ZPE) corrections [20]. Spin contamination for all of the stationary points was minimal (i.e., $0.75 < S^2 < 0.76$). The computational structures were displayed with MacMolPlt v7.4 [21].

3. Results and discussion

The present work starts with the calculations of the methyl transfer from nitrogen to oxygen in tertiary amine N-oxides, such as **M1** to **M4** (**M1**: $(CH_3)_3NO$, **M2**: $(CH_3)_2C_6H_5NO$, **M3**: $(CH_3)_2C_7H_6NO$ and **M4**: $(CH_3)_2C_3H_5NO$), as is shown in Fig. 3a–d. On the one hand, as for the concerted sigmatropic rearrangement mechanism in the Meisenheimer reaction, namely pathway i (Fig. 2c), the reaction rate is determined by the activation energy. On the other hand, in the homolytic dissociation–recombination mechanism, namely pathway (ii) (Fig. 2c), the rate-determining step is the homolytic dissociation of the N–C bond. Fig. 3a–d shows the dissociation energies of the N–C bond (BDE) in **M1** to **M4** and

the activation energies of corresponding methyl transfer in the concerted sigmatropic rearrangement (the corresponding transition states are **TS1** to **TS4**). In **M1** (Fig. 3a), BDE of the N–C bond is 36.3 kcal/mol, which is less than the activation energy of methyl transfer in **TS1** by 20.9 kcal/mol. This phenomenon indicates that in **M1** the homolytic dissociation–recombination mechanism is more reasonable than the concerted sigmatropic rearrangement one. In addition, similar conclusion has also been obtained from **M2** (Fig. 3b), **M3** (Fig. 3c) and **M4** (Fig. 3d). The details are as follows: BDEs of N–C bonds in **M2**, **M3** and **M4** are 28.0, 36.3 and 36.6 kcal/mol, respectively, while the corresponding activation energies of methyl transfer in **TS2**, **TS3** and **TS4** are 52.4, 58.0 and 58.3 kcal/mol, respectively. Based on the comparison of these energies, in **M2**, **M3** and **M4**, the methyl transfer favors the homolytic dissociation–recombination mechanism, namely the radical mechanism (pathway ii, Fig. 2c) is more likely to happen.

Besides methyl, we have also taken into account other functional groups, such as ethyl, isopropyl, benzyl and 3-homoadamantyl [22], which shift from nitrogen to oxygen in **M3**, **M5**, **M6** and **M7**, respectively (**M5**: $(CH_3)_2C_2H_5NO$, **M6**: $(CH_3)_2C_3H_7NO$, **M7**: $(CH_3)_2C_{11}H_{17}NO$), as is shown in Fig. 3e–h. In this figure, we present their respective activation energies of the concerted sigmatropic rearrangement (the transition states are TS5, TS3′, TS6 and TS7) and the corresponding dissociation energies of the N–C bond. As

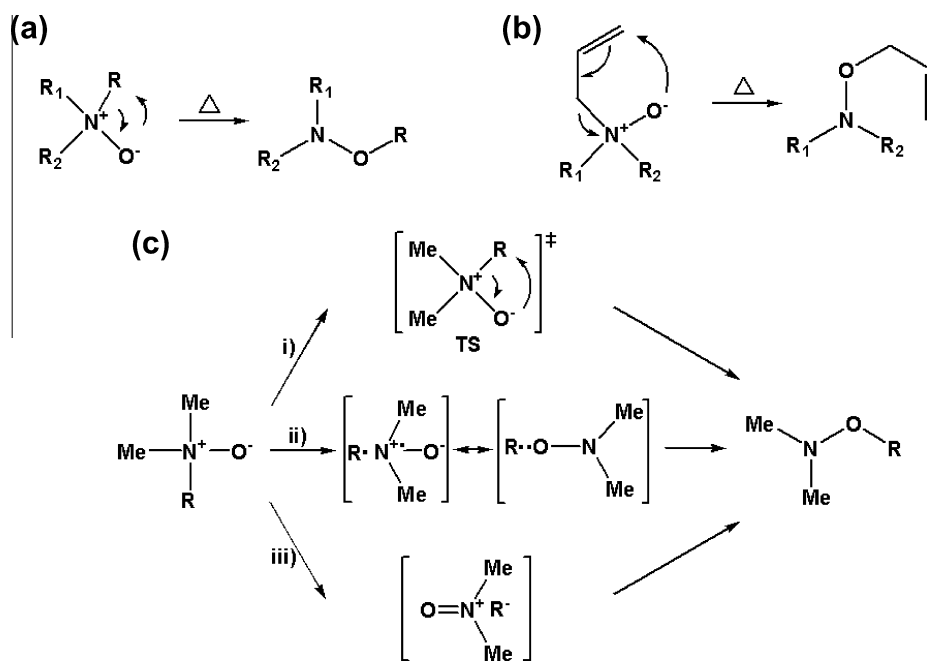**Fig. 2.** Mechanisms for [1,2]- and [2,3]-Meisenheimer rearrangement.