Intra- versus Intermolecular Carbon-to-Carbon Proton Transfers in the Reactions of Arynes with Nitrogen Nucleophiles: A DFT Study

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S *Supporting Information*

ABSTRACT: Carbon-to-carbon proton transfer (PT) is an elementary reaction in organic chemistry. Herein we report a systematic DFT study on the carbon-to-carbon proton transfers in the reactions of arynes with nitrogen nucleophiles, including tertiary amines, aziridines, imines, and *N*-heteroarenes. DFT calculations indicated that the Gibbs energies of activation for the 1,4- and 1,5-proton transfers involved are lower than 20 kcal/mol in most cases. We also found that the Bell−Evans−Polanyi principle applies to the 1,4-proton transfers, indicating that the more exergonic an intramolecular proton transfer is (the more stable a carbanion is generated), the faster it will be. Previous experimental studies have

shown that, in the presence of a carbon nucleophile (NuH; e.g., CHCl₃ and MeCN) as the third component (also as the solvent), intermolecular proton abstractions may compete with the intramolecular proton transfers and lead to different products. Our theoretical rationalization of these competitions is that the introduction of an electron-withdrawing group at the acidic site can accelerate the intramolecular proton transfer dramatically (owing to the generation of a more stable carbanion), making it compete with the intermolecular processes. In addition, we have also discussed the competition between intra- and intermolecular proton transfers when NuH is used as the reactant rather than the solvent.
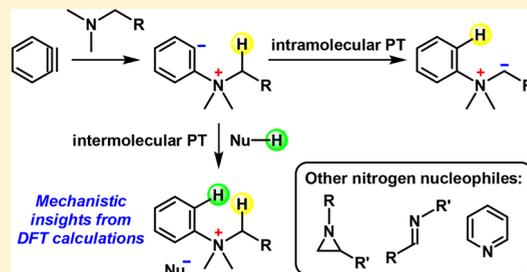
INTRODUCTION

Arynes are highly reactive species in organic synthesis. Tremendous efforts have been devoted to the development of new synthetic methodologies utilizing arynes as reaction partners.[1] Among them, the reactions of arynes with nitrogen nucleophiles, such as amines and imines, have been widely used in the synthesis of aniline derivatives and benzannulated *N*-heterocycles.[2−11] Mechanistically, these reactions usually start with the nucleophilic addition of a nitrogen nucleophile to aryne, generating an aryl anion intermediate (Scheme 1). Then the intramolecular carbon-to-carbon proton transfers (PTs) may take place. The intramolecular 1,4-proton transfer generates an ammonium ylide intermediate (Scheme 1a), whereas the intramolecular 1,5-proton transfer triggers a Hofmann-type elimination (Scheme 1b).[2] Nevertheless, in the presence of a third component (also as the solvent), a carbon nucleophile (NuH; e.g., CHCl₃), an intermolecular proton abstraction from NuH to the aryl anion intermediate (Scheme 1c) may compete with the intramolecular proton transfers.[2]

For instance, Hoye and co-workers recently reported the mechanistic duality in the reactions of hexadehydro-Diels−Alder (HDDA)-generated benzynes with tertiary amines (eqs 1 and 2).[2g] When there are no functional groups at the *β*-position, an intermolecular proton abstraction from the solvent (CHCl₃) and the subsequent substitution reaction take place (eq 1 and Scheme 1c). In contrast, when there is an electron-withdrawing group (EWG) at the *β*-position of the amine, a

Scheme 1. Carbon-to-Carbon Proton Transfers in the Reactions of Arynes with Tertiary Amines
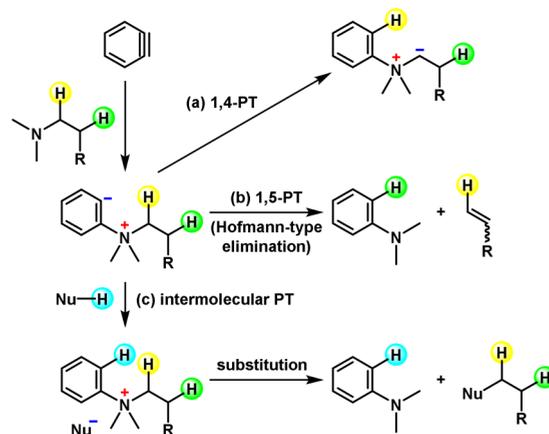
Hofmann-type elimination (triggered by an intramolecular 1,5-proton transfer) occurs (eq 2 and Scheme 1b).

The competition between intra- and intermolecular proton transfers also exists in the reactions of arynes with imines (Scheme 2).[4] Hwu and co-workers reported a 1:2 coupling of arynes with imines, generating functionalized imidazolidines in a highly diastereoselective manner (Scheme 2a).[4a] They
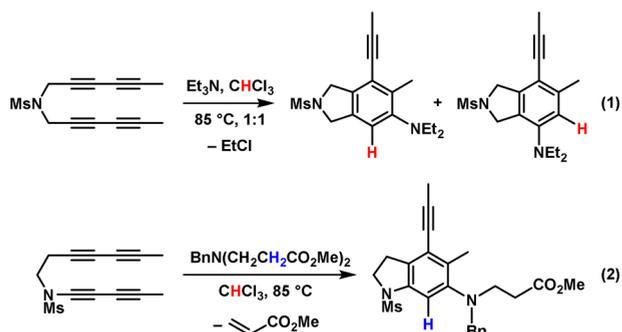
Scheme 2. Reactions of Arynes with Imines Reported by Hwu[4a] and Tian[4e]
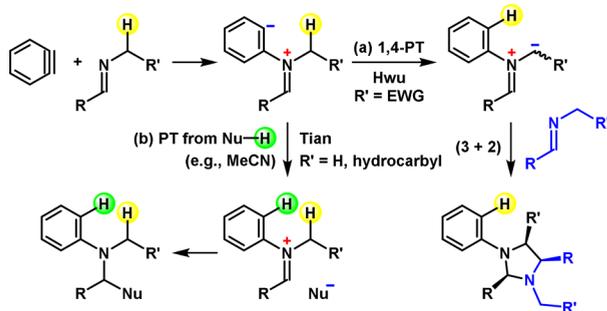
proposed that the reaction proceeds through a nucleophilic addition, followed by an intramolecular 1,4-proton transfer to generate an azomethine ylide species, which then undergoes a (3+2) cycloaddition to afford the final product. No deuterium labeling experiments have been conducted by the Hwu group to confirm the intramolecular nature of the 1,4-proton transfer, possibly because such experiments may not provide convincing evidence for the proposed mechanism, considering that there are fast H/D scramblings at the α-position of the imine nitrogen under basic conditions. Recently, Tian and co-workers discovered a three-component carboarylation of imines with arynes and carbon nucleophiles (e.g., MeCN) (Scheme 2b).[4e] Their deuterium labeling experiments indicated that the aryl anion directly deprotonates the carbon nucleophile, rather than undergoing the intramolecular 1,4-proton transfer.

A similar mechanistic switch has also been observed in the reactions of arynes with N-heteroarenes.[5] The three-component reaction of arynes, pyridines, and isatins in THF was reported by Biju[5b] and Rodriguez and Coquerel (Scheme 3a).[5c] Pyrid-2-ylidene was proposed as the key reaction intermediate, which reacts with isatin to generate an indolin-2-one derivative as the final product. Deuterium labeling experiments and DFT

Scheme 3. Reactions of Arynes with N-Heteroarenes Reported by Cheng,[5a] Biju,[5b] and Rodriguez and Coquerel[5c]
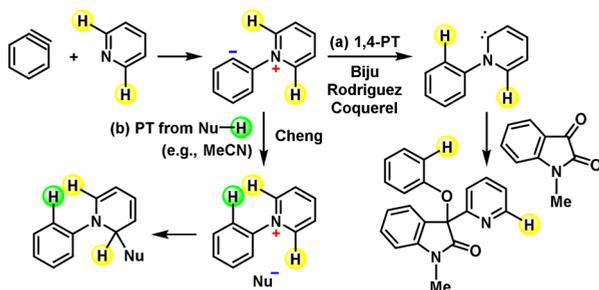
calculations at the B3LYP/6-311++G(d,p) level of theory (the predicted Gibbs energy of activation is 12.9 kcal/mol) have proven that the 1,4-proton transfer, which leads to the pyrid-2-ylidene intermediate, takes place intramolecularly. Nevertheless, the intramolecular proton transfer is not always the most favored reaction pathway. As reported by Jeganmohan and Cheng, the reaction of arynes with N-heteroarenes in nitrile-containing solvents does not proceed through the intramolecular proton transfer (Scheme 3b).[5a] Deuterium labeling experiments indicated that the intermolecular proton transfer from CD_3CN to aryl anion is favored over the intramolecular 1,4-proton transfer. Otherwise, the deuterium atom should be incorporated into the N-heterocycle of the final product, rather than into the phenyl ring.

Previously we reported a detailed quantum chemical study on the carbon-to-carbon $1,n$-proton transfers (Scheme 4).[12] We

Scheme 4. Our Previous Work on Carbanion Translocations via Proton Transfers[12]
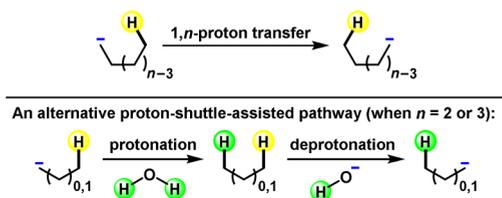
found that when $n = 2$ or 3, the intramolecular proton transfer is difficult to occur and requires the assistance of proton shuttles. In contrast, when $n > 3$, the intramolecular proton transfer becomes much easier. For carbon-to-carbon $1,n$-proton transfers involved in the reactions of arynes with nitrogen nucleophiles (Schemes 1−3), n is always larger than 3. Therefore, we predicted that these intramolecular proton transfers can take place under mild conditions even without the assistance of proton shuttles. However, as mentioned above, in the presence of carbon nucleophiles, the intermolecular proton transfers may compete with these intramolecular proton transfers and then affect the reaction mechanism and product selectivity (Schemes 1−3). To the best of our knowledge, no theoretical rationalization for these competitions has been reported.

Here we report our systematic DFT study on the carbon-to-carbon proton transfers in the reactions of arynes with nitrogen nucleophiles, including tertiary amines, aziridines, imines, and N-heteroarenes. Proton transfers involved in the reactions with these nitrogen nucleophiles will be discussed in turn. We have disclosed the origins affecting the mechanistic switch between intra- and intermolecular proton transfers. In addition, we have also investigated the regioselectivity of the intramolecular proton transfer processes. These mechanistic insights may help chemists to understand the proton transfer processes in aryne chemistry and to design new reactions.

■ COMPUTATIONAL METHODS

All DFT calculations were performed using Gaussian 09 software.[13] Pruned integration grids with 99 radial shells and 590 angular points per shell were used. Solution-phase geometry optimizations of all of the minima and transition states involved were carried out using the SMD solvation model[14] at the M06-2X[15]/6-31+G(d,p)[16] level of theory without any constrains. The M06-2X functional was chosen because it not only can provide accurate values for free energies of solvation[17] but also has an excellent performance on the intra-

molecular carbon-to-carbon proton transfers.[12,18] Unscaled harmonic frequency calculations at the same level were performed to validate each structure as either a minimum or a transition state and to evaluate its zero-point energy and thermal corrections at 298 K. Quasiharmonic corrections were applied during the entropy calculations by setting all of the positive frequencies that are less than 100 cm^{-1} to 100 cm^{-1}.[17,19] On the basis of the optimized structures, single-point energy calculations were carried out at the SMD/M06-2X/maug-cc-pVTZ[20] level of theory. All of the discussed energy differences were based on Gibbs energies at 298 K. Unless otherwise specified, all of the conformers were located but only the ones with the lowest Gibbs energies were reported. Standard state concentrations of 12.4,[21] 18.9,[22] 11.2,[23] 7.6,[24] and 1.0 mol/L were used for CHCl$_3$, MeCN, benzene, n-hexane, and other species, respectively. The 3D structure for **TS16** was prepared using CYLview.[25]

■ RESULTS AND DISCUSSION

Generally, the nucleophilic addition to aryne is rapid, in some cases, even under diffusion control.[26] Meanwhile, the regioselectivity of such a nucleophilic addition has also been well studied in literature.[27] Thus, herein we only report the computational results of proton transfer processes.

Tertiary Amines and Aziridines as Nucleophiles. First, we investigated the 1,4-proton transfers in the reactions of benzyne with tertiary amines (**1a**−**g**) and aziridines (**1h** and **1i**) in THF (Table 1).[2,3] Most of these proton transfers are exergonic except for the transformation of the aryl anion **2a** into an unstable primary alkyl anion **3a** (Table 1, entry 1). The predicted Gibbs energies of activation are all lower than 20 kcal/mol, indicating that these 1,4-proton transfers take place easily. Our previous works on intramolecular carbon-to-carbon proton transfers[12,28] indicated that the thermodynamic driving force plays an important role in determining the relative ease of intramolecular proton transfers. Generally, the larger the thermodynamic driving force is, the faster the intramolecular proton transfer will be (i.e., the Bell−Evans−Polanyi principle[29]). Here, the same conclusion holds for the intramolecular 1,4-proton transfers in aryne chemistry. As depicted in Figure 1, there indeed exists a positive linear correlation between the Gibbs energy change and the Gibbs energy of activation (the corresponding data are given in Table 1). Moreover, a linear correlation was also found between the Gibbs energy change and the difference between the aryl···proton and alkyl···proton distances in the intramolecular 1,4-proton transfer transition state (ΔR) (Figure 2). The negative slope indicates that the larger the thermodynamic driving force is, the earlier the transition state will be (i.e., the Hammond−Leffler postulate[30]).

The thermodynamic driving force not only affects the reactivity, but also results in regioselectivity. For example, the intramolecular proton transfer from the methine (CH) position of the benzyne−aziridine adduct **2i** is favored over that from the methylene (CH$_2$) position by 7.6 kcal/mol (Table 1, entries 9 and 10; the Gibbs energies of activation for **TS9** (CH) and **TS9′** (CH$_2$) are 3.0 and 10.6 kcal/mol, respectively). So the deprotonation takes place at the methine position exclusively.[3e] Such an excellent regioselectivity (kinetic preference) originates from the fact that the electron-withdrawing cyano group increases the acidity of its α-position more significantly than its β-position, as judged by the larger thermodynamic driving force for the α-deprotonation (−27.5 kcal/mol) than that for the β-deprotonation (−13.9 kcal/mol).

Then, we investigated the competition between inter- and intramolecular proton transfers in Hoye's work, as mentioned

Table 1. Intramolecular 1,4-Proton Transfers in the Reactions of Benzyne with Tertiary Amines and Aziridines in THF[a]

$$\Delta R = R_1 - R_2$$
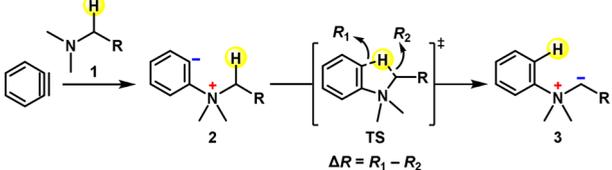
entry	1	2	TS	3	ΔR (Å)	ΔG	$\Delta G^{\ddagger}$
1	**1a**	**2a**	TS1	**3a**	−0.107	2.8	19.6
2	**1b**	**2b**	TS2	**3b**	0.263	−26.9	6.2
3	**1c**	**2c**	TS3	**3c**	0.208	−22.9	6.5
4	**1d**	**2d**	TS4	**3d**	0.222	−22.8	4.6
5	**1e**	**2e**	TS5	**3e**	0.170	−17.6	10.0
6	**1f**	**2f**	TS6	**3f**	0.015	−5.6	14.9
7	**1g**	**2g**	TS7	**3g**	−0.042	−2.5	15.9
8	**1h**	**2h**	TS8	**3h**	0.013	−6.6	14.9
9	**1i**	**2i**	TS9	**3i**	0.262	−27.5	3.0
10	**1i**	**2i**	TS9'	**3i'**	0.092	−13.9	10.6

[a]Energies are reported in kcal/mol.

above (eqs 1 and 2).[2g] The HDDA-generated benzyne and tertiary amine substrates were simplified as benzyne, Me$_2$NEt (**1j**), and Me$_2$NCH$_2$CH$_2$CO$_2$Me (**1k**), respectively. As shown in Figure 3, DFT calculations indicated that the Gibbs energies of activation for the intermolecular proton transfers from
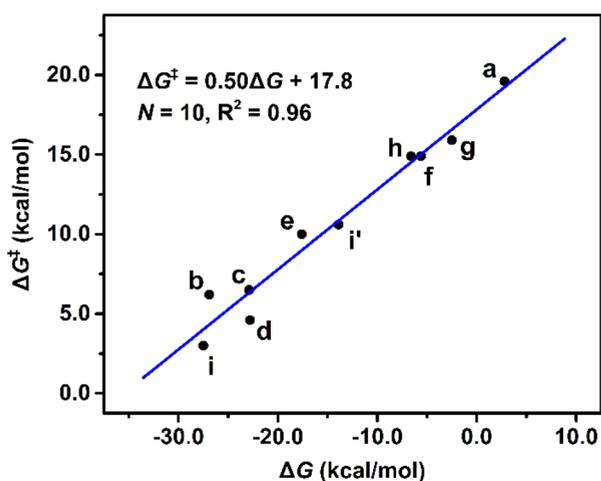
Figure 1. Plot of the Gibbs energies of activation ($\Delta G^{\ddagger}$) versus the Gibbs energy changes (ΔG) for intramolecular 1,4-proton transfers.
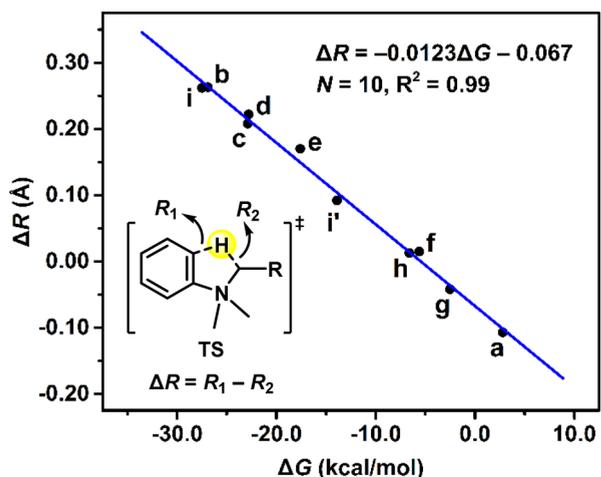
Figure 2. Plot of the difference between the aryl···proton and alkyl···proton distances in the proton transfer transition state (ΔR) versus the Gibbs energy changes (ΔG) for intramolecular 1,4-proton transfers.

Figure 3. Competition between inter- and intramolecular proton transfers in the reactions of benzyne with Me_2NEt (**1j**) and $Me_2NCH_2CH_2CO_2Me$ (**1k**) in $CHCl_3$.

CHCl$_3$ to the aryl anions **2j** and **2k** are both lower than 6 kcal/mol. For adduct **2j** without any functional groups at the β-position of the amine, the Gibbs energy of activation for the concerted asynchronous Hofmann-type elimination (triggered by an intramolecular 1,5-proton transfer) is as high as 23.0 kcal/mol (Figure 3a). As a result, the intermolecular proton transfer pathway is favored over the intramolecular one, which is in good accordance with Hoye's results (eq 1). For adduct **2k** with an electron-withdrawing methoxycarbonyl group at the β-position of the amine, the Gibbs energy of activation for the Hofmann-type elimination is reduced to 8.2 kcal/mol due to the larger thermodynamic driving force (Figure 3b). In this case, the intramolecular proton transfer still cannot compete against the intermolecular proton transfer, which disagrees with Hoye's experiments (eq 2).

We reasoned that such a disagreement may result from the oversimplification of the substrates in our calculations. In Hoye's experiment (eq 2), the fully substituted benzyne **8** (see Figure 4 for the structure) was used; while in our computations, the unsubstituted benzyne was used as the model substrate. To verify this hypothesis, we carried out DFT calculations using the real substrate **8** (Figure 4). For the intramolecular proton

transfer, the Gibbs energy of activation increases by 1.6 kcal/mol (from 8.2 kcal/mol for **TS12** to 9.8 kcal/mol for **TS14**), possibly due to the fact that the introduction of the electron-donating groups decreases the basicity of the aryl anion intermediate. In contrast, the energy change (7.6 kcal/mol) is much larger in the intermolecular case (to simplify the computations, the symmetric NMe_3 was used instead of **1k**; otherwise, hundreds of transition states should be located, which is beyond our ability). The Gibbs energy of activation for the intermolecular proton transfer between $CHCl_3$ and **2a** is 4.6 kcal/mol, while the intermolecular proton transfer between $CHCl_3$ and **10**, which is the adduct of **8** and NMe_3, increases dramatically to 12.2 kcal/mol, mainly due to the steric repulsion among the CCl_3, NMe_3, and Ms moieties in **TS16** (Figure 4c; the electronic effect is estimated to be similar to the intramolecular case as shown in Figure 4a, i.e., 1.6 kcal/mol). Consequently, for the real substrate **8**, the intermolecular proton transfer is disfavored over the intramolecular one by ca. 2 kcal/mol (estimated by the energy difference between **9**→**TS14** and **10**→**TS16**), which agrees with Hoye's experiments
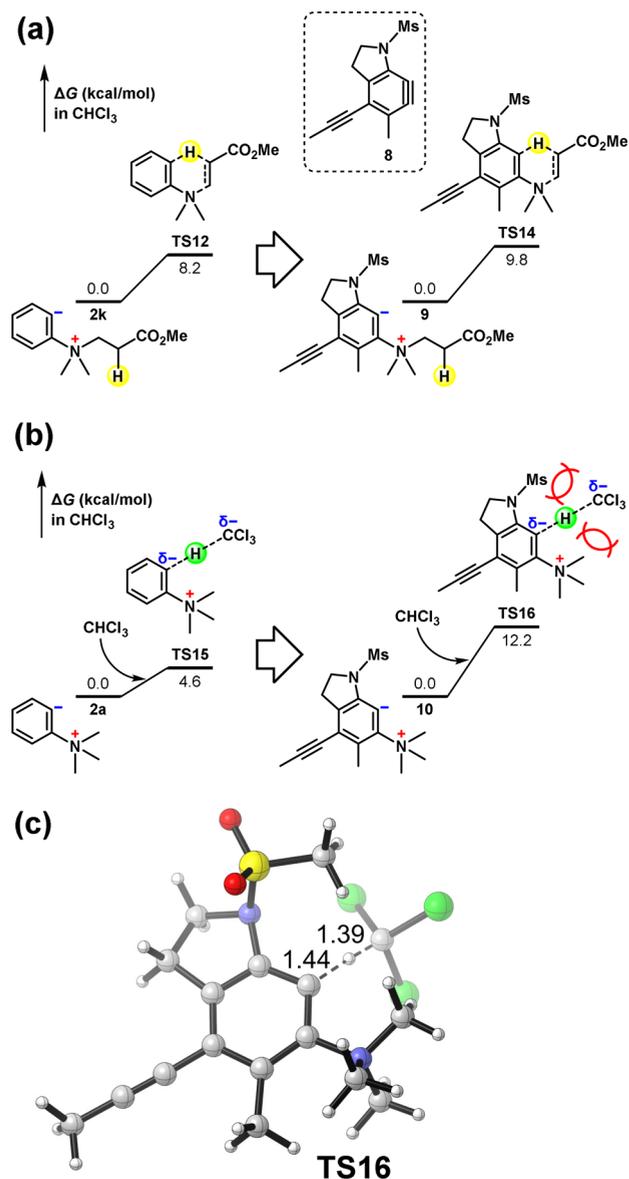
Figure 4. (a) Comparison of the intramolecular proton transfers in the reactions of Me$_2$NCH$_2$CH$_2$CO$_2$Me (**1k**) with benzyne and the real substrate **8** in CHCl$_3$. (b) Comparison of the intermolecular proton transfers in the reactions of NMe$_3$ (**1a**) with benzyne and **8** in CHCl$_3$. (c) Optimized geometries for **TS16**. Color scheme: H, white; C, gray; N, blue; O, red; S, yellow; and Cl, green. Bond distances are reported in Å.

(eq 2). These results suggest that both the electronic and steric effects can affect the relative ease of intra- and intermolecular proton transfers, which should be kept in mind when proposing the reaction mechanism in aryne chemistry.

Imines as Nucleophiles. To understand the mechanistic switch between 1:2 coupling[4a] and carboarylation,[4e] as shown in Scheme 2, we performed DFT calculations on the reactions of benzyne with imines **11a** and **11b** (see Figure 5 for the structures).

First, we investigated the reaction of benzyne with **11a** in MeCN (Figure 5a). We chose this model reaction because of its similarity to Tian's report (eq 3).[4e] The iminium zwitterionic species **12a** may undergo two reaction pathways. One is the formation of the azomethine ylide **13a** through an intramolecular 1,4-proton transfer via **TS17a** (the Gibbs energy of activation is 20.8 kcal/mol). The other is the intermolecular proton abstraction from MeCN via **TS18a** (the Gibbs energy of activation is 13.0 kcal/mol), leading to an ion pair **15a**. DFT calculations indicated that the intermolecular proton transfer is favored over the intramolecular one by 7.8 kcal/mol. Considering that the subsequent nucleophilic addition is easy and irreversible, the intermolecular proton transfer pathway

Figure 5. Competition between inter- and intramolecular proton transfers in the reactions of benzyne with imines **11a** and **11b** in MeCN.

should take place exclusively, which is in accordance with the experimental observations by the Tian group (eq 3).

Then, we investigated the reaction between benzyne and **11b** in MeCN (Figure 5b). This reaction has been investigated experimentally by Hwu and co-workers (eq 4).[4a] As shown in Figure 5b, the shape of the Gibbs energy profile differs dramatically from that of the reaction between benzyne and **11a** (Figure 5a). In this case, the intramolecular proton transfer is favored over the intermolecular one by 5.6 kcal/mol (the relative Gibbs energies of **TS17b** and **TS18b** are 8.1 and 13.7 kcal/mol, respectively). This result supports Hwu's proposal that the 1,4-proton transfer takes place intramolecularly.[4a] Meanwhile, considering that the intramolecular proton transfer is highly exergonic (−35.6 kcal/mol) and thus irreversible, the azomethine ylide **13b** should be formed. **13b** and its stereomers then undergo the (3+2) cycloaddition with **11b** to give imidazolidines as the final products. These calculations are in agreement with the experimental results from the Hwu group (eq 4).

By comparing the two Gibbs energy profiles, we speculated that the mechanistic switch between Hwu's (triggered by an intramolecular proton transfer) and Tian's chemistry (triggered by an intermolecular proton transfer) may originate from the substituent effect. The introduction of the cyano group affects the intermolecular proton transfer by only 0.7 kcal/mol (13.0 kcal/mol for **TS18a** versus 13.7 kcal/mol for **TS18b**). In contrast, it accelerates the intramolecular proton transfer significantly (20.8 kcal/mol for **TS17a** versus 8.1 kcal/mol for **TS17b**) due to the presence of a larger thermodynamic driving force (the Gibbs energy changes of **12a→13a** and **12b→13b** are −17.5 and −35.6 kcal/mol, respectively; Bordwell's pK_a values in DMSO[31] for methane and MeCN are ca. 56 and 31.3, respectively, indicating the generation of a more stable carbanion in the latter case).

***N*-Heteroarenes as Nucleophiles.** Similarly, our DFT calculations indicated that the intramolecular 1,4-proton transfer that generates pyrid-2-ylidene **17** is disfavored over the intermolecular proton transfer from MeCN by 2.3 kcal/mol (Figure 6; the Gibbs energies of activation for the intra- and intermolecular proton transfers are 15.8 and 13.5 kcal/mol, respectively). This result suggests that the reaction of benzyne

and pyridine in MeCN should proceed through the intermolecular proton transfer/nucleophilic addition pathway, which is in accordance with the experimental observations by Jeganmohan and Cheng (Scheme 3b).[5a]

Activation versus Diffusion Control. In the above discussion, the carbon nucleophiles are the solvents, which are always close to the reactive carbanionic centers. Therefore, the reaction rates of these bimolecular processes are not limited by the diffusion process. However, as depicted in Figure 7, if
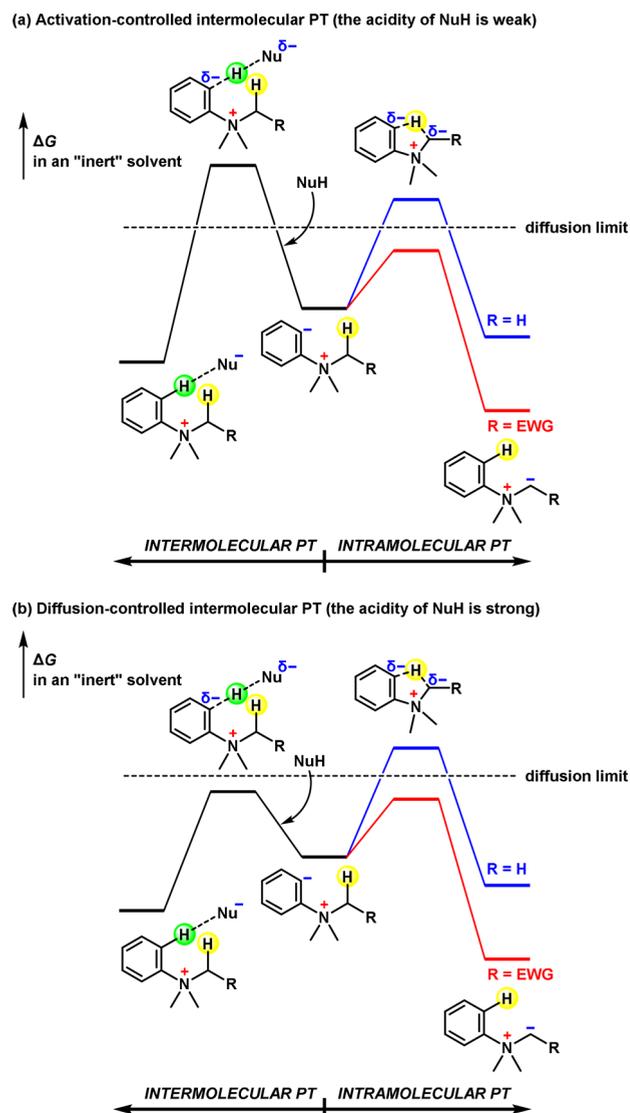
Figure 7. Competition between inter- and intramolecular proton transfers in the presence of a carbon nucleophile (NuH) in an "inert" solvent.

the carbon nucleophile is not used as the solvent but as a reactant in an "inert" solvent (e.g., benzene and *n*-hexane), one can envision that the diffusion process may influence the reaction rate of the intermolecular proton transfer between the carbon nucleophile and the aryl anion, especially when the acidity of the carbon nucleophile is strong (Figure 7b). Here the "inert" solvent does not participate in the proton transfer because such a process is difficult compared to the two competing processes shown in Figure 7 (the computed Gibbs energies of activation for the intermolecular proton transfer

Figure 6. Competition between inter- and intramolecular proton transfers in the reaction of benzyne with pyridine in MeCN.

from benzene and *n*-hexane to **2a** are 27.5 and 36.8 kcal/mol, respectively, see the Supporting Information for details).

The first-order rate constant for the diffusion-controlled intermolecular proton transfer is ca. 10^8 M^{-1} s^{-1} (the typical second-order diffusion rate constant in water)[32] × 0.01−1 M (the typical range for the concentration of a carbon nucleophile). The corresponding Gibbs energy of activation at 1 M (aryl anion) and 298 K is ca. 7−9 kcal/mol. For a fast intramolecular proton transfer (e.g., R = EWG), whose Gibbs energy of activation is smaller than ca. 7−9 kcal/mol, neither the activation-controlled (Figure 7a) nor the diffusion-limited (Figure 7b) intermolecular proton transfers can compete against the intramolecular proton transfer. In contrast, if the Gibbs energy of activation for an intramolecular proton transfer is larger than ca. 7−9 kcal/mol (e.g., R = H), it cannot compete against the diffusion-controlled intermolecular proton transfer (Figure 7b), but may compete with the activation-controlled intermolecular proton transfer if the acidity of the carbon nucleophile is weak (Figure 7a).

CONCLUSIONS

We have systematically investigated the carbon-to-carbon proton transfer processes in the reactions of arynes and nitrogen nucleophiles, including tertiary amines, aziridines, imines, and *N*-heteroarenes, based on DFT calculations. In most cases, the intramolecular 1,4- and 1,5-proton transfers are easy processes, especially in the presence of large thermodynamic driving forces. The regiochemistry has also been explored computationally, suggesting that the introduction of an electron-withdrawing group can result in excellent regiocontrol. We have also investigated the competition between the intramolecular proton transfer and the intermolecular proton abstraction from the carbon nucleophile (e.g., CHCl$_3$ and MeCN), whether or not it serves as the solvent. The substituents may have a significant influence on the inter- and/or intramolecular proton transfers through electronic and/or steric effects, and they tune the mechanistic switch between the inter- and intramolecular reaction pathways. The acidity of the carbon nucleophile may also affect the selectivity. These computational results and theoretical rationalizations further deepen the understanding of the carbon-to-carbon proton transfers in aryne chemistry.

ASSOCIATED CONTENT

⑤ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b03109.

> Additional computational results, computed energies, and Cartesian coordinates of all of the stationary points (PDF)

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Notes
The authors declare no competing financial interest.

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