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Sigmatropic Rearrangement

Stereospecific Diaza-Cope Rearrangement Driven by Steric Strain**

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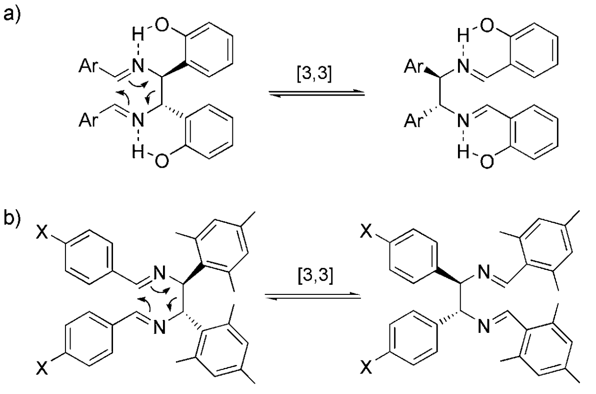
Vögtle and Goldschmitt[1] were the first to use hydrogen bonds to drive diaza-Cope rearrangement reactions to completion over thirty years ago. Although many interesting publications on the topic have since appeared,[2] no other weak forces have been found to drive the rearrangement reaction to completion. The diaza-Cope rearrangement is useful for synthesizing a wide variety of chiral vicinal diamines (Scheme 1)[3] that may be valuable for the development of catalysts[4] and drugs.[2,5] [3,3] Sigmatropic reactions, including the Cope, Claisen, oxy-Cope, and aza-Cope reactions, have received much interest on both a theoretical[6] and a practical[7] level. The diaza-Cope rearrangement provides an ideal platform for studying the effects of weak forces in [3,3] sigmatropic reactions, as the systematic variation in the structure of the starting materials that is needed for these investigations can be achieved readily through simple synthesis. It is well known that strained molecules show remarkable reactivity.[8] Herein, we report the effect of steric strain on the rate and equilibrium constants of the diaza-Cope rearrangement reaction. Although ring strain has been used to drive [3,3] sigmatropic rearrangements,[1a,9] this reaction is the first example of a [3,3] sigmatropic rearrangement driven by steric strain.



1a: X = NO_2
2a: X = OCH_3
3a: X = H

1b: X = NO_2
2b: X = OCH_3
3b: X = H

Scheme 1. a) Hydrogen-bond-driven and b) steric-effect-driven diaza-Cope rearrangement reaction.

We prepared (*S*,*S*)-1,2-bis(2,4,6-trimethylphenyl)-1,2-diaminoethane (TPEN)[10] through the diaza-Cope rearrangement of the diimine formed from (*R*,*R*)-1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (HPEN) and mesitaldehyde.[3] The addition of benzaldehydes (2.5 equiv) with electron-donating or electron-withdrawing substituents to (*S*,*S*)-1,2-bis(2,4,6-trimethylphenyl)-1,2-diaminoethane in ethanol and subsequent stirring of the reaction mixture overnight at ambient temperature gave the corresponding rearranged diimines **1b**–**3b** in good yields (80–85%). The identity of products **1b**–**3b** of the rearrangement reaction was confirmed by comparing their ^{1}H NMR spectra with those of the diimines prepared from the corresponding diamines and mesitaldehyde. Although the initial diimines **1a**–**3a** were not isolated, their clean formation ($\delta_H = 5.6$ ppm for **3a**, Figure 1) and conversion into the product diimines ($\delta_H = 4.8$ ppm for **3b**) could be monitored readily by ^{1}H NMR spectroscopy. The equilibrium constants for the rearrangement reactions in Scheme 1 must be greater than 10^2, as we did not observe any of the initial diimines by ^{1}H NMR spectroscopy after equilibration. We were pleasantly surprised that the steric effect was so dramatic and complete for the rearrangement reactions (Figure 1).

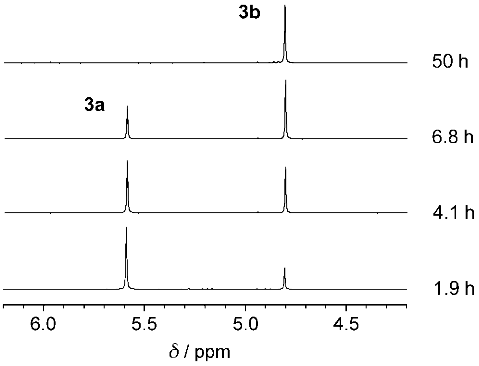


Figure 1. Monitoring the conversion of **3a** into **3b** by ^{1}H NMR spectroscopy in [D$_6$]DMSO. DMSO = dimethyl sulfoxide.

Figure 2a shows the crystal structure of **1b** formed through the rearrangement of **1a**.[11] This structure is "preorganized"[3c] for the reversible rearrangement reaction and resembles the computed transition-state (TS) structure for the rearrangement of **3a** (Figure 2b).[12]

We investigated the effect of steric strain on the rate and equilibrium constants for the rearrangement of **3a** to **3b** by DFT computation (B3LYP at the 6-31G* level). The difference in the computed energies of **3b** and **3a** (5.5 kcal mol^{-1})

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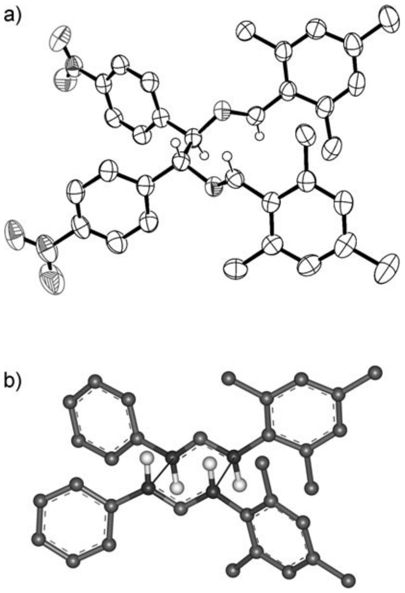


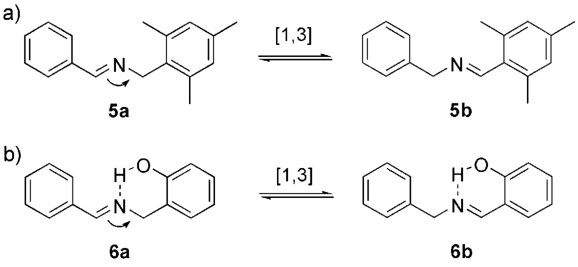
Figure 2. a) Crystal structure of **1b** (ORTEP diagram with thermal ellipsoids drawn at 50% probability). b) Computed structure (DFT) of the transition state for the rearrangement of **3a** to **3b**. All hydrogen atoms except those in the imine and diamine backbone have been omitted for clarity.

translates into an equilibrium concentration ratio of about 10^4:1 in favor of **3b** at 25°C. This ratio is consistent with the result observed by ^{1}H NMR spectroscopy, which showed complete conversion of **3a** into **3b**.

Computation further revealed that the energy barrier for the conversion of **3a** into **3b** (19.4 kcal mol^{-1}) is lower than the energy barrier (21.5 kcal mol^{-1}) for the rearrangement of the diimine **4** formed from diphenylethylenediamine (DPEN) and benzaldehyde. Consistent with these computation results, the experimental rate constant for the rearrangement of **3a** to **3b** (4.19×10^{-5} s^{-1} at 25°C) is greater than that for the rearrangement of **4** (1.74×10^{-5} s^{-1}).[13] Our kinetic experiment shows that only a small amount of the steric strain is released at the transition state.[14]

It is not intuitively obvious how the steric effect in **3a** (or **1a** and **2a**) manifests itself in driving the rearrangement reaction to completion. One possibility is that the steric repulsion between the two mesityl groups in **3a** weakens the C–C bond that is cleaved in the rearrangement reaction. To gain insight into the steric effect on the reaction (Scheme 1b), we dissected the rearrangement by dividing **3a** in two (Scheme 2) and examined the energetics of the "half" compound **5a**. The rearrangement of the "half" compound corresponds to a [1,3] sigmatropic shift.

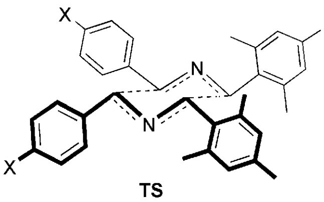
Interestingly, DFT computation showed that the rearrangement of **5a** (Scheme 2) is disfavored by about 1.9 kcal mol^{-1}, whereas the rearrangement of the "full" compound **3a** is favored by about 5.5 kcal mol^{-1}. We suggest that the rearrangement of **5a** is disfavored at least in part because of the decease in imine conjugation. The C=N bond in the imine **5a** can be planar with the phenyl group, whereas that in **5b** can not be fully planar or conjugated with the mesityl group owing to steric effects. A loss in imine conjugation is also expected for the rearrangement of **3a.** However, the destabilization **3a** as a result of the steric repulsion of the two mesityl groups appears to be greater than the resonance stabilization of the imine group.



Scheme 2. Computed [1,3] sigmatropic shifts directed by a) a steric effect and b) hydrogen bonding.

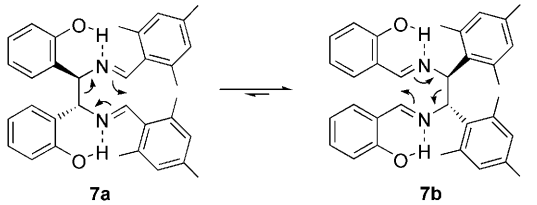
In sharp contrast to the reactions driven by steric energy, DFT computation showed that the rearrangement of the "half" compound **6a** for the hydrogen-bond-directed reaction is favored by about the same amount (3.8 kcal mol^{-1}) as the rearrangement of the corresponding full compound (6.8/2 kcal mol^{-1}) after statistical correction. We showed that a subtle difference in the strengths of the hydrogen bonds can drive diaza-Cope rearrangement reactions to completion.[3] The resonance-assisted hydrogen bond[15,16] (RAHB) in **6b** is expected to be a few kilocalories per mole more stable than the regular hydrogen bond in **6a**.

The rearrangement reactions in Scheme 1 most likely proceed via chairlike six-membered-ring transition states (**TS**) with all substituents in equatorial positions (Figure 2b). Consistent with this hypothesis, the rearrangements of the initial diimines **1a**–**3a** proceed with 100% chirality transfer, as observed for the RAHB-directed[15,16] rearrangement reactions.[3c] HPLC on a chiral phase showed that the stereospecificity for the conversion of **3a** into **3b** is exceptionally high (> 99.5%), even though no hydrogen bonds are involved (see the Supporting Information).



TS

We studied the rearrangement of **7a** to **7b** and the reverse reaction (Scheme 3) in detail to compare the steric effect and the hydrogen-bonding effect on the diaza-Cope rearrangement. The same ratios of **7a** to **7b** were observed at equilibrium whether we started with **7a** or **7b**. Diimine **7b** is favored over **7a** by a ratio of about 14:1 in $CDCl_3$ at 25°C. The solvent effect on the equilibrium is small ([D$_8$]toluene: 17:1; [D$_6$]DMSO: 6:1). DFT computation showed that **7b** is more stable than **7a** by 1.6 kcal mol^{-1}. This translates into an equilibrium ratio of **7a** to **7b** of about 15:1 at 25°C. Both experiment and computation showed that **7b** is more stable



Scheme 3. Competition between steric and hydrogen-bonding effects.

than **7a**. Thus, the hydrogen-bond effect appears to be somewhat stronger than the steric effect for the rearrangement reaction.

We determined the activation parameters for the interconversion of **7a** and **7b** by measuring the rate constants of the forward and reverse reactions at different temperatures (60–100 °C). At 60 °C, the rate constants for the forward and reverse reactions are 1.1×10^{-4} and $2.8 \times 10^{-5}\,\mathrm{s}^{-1}$, respectively. The values of the activation entropy and activation enthalpy for the conversion of **7a** into **7b** are $-8.2\,\mathrm{cal\,mol^{-1}\,K^{-1}}$ and $22.9\,\mathrm{kcal\,mol^{-1}}$, respectively (Figure 3).

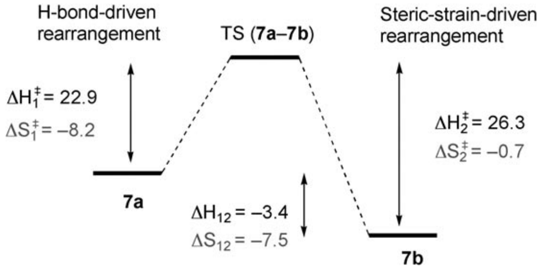
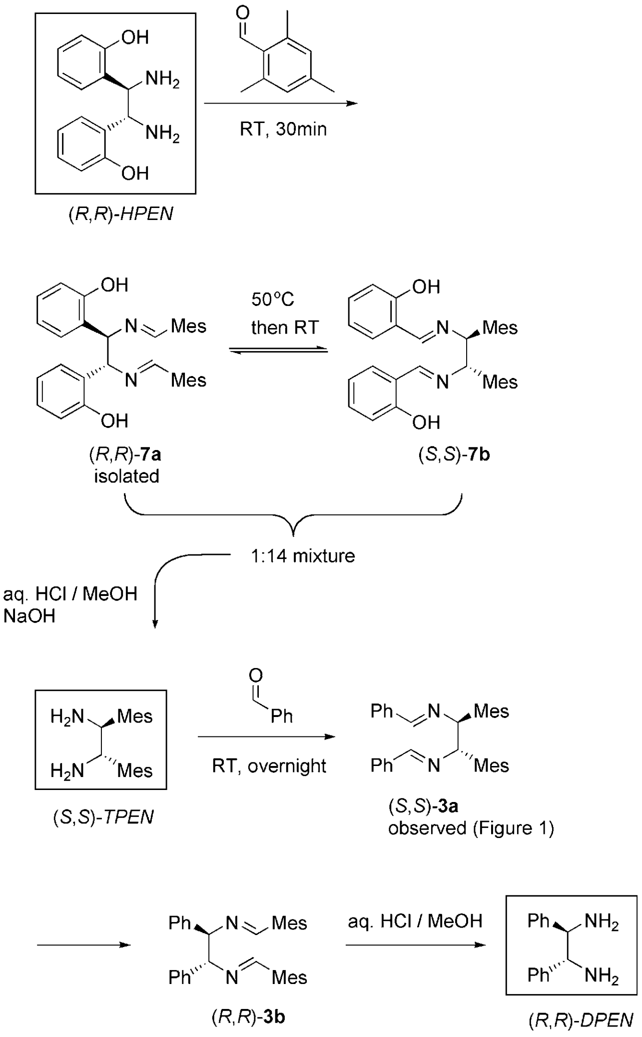


Figure 3. Energy profile for the interconversion of **7a** and **7b** (ΔH and $\Delta H^{\ddagger}$ values in $\mathrm{kcal\,mol^{-1}}$, ΔS and $\Delta S^{\ddagger}$ values in $\mathrm{cal\,mol^{-1}\,K^{-1}}$).

For the reverse reaction, these values are $-0.7\,\mathrm{cal\,mol^{-1}\,K^{-1}}$ and $26.3\,\mathrm{kcal\,mol^{-1}}$. Interestingly, there is a considerable entropic driving force ($\Delta S = 7.5\,\mathrm{cal\,mol^{-1}}$) for the steric-effect-driven diaza-Cope rearrangement of **7b** to **7a**. Thus, the equilibrium constant for the formation of **7b** increases with decreasing temperature ($-T\Delta S$; see the Supporting Information). The conversion of **7a** into **7b** is expected to result in a favorable enthalpy change due to the strengthening of the hydrogen bonds and an unfavorable enthalpy change due to the increase in strain energy associated with the steric effect. The net favorable enthalpy change ($\Delta H = -3.4\,\mathrm{kcal\,mol^{-1}}$) indicates that more is gained from the strong hydrogen bonds than lost because of the steric effects. The value of this experimental enthalpy change is in reasonably good agreement with the computed value ($-1.6\,\mathrm{kcal\,mol^{-1}}$). The change in Gibbs free energy (ΔG) for the conversion of **7a** into **7b** is $-1.2\,\mathrm{kcal\,mol^{-1}}$ ($-3.4 + 298 \times 7.5 \times 10^{-3}$) at 25 °C.



Scheme 4. Consecutive diaza-Cope reactions.

Two consecutive diaza-Cope rearrangement reactions can be used to form (*R*,*R*)-diphenylethylenediamine ((*R*,*R*)-DPEN) from (*R*,*R*)-HPEN with exceptionally high overall stereospecificity (Scheme 4). Although this approach does not serve as a highly practical synthetic route to (*R*,*R*)-DPEN, it demonstrates the excellent stereospecificity of the rearrangement reaction with and without RHABs.

In conclusion, we have demonstrated that steric strain can dramatically influence the equilibrium in [3,3] sigmatropic reactions. Its effect can overcome electronic effects and compete with the effect of resonance-assisted hydrogen bonds. Dissection of the rearrangement reaction (Scheme 2) provided interesting insight into the steric effect. Computation showed that the mesityl group has opposite effects on the [3,3] and [1,3] sigmatropic reactions.

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[11] Crystal data for **1b**: $C_{34}H_{34}N_4O_4$, $T = 150(2)$ K, monoclinic, $C2$, $Z = 4$, $a = 27.2150(16)$, $b = 8.7120(3)$, $c = 14.1740(9)$ Å, $\alpha = 90$, $\beta = 115.134(2)$, $\gamma = 90°$, $V = 3042.4(3)$ Å^3, $R_1 = 0.0480$, $wR_2 = 0.1120$ for $I > 2\sigma(I)$, GOF(F^2) $= 1.009$.

[12] Global-minimum-energy structures **3a** and **3b** were obtained by molecular-mechanics computation. These structures and the transition-state structure (Figure 2b) were optimized further by DFT computation at the B3LYP/6-31G* level.

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