ACCOUNTS
of chemical research

Understanding the Interplay of Weak Forces in [3,3]-Sigmatropic Rearrangement for Stereospecific Synthesis of Diamines

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RECEIVED ON JANUARY 18, 2012

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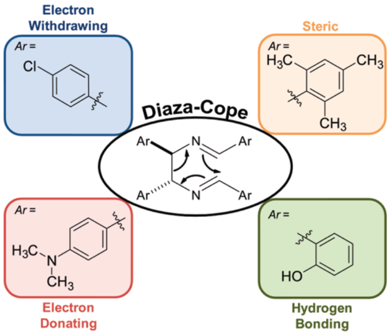

Chiral diamines are important building blocks for constructing stereoselective catalysts, including transition metal based catalysts and organocatalysts that facilitate oxidation, reduction, hydrolysis, and C—C bond forming reactions. These molecules are also critical components in the synthesis of drugs, including antiviral agents such as Tamiflu and Relenza and anticancer agents such as oxaliplatin and nutlin-3. The diaza-Cope rearrangement reaction provides one of the most versatile methods for rapidly generating a wide variety of chiral diamines stereospecifically and under mild conditions. Weak forces such as hydrogen bonding, electronic, steric, oxyanionic, and conjugation effects can drive this equilibrium process to completion.

In this Account, we examine the effect of these individual weak forces on the value of the equilibrium constant for the diaza-Cope rearrangement reaction using both computational and experimental methods. The availability of a wide variety of aldehydes and diamines allows for the facile synthesis of the diimines needed to study the weak forces. Furthermore, because the reaction generally takes place cleanly at ambient temperature, we can easily measure equilibrium constants for rearrangement of the diimines. We use the Hammett equation to further examine the electronic and oxyanionic effects. In addition, computations and experiments provide us with new insights into the origin and extent of stereospecificity for this rearrangement reaction.

The diaza-Cope rearrangement, with its unusual interplay between weak forces and the equilibrium constant of the reaction, provides a rare opportunity to study the effects of the fundamental weak forces on a chemical reaction. Among these many weak forces that affect the diaza-Cope rearrangement, the anion effect is the strongest (10.9 kcal/mol) followed by the resonance-assisted hydrogen-bond effect (7.1 kcal/mol), the steric effect (5.7 kcal/mol), the conjugation effect (5.5 kcal/mol), and the electronic effect (3.2 kcal/mol). Based on both computation and experimental data, the effects of these weak forces are additive. Understanding the interplay of the weak forces in the [3,3]-sigmatropic reaction is interesting in its own right and also provides valuable insights for the synthesis of chiral diamine based drugs and catalysts in excellent yield and enantiopurity.

Introduction

There has been much interest in chiral vicinal diamines over the last couple of decades (Figure 1). The wide availability of dach (1,2-diaminocyclohexane) and dpen (1,2-diphenylethylenediamine) led to the development of some of the most useful stereoselective catalysts for oxidation,[1] hydrogenation,[2] and hydrolysis[3] reactions. Furthermore, invention of the anticancer drug oxaliplatin would have been difficult if dach was not readily available (Figure 1). A general method for making chiral diamines beyond dach and dpen would thus be useful for developing stereoselective catalysts and bioactive compounds.

We recently developed a simple and unified approach to creating a wide variety of chiral diamines in enantiomerically pure form starting from a single compound, hpen (1,2-bis(2-hydroxyphenyl)ethylenediamine), that we call the "mother" diamine (Scheme 1).[4−6] In general, simple mixing of aldehydes with hpen in ethanol at ambient temperature results in formation of the initial diimine followed by the diaza-Cope rearrangement (DCR) and precipitation of the

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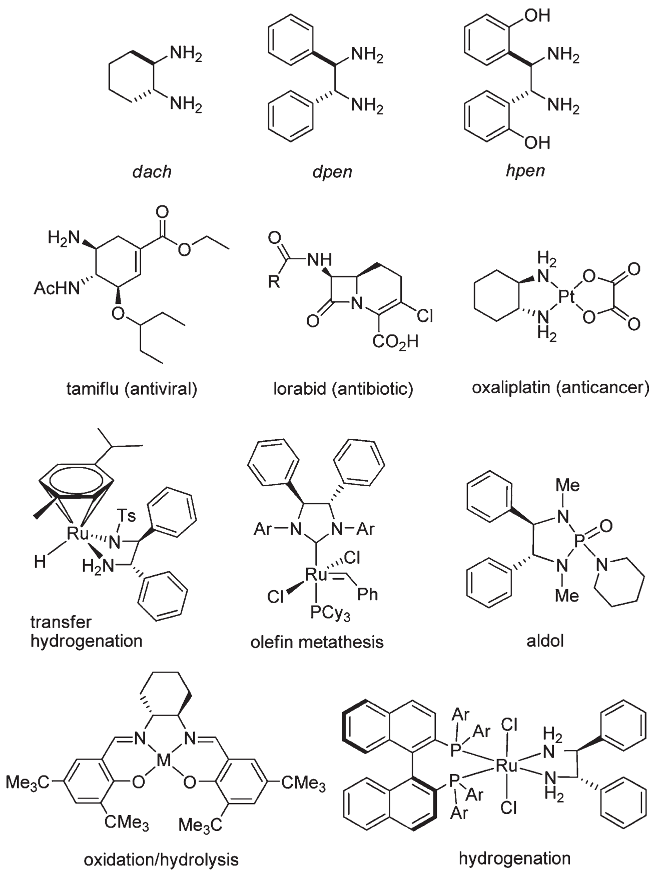
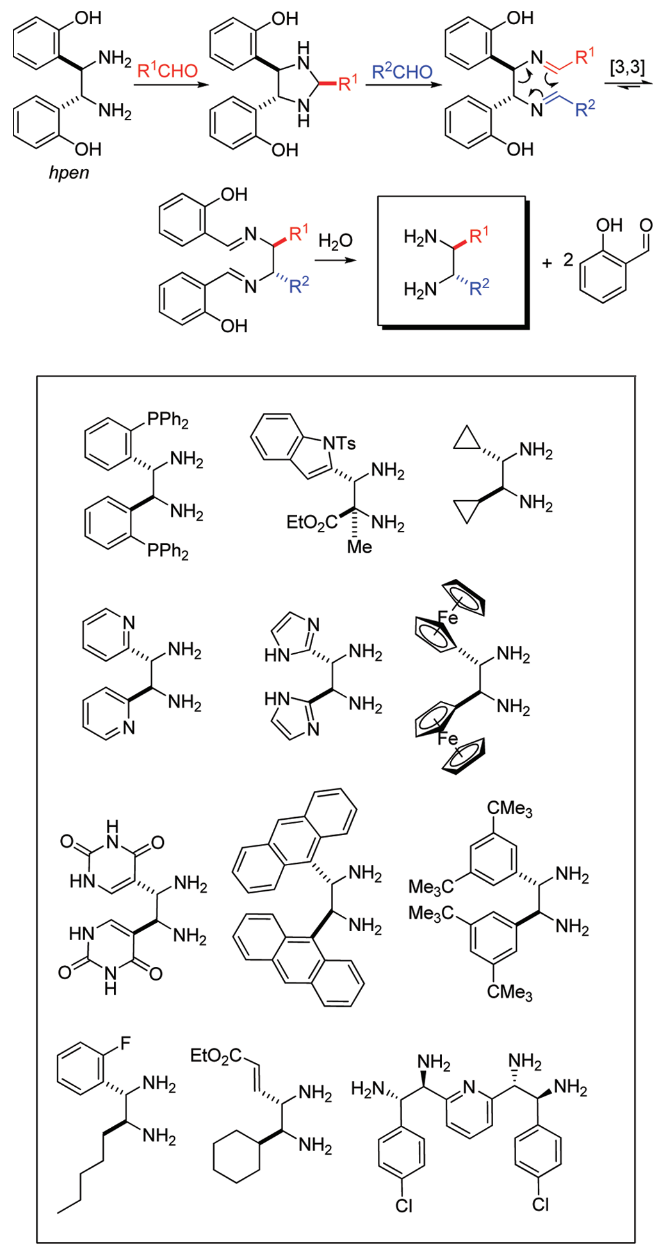


FIGURE 1. Chiral vicinal-diamine-based drugs and catalysts.

rearranged diimine, which can be easily filtered and hydrolyzed to give the C_2 symmetric or unsymmetric "daughter" diamines with alkyl or aryl substituents (Scheme 1).

Ready availability of hpen and the ease of the diaza-Cope rearrangement have led to a number of interesting applications (Figure 2). Steric and electronic tuning of diamine-based catalysts can now be easily accomplished by making the appropriate chiral diamines from hpen. Thus, we tuned the stereoselectivity of a diamine-based organocatalyst (**a**) for making warfarin.[7] Fu,[8] Carreira,[9] and Busacca[10] optimized their transition metal based catalysts (**b**, **c**, **d**) by tuning the diamines with hpen. Ding[11] showed how hpen can be used in chiral monophos ligands (**e**) for stereoselective hydrogenation reactions. Hong and Kim[12] used hpen and the DCR reaction to make a novel diamine-based cyanide sensor (**f**), while Akine and Nabeshima[13] developed a helical lever (**g**) by the same process. Huang and Xia[14] developed diamines with rigid backbones (**h**, **i**) from hpen. Furthermore, Vögtle[15] used *meso* hpen and DCR to make *meso* diamine-based dendrimers (**j**), while Vu[16] synthesized an anticancer agent nutlin-3 (**k**) by using the same process.

SCHEME 1. Conversion of hpen to Other Chiral Diamines by DCR



Here we review the effect of weak forces (hydrogen bonding,[17] electronic,[18] steric,[19] oxyanionic, and conjugation[20] effects) in controlling the equilibrium of the DCR reaction for making chiral diamines (Scheme 2). Study of the weak forces in the DCR reaction not only may be useful for making chiral diamines but may also be useful for comparisons with other studies on the effects of weak forces in a large variety of [3,3]-sigmatropic reactions[21−23] including the Claisen,[24] Cope,[25] oxy-Cope,[26] aza-Cope,[27] and aza-Claisen[28] rearrangements and their pioneering computational studies.[29−31] The DCR reaction is ideally set up for studying the role of weak forces. The availability of hpen

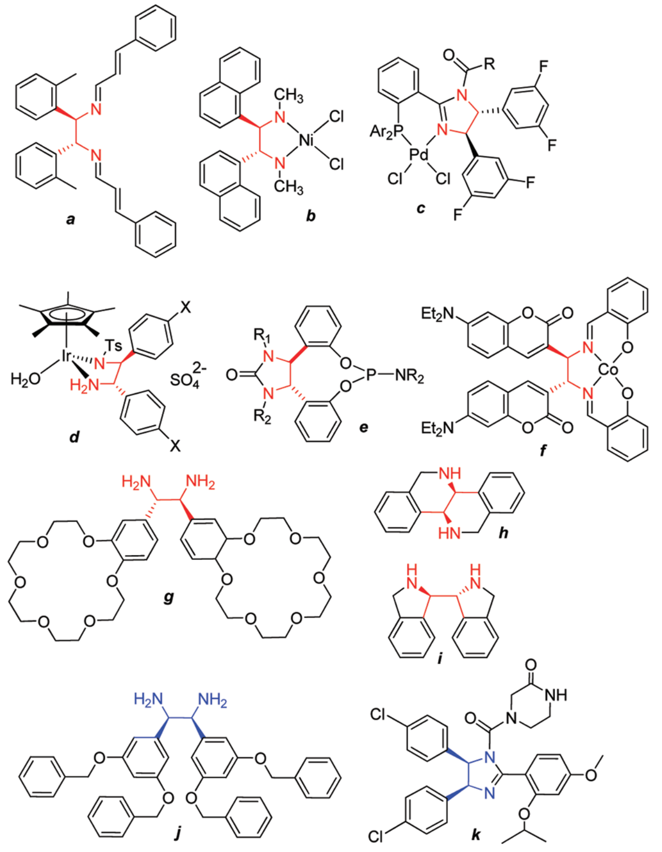


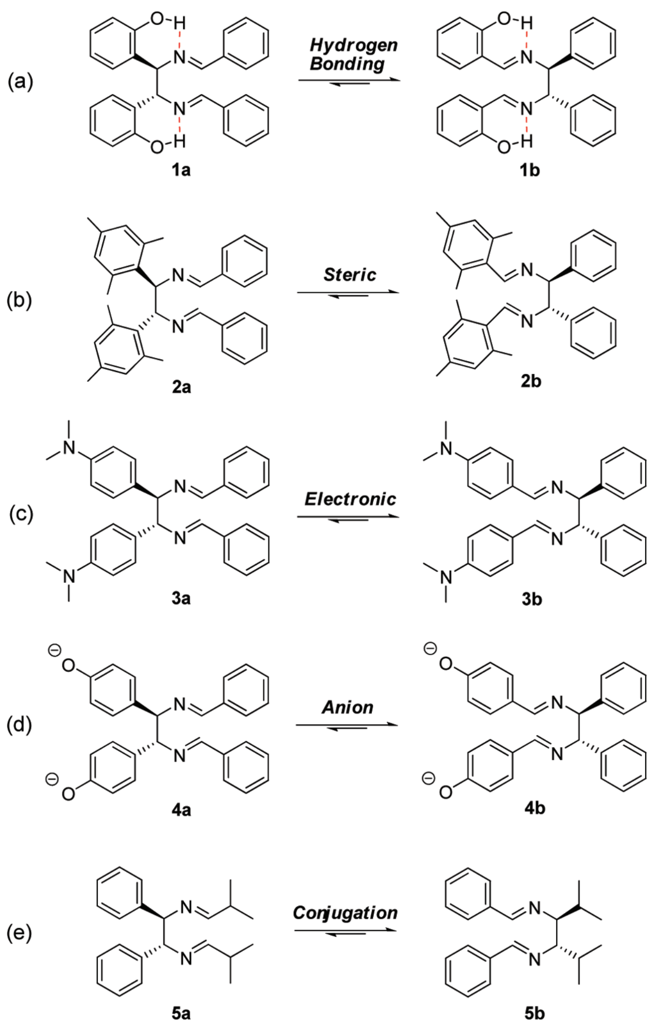
FIGURE 2. Application of hpen.

has facilitated our study of the weak forces in the DCR reaction. Systematic variation in the structure of the diimines that is needed for the study of weak forces in DCR (Scheme 2b–e) can be readily accomplished by synthesizing the required diamines from hpen and aldehydes. Systematic variation in the structures of the starting materials for the other [3,3]-sigmatropic reactions would be much more difficult than for the DCR reaction. Furthermore, the DCR reactions generally take place cleanly under mild conditions making it easier to measure the equilibrium constant.

Thermodynamic Perturbations

There are several interesting weak forces that can be used to control the equilibrium in the diaza-Cope rearrangement including (a) H-bonding, (b) steric, (c) electronic, (d) anionic, and (e) conjugation effects (Scheme 2). All five effects are well suited for both experimental and computational investigations. Thermodynamic effects of the weak forces are discussed below.

SCHEME 2. Diaza-Cope Rearrangements Controlled by (a) Hydrogen Bonding, (b) Steric, (c) Electronic, (d) Anionic, and (e) Conjugation Effects



(a). Hydrogen Bonding Effect. Seminal reports by Vögtle[32] on diaza-Cope rearrangement and by Gilli[33] on resonance assisted hydrogen bonds (RAHBs) led to our development of RAHB-directed diaza-Cope rearrangement[17] for making chiral diamines (Scheme 2a).[34] Subtle changes in the strength of H-bonds can have dramatic effects on the equilibria for diaza-Cope rearrangements. In order to understand the difference in the strength of the H-bonds in **1a** and **1b** (Scheme 2), it is instructive to first examine the H-bonds in **6a** and **6b** (Figure 3). The term RAHB was introduced by Gilli to explain the synergistic interplay between π-delocalization and H-bonding. Delocalization of the lone pair electrons on the oxygen of **6a** should result in some charge separation (Figure 3). Charged H-bonds are stronger than neutral H-bonds since they are reinforced by favorable electrostatic interactions. Unlike in **6a**, resonance-assisted charge separation is not possible in **6b**. This explanation provides some intuitive insight into why the H-bond in **6a** may be stronger than that in **6b**. NMR, IR, and crystal data all indicate that RAHBs are stronger than regular H-bonds.[33]

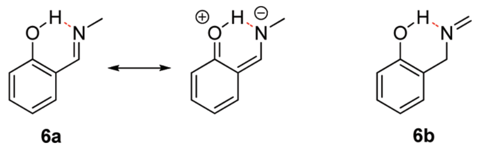
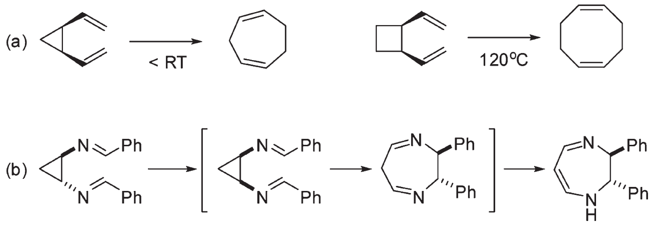


FIGURE 3. Resonance-assisted hydrogen bond in **6a** and hydrogen bond in **6b**.

SCHEME 3. [3,3]-Sigmatropic Rearrangements Driven by Ring Strain



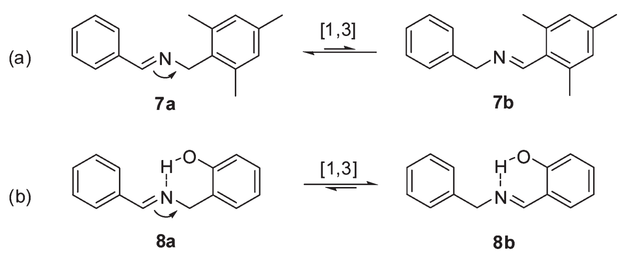
DFT computation shows that the RAHB in **6a** is about 2.7 kcal/mol stronger than regular hydrogen bonds.[33]

Following the above argument, the two RAHBs in **1b** are expected to be about 2.7 kcal/mol stronger than the two regular hydrogen bonds in **1a** (Scheme 2). If the relative stability of compounds **1a** and **1b** is solely dependent on the strengths of the H-bonds, **1b** should be more stable than **1a** by about 5.4 kcal/mol. In close agreement with this assumption, DFT computation (B3LYP at the 6-31G(d) level) reveals that **1b** is about 6.8 kcal/mol more stable than **1a**. This energy difference translates to an equilibrium constant of 9.3×10^4 at 25 °C for the rearrangement. ^{1}H NMR indeed reveals that **1a** rearranges to **1b** to completion within detection limits. It appears that the equilibrium for the rearrangement of **1a** is largely controlled by the strength of the H-bonds. It is remarkable that subtle changes in the strength of H-bonds can dramatically shift the equilibria for diaza-Cope rearrangements.

(b). Steric Effect. In 1960, Vogel was the first to show that three- or four-membered ring strain can be used to drive the Cope rearrangement to completion (Scheme 3a).[35] The ring-strain-driven Cope rearrangement of *cis*-1,2-divinylcyclopropane to 1,4-cycloheptadiene goes to completion even at −20 °C and the half-life for the rearrangement at 35 °C is about 90 s.[36] Since the early studies by Vogel, ring strain has been widely used to control the equilibria in [3,3]-sigmatropic rearrangement reactions.[37,38] Vögtle used ring strain to control the diaza-Cope reaction (Scheme 3b).[39]

In addition to ring strain, steric strain can be used to control the equilibria in diaza-Cope rearrangements (Scheme 2b).[19] ^{1}H NMR data showed that compound **2a** cleanly undergoes diaza-Cope rearrangement to completion to give **2b**. Consistent with the experimental data, DFT computation reveals that **2b** is more stable than **2a** by about 5.5 kcal/mol, which translates to an equilibrium concentration ratio of about 10^4:1 for [**2b**]/[**2a**] at 25 °C. It appears that the steric repulsion between the two mesityl groups in **2a** weakens the C−C bond that is cleaved in the rearrangement reaction.

SCHEME 4. Computed [1,3]-Sigmatropic Rearrangements



To gain insight into the steric effect for the rearrangement of **2a** (Scheme 1b), the energetics of the "half" reaction (Scheme 4a) was examined. The rearrangement of the "half" compound (**7a**) corresponds to a [1,3]-sigmatropic shift reaction. Interestingly, DFT computation shows that the rearrangement of **7a** is disfavored by about 1.9 kcal/mol, whereas the rearrangement of the "full" compound (**2a**) is favored by about 5.5 kcal/mol. We suggest that the rearrangement of **7a** is disfavored at least in part because of the decrease in imine conjugation in **7b**. The C=N bond in the imine **7a** can be planar with the phenyl group, whereas that in **7b** cannot be fully planar or conjugated with the mesityl group owing to steric effects. A loss in imine conjugation is also expected for **2b**. However, the destabilization of **2a** as a result of the steric repulsion of the two mesityl groups appears to be greater than the resonance stabilization of the imine group. In sharp contrast to the rearrangement of **7a** to **7b**, DFT computation shows that the rearrangement of the "half" compound (**8a**, Scheme 4b) for the RAHB-directed reaction is favored by a comparable amount (3.8 kcal/mol) as the rearrangement of the corresponding full compound (**1a** to **1b**) after statistical correction (6.8/2 kcal/mol).

It is interesting that the steric strain generated by the mesityl group can dramatically shift the equilibria for diaza-Cope rearrangements. The steric effect largely disappears if the mesityl groups are replaced by other less hindered groups such as 2-methylphenyl or 2,4,6-trimethoxyphenyl groups.

(c). Electronic Effect. Vögtle and Goldschmitt showed that the racemic diimine prepared from *rac*-1,2-bis(4-methoxyphenyl)-1,2-diaminoethane and 4-nitrobenzaldehyde undergoes diaza-Cope rearrangement to completion.[32] Systematic investigation of the electronic effect on

SCHEME 5. Diaza-Cope Rearrangements Controlled by Electronic Effects

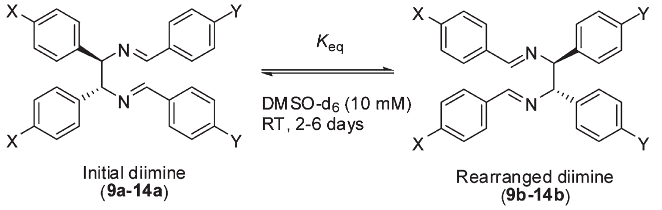


TABLE 1. Experimental and Computed Energy Change for the Rearrangement of **9a**–**14a**[a]

diimine	X	Y	$\Delta\sigma^{+b}$	$K_{eq}{}^c$	ΔG^d	$\Delta H_{calcd}{}^e$
9a	H	H	0	1	0	0
10a	H	OMe	−0.78	0.12	1.3	1.6
11a	H	Me	−0.31	0.31	0.69	0.55
12a	H	Cl	0.11	3.0	−0.65	−0.62
13a	OMe	Me	0.47	3.0	−0.65	−1.2
14a	OMe	NMe_2	−0.92	0.056	1.7	1.6

[a] Energy values in kcal/mol. [b] $\Delta\sigma^+ = \sigma^+(Y) - \sigma^+(X)$. [c] Equilibrium constant measured by ^1H NMR at 25 °C. [d] $\Delta G = -RT \ln K_{eq}$. [e] DFT at the B3LYP/6-31G(d) level.

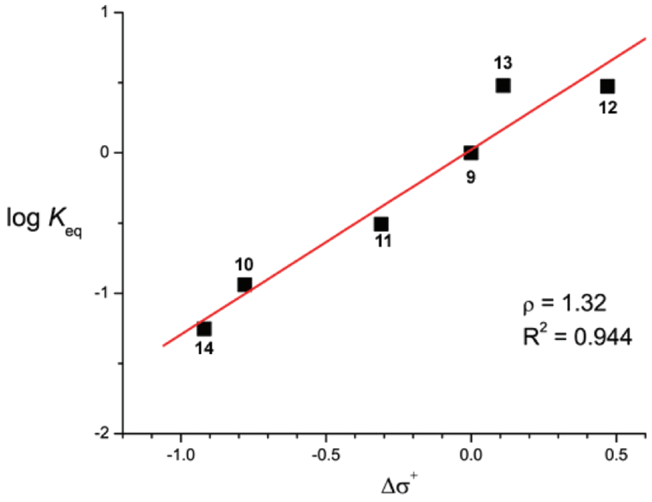


FIGURE 4. Hammett plot for the diaza-Cope rearrangement of **9a**–**14a**.

the diaza-Cope rearrangement became recently possible with the greater availability of chiral vicinal diamines (Scheme 5 and Table 1).[40]

The measured equilibrium constants for the rearrangement of five diimines (**9a**–**14a** in Scheme 5) are listed in Table 1. It can be seen from Table 1 that the equilibrium favors the side with the more electron-rich imine. Electron-donating groups are expected to stabilize the imine bond by conjugation. A Hammett plot[41] (Figure 4) shows that there is excellent linear relationship between the logarithm of the equilibrium constant for the rearrangement of **9a**–**14a** and $\Delta\sigma^+$ (where $\Delta\sigma^+$ represents $\sigma^+(Y) - \sigma^+(X)$ for substituents X and Y in Scheme 5) with a ρ^+ value of 1.32 and a correlation coefficient (R^2) of 0.944. According to this plot the equilibrium constant for the rearrangement of the above-mentioned diimine prepared by Vögtle and Goldschmitt (X = OMe and Y = NO_2, Scheme 5) is estimated to be over 100 ($10^{(\rho\Delta\sigma+)} = 10^{\{1.32(0.79+0.78)\}}$). In Scheme 5, if X is a dimethylamino group ($\sigma^+ = -1.70$), and Y is any electron-withdrawing group ($\sigma^+ > 0$), the equilibrium constant (K_{eq}) for the rearrangement is expected to be greater than 100 ($10^{(\rho\Delta\sigma+)} = 10^{(1.32\times1.70)}$). Consistent with this calculation, the diimine **3a** in Scheme 2 where X = NMe_2 and Y = H rearranges to completion as measured by ^1H NMR.

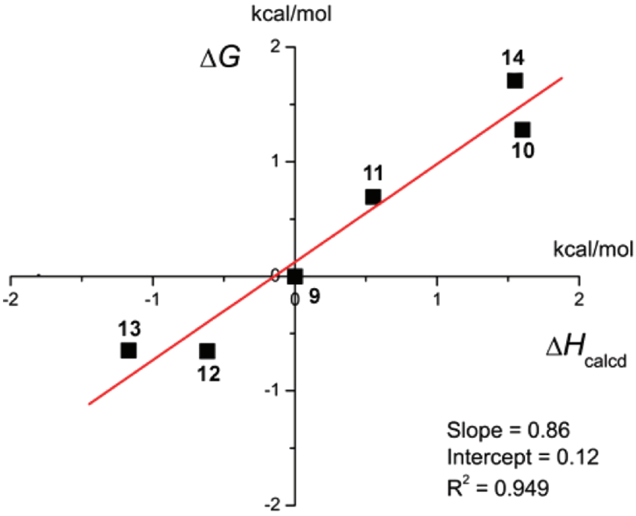
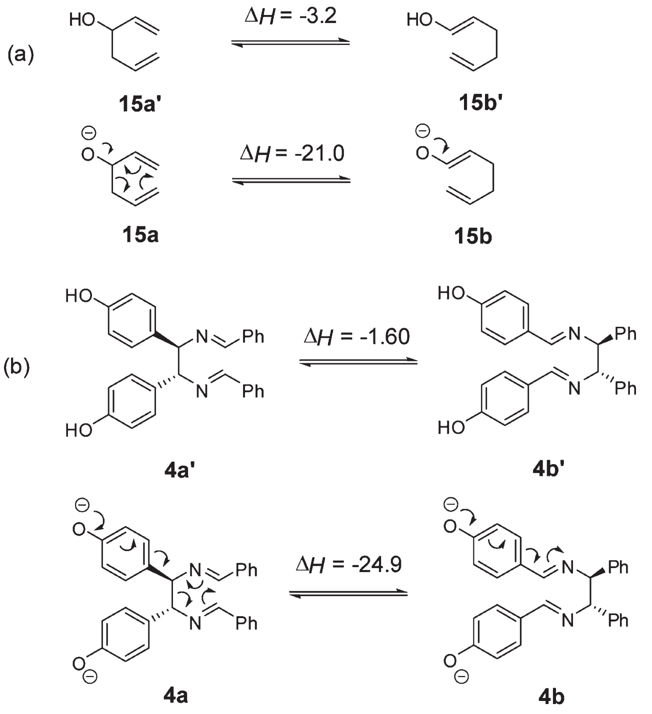


FIGURE 5. Linear plot between the experimental ΔG values and DFT computational ΔH values for diaza-Cope rearrangements of **9a** to **14a**.

In addition to the Hammett plot (Figure 4), it is interesting to relate the equilibrium constants for diaza-Cope rearrangements of **9a**–**14a** determined by ^1H NMR to the computed energy differences between the starting diimines (**9a**–**14a**) and the product diimines (**9b**–**14b**). In Figure 5, the energy differences between the starting diimines (**9a**–**14a**) and the corresponding product diimines (**9b**–**14b**) obtained from the experimentally determined equilibrium constants are plotted against those values obtained from DFT computation (B3LYP at 6-31G(d) level). The agreement between the experiment and computation is remarkably good with the value of the slope (0.86) and intercept (0.12) approaching the theoretical values of one and zero, respectively. DFT computation shows that **3b** is more stable than **3a** (Scheme 2c) by about 3.2 kcal/mol (or $K = 230$) in good agreement with the value obtained from extrapolation of the Hammett plot (Figure 4, $K = 175$, $\Delta G = -3.1$ kcal/mol). Although DFT computations gave excellent results, semiempirical computations (AM1 or PM3) gave poor

SCHEME 6. Thermodynamic Effect of the Hydroxyl and Oxyanion Groups for (a) the Oxy-Cope and (b) the Diaza-Cope Rearrangement[a]



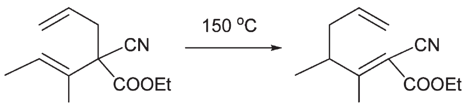
[a]Energy values in kcal/mol.

fits (AM1, slope = 7.54, $R^2 = 0.587$; PM3, slope = 0.334, $R^2 = 0.304$).

(d). Anion Effect. The oxy-Cope rearrangement is a useful synthetic route to δ,ε-unsaturated carbonyl compounds (Scheme 6a, **15a**′).[26] However, this process generally requires harsh thermal conditions (200−400 °C) and is frequently accompanied by competing fragmentation reactions. A major advance in synthetic applications of the oxy-Cope rearrangement occurred in 1975, when Evans and Golob reported their remarkable findings.[42] They showed that deprotonation of the hydroxyl group in the oxy-Cope substrate results in a striking rate acceleration of 10^{10}−10^{17}-fold for the rearrangement reaction. Since then, the anionic oxy-Cope rearrangement has been widely used in natural and unnatural product synthesis.[38] Baumann and Chen[43] showed by DFT computation (B3LYP/6-31G(d) level) that the equilibrium constant for the oxy-Cope rearrangement is increased by 10^{13}-fold upon deprotonation of the hydroxyl group (Scheme 6a).

Inspired by the anionic oxy-Cope reaction (Scheme 6a), we studied the anionic diaza-Cope rearrangement (**4a** to **4b** in Scheme 6b).[44] DFT computation reveals that the phenoxyanion group (**4a**) directed diaza-Cope rearrangement ($\Delta H = -24.9$ kcal/mol) is much more favorable than the hydroxyl group (**4a**′) directed reaction ($\Delta H = -1.6$ kcal/mol). This translates to about a 10^{17}-fold increase in the equilibrium constant for the gas-phase oxyanion-directed rearrangement. Although the calculated phenoxyanion effect ($\Delta H = -10.9$ kcal/mol) is much smaller in DMSO ($\varepsilon = 46.8$) than in the gas phase, it is still greater than the calculated H-bond effect (Scheme 2a, 7.1 kcal/mol), the steric effect with the mesityl group (Scheme 2b, 5.7 kcal/mol), or the electronic effect with the dimethylamino group (Scheme 2c, 3.2 kcal/mol) for the rearrangement reaction. Consistent with computation, **4a**′ did not undergo diaza-Cope rearrangement to completion. However, upon addition of *tert*-butoxide, the rearrangement smoothly went to completion (**4a** to **4b** in Scheme 2).

SCHEME 7. Cope Rearrangement Controlled by Conjugation Effect

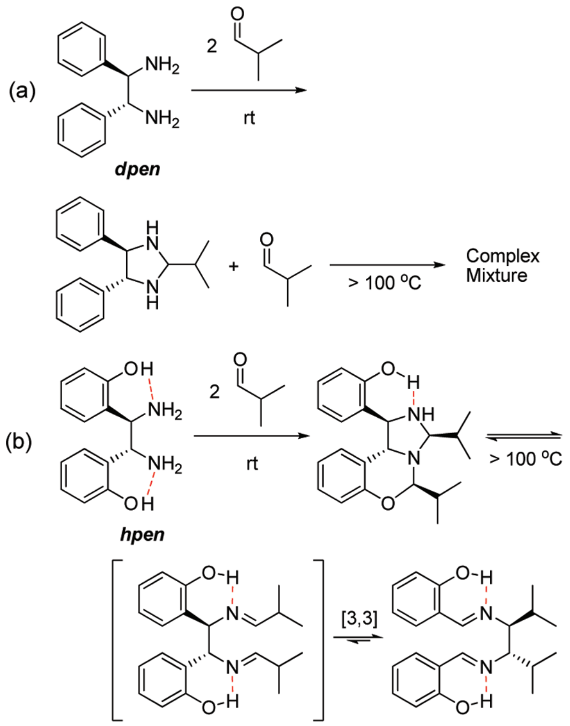


The above anion effect in DMSO from DFT computation (10.9 kcal/mol) can be compared with that obtained from the Hammett plot (Figure 4). The Hammett σ^+ value for the oxyanion group (−4.27)[45] is significantly greater than that for the dimethylamino group ($\sigma^+ = -1.7$). Thus the equilibrium constant for rearrangement of **4a** is expected to be about 4.3×10^5 ($\rho\Delta\sigma^+ = 1.32 \times 4.27$), which translates to about 7.7 kcal/mol. This is in reasonable agreement with that obtained from computation (10.9 kcal/mol) considering the extrapolations involved.

(e). Conjugation Effect. Cope rearrangements can be directed by conjugation.[21] For example, the equilibrium in the Cope rearrangement in Scheme 7 is controlled by the conjugation of the rearranged double bond with the carbonyl and cyano groups in the product.[24]

The imine bonds in **5b** (Scheme 2e) are conjugated with the aromatic rings and are expected to be more stable than the isolated imines in **5a**. DFT computation shows that diimine **5a** is about 5.5 kcal/mol less stable than the rearranged diimine **5b**. In principle, **5a** should rearrange to completion to give **5b**. In practice, the initial diimine **5a** is difficult to prepare due to the stability of the five-membered ring aminal intermediate (Scheme 8a). Heating a mixture of two or more equivalents of isobutyraldehyde with diphenylethylenediamine (dpen) gave a complex mixture of products (Scheme 8a). While computation can be used to evaluate the conjugation effect for diaza-Cope rearrangement, it is difficult to study this effect by experiment. Interestingly,

SCHEME 8. Synthesis of Alkyl-Substituted Diamines from (b) hpen but Not (a) dpen



adding 2 equiv of isobutyraldehyde to 1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (hpen) cleanly gives the bicyclic adduct (Scheme 8b), which upon heating gives the rearranged diimine.[20] It has recently been shown that activated alkyl ketones such as pyruvate can be used in DCR to make α-substituted diamino acids in agreement with DFT computation.[46] In contrast, aromatic ketones cannot be used because both kinetic and thermodynamic barriers to the rearrangement reaction become too large. DFT computation in this regard is useful not only for rationalizing experimental results but also for predicting them.

(f). Competition of Weak Forces. Figure 6 and Table 2 summarize the relative strengths of weak forces on the diaza-Cope rearrangement (Scheme 2). DFT computation shows that the anion effect (10.9 kcal/mol) is the greatest followed by the RAHB effect (7.1 kcal/mol), steric effect (5.7 kcal/mol), conjugation effect (5.5 kcal/mol), and electronic effect (3.2 kcal/mol). It is difficult to measure the equilibrium constants for these reactions directly since the rearrangements are essentially complete and the starting diimines are not detectible by ^{1}H NMR after equilibration. Interestingly, direct competition experiments can be set up using the diaza-Cope rearrangement to evaluate the relative strength of the anion, RAHB, steric, and electronic effects (Schemes 9 and 10). The competing weak forces in Scheme 9a are due to the steric (mesityl) and the electronic effects (dimethylamino). The equilibrium constant for the rearrangement of **16a** as measured by ^{1}H NMR is about 6.0. Thus the steric effect due to the mesityl group is stronger than the electronic effect due to the dimethyl amino group by about 1.1 kcal/mol. DFT computation shows that **16b** is about 2.8 kcal/mol

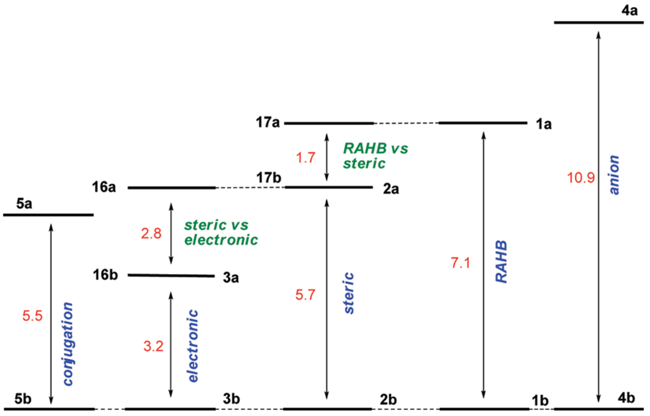


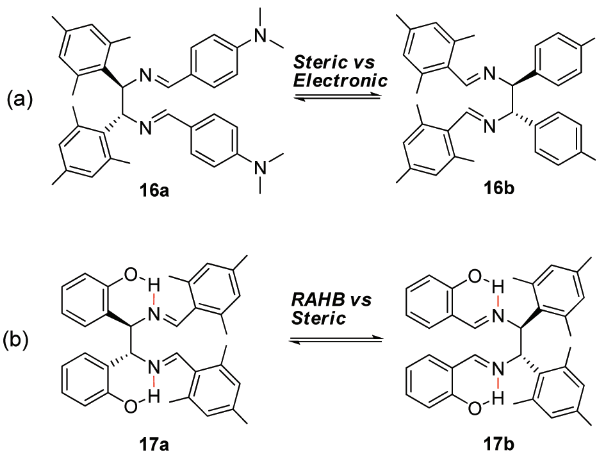
FIGURE 6. Effect and interplay of weak forces in the diaza-Cope rearrangement (computed energies in kcal/mol).

TABLE 2. Experimental and Computed Thermodynamic Data for the Rearrangement of Diimines

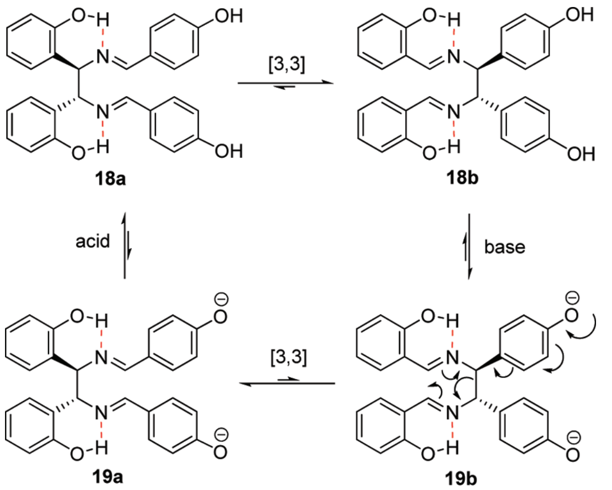
diimine	ΔH_{calcd}[a]	K_{calcd}	K[b]	ΔG
1a	−7.1	1.6×10^{5}	>20[c]	*d*
2a	−5.7	1.4×10^{4}	>20[c]	*d*
3a	−3.2	2.3×10^{2}	>20[c]	*d*
4a	−25.3	4.4×10^{17}	>20[c]	*d*
5a	−5.5	9.1×10^{3}	*d*	*d*
16a	−2.8	1.0×10^{2}	6.0	−1.1
17a	−1.7	1.9×10^{1}	14	−1.6

[a] B3LYP/6-31G(d) level (values in kcal/mol). [b] Measured by ^{1}H NMR at 25 °C. [c] Initial diimines were not detected after equilibration. [d] Not determined.

SCHEME 9. Competition of Weak Forces: (a) Steric vs Electronic and (b) RAHB vs Steric



SCHEME 10. Recycling of Diaza-Cope Rearrangement



more stable than **16a** in reasonable agreement with the experimental data. Table 2 shows that the calculated change in energy due to the rearrangement of **16a** is approximately equal to the difference in the calculated change in energies due to the rearrangements of **2a** and **3a** (ΔH_{calcd}(**16a**) = ΔH_{calcd}(**2a**) − ΔH_{calcd}(**3a**)). Thus it appears that the effects of the two weak forces (steric and electronic) are additive (Figure 6).

The competing weak forces in Scheme 9b are due to the RAHB and the steric effects (mesityl). The equilibrium constant for the rearrangement of **17a** as measured by ^{1}H NMR is about 14. Thus the RAHB effect is stronger than the steric effect due to the mesityl group by about 1.6 kcal/mol. DFT computation shows that **17b** is about 1.7 kcal/mol more stable than **17a**, in close agreement with the experimental data. Table 2 shows that the calculated change in energy due to the rearrangement of **17a** is approximately equal to the difference in the calculated change in energies due to the rearrangements of **1a** and **2a** (ΔH_{calcd}(**17a**) = ΔH_{calcd}(**1a**) − ΔH_{calcd}(**2a**)). Here again it appears that the effects of the two weak forces (H-bonding and steric effects) are additive (Figure 6).

The equilibrium constants for the rearrangement of **1a**, **2a**, and **3a** may be obtained from the experimental data as follows. Extrapolation of the Hammett plot gives the equilibrium constant for the rearrangement of **3a** as 175 (Figure 4). The equilibrium constant for rearrangement of **2a** may be approximated as a product of the equilibrium constants for rearrangement of **16a** and **3a** ($6 \times 175 = 1.0 \times 10^3$) assuming that the weak forces due to steric and electronic effects are additive (Figure 6). Similarly, the equilibrium constant for rearrangement of **1a** may be approximated as a product of the equilibrium constants for rearrangement of **17a**, **16a**, and **3a** ($14 \times 6 \times 176 = 1.4 \times 10^4$). Table 2 shows both DFT computational and experimental data on the rearrangement of a variety of diimines. It is remarkable that there is such good agreement between the computational and experimental data on the effect and interplay of wide ranging weak forces such as H-bonding, steric, and electronic effects in diaza-Cope rearrangement.

While the RAHB effect is stronger than the steric or electronic effects, DFT computation indicated to us that the anion effect (24.9 kcal/mol in gas phase and 10.9 kcal/mol in DMSO) may be even stronger than the RAHB effect (7.1 kcal/mol) for controlling the diaza-Cope rearrangement (Scheme 2a,d). A direct competition experiment was set up to investigate the relative strength of the phenoxyanion and RAHB effects (Scheme 10).

Diimine **18a** rearranges smoothly in DMSO-d_6 to give **18b** at ambient temperature. Interestingly, **18a** can be regenerated by adding of 2 equiv of *tert*-butoxide to **18b** followed by addition of 2 equiv of acetic acid. We suggest that deprotonation of **18a** gives **19b**, which rearranges to give **19a**. Protonation of **19a** with acetic acid then gives back **18a**. ^{1}H NMR data indicates that conversion of **18a** to **18b** is essentially complete. There is no detectible amount of the starting diimine (**18a**) after equilibration. Similarly conversion of **19b** to **19a** is essentially complete. The clean interconversion of **18b** and **19a** can be monitored by ^{1}H NMR. This represents stereospecific recycling of a [3,3]-sigmatropic rearrangement. 1,2-Bis(4-hydroxyphenyl)-1,2-diaminoethane (4-hpen) can be obtained by hydrolysis of **18b**, while 2-hpen (1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane) can be obtained by trapping **19a** with hydroxylamine hydrochloride. It is interesting that the anion effect drives the diaza-Cope rearrangement against the RAHB effect to near completion.

It is interesting to compare 2-hpen and 4-hpen for making chiral diamines through the diaza-Cope rearrangement. When 2-hpen is reacted with 9-anthracenecarboxaldehyde, the initial diimine partially rearranges (about 65%) to the product diimine over the course of several days. It appears that the steric effect of the anthracene groups increases both the kinetic and thermodynamic barriers for the diaza-Cope rearrangement. Resonance-assisted H-bond (RAHB) is not strong enough for rapid and efficient synthesis of 1,2-bis(9-anthracenyl)-1,2-diaminoethane. When 4-hpen is allowed to react with 9-anthracenecarboxaldehyde, the initial diimine rearranges to completion within minutes of adding 2 equiv of *tert*-butoxide. Thus the anion effect can be used to overcome the steric effect for the rearrangement reaction.

Hydroxylamine hydrochloride was added to the rearranged diimine to obtain 1,2-bis(9-anthracenyl)-1,2-diaminoethane.

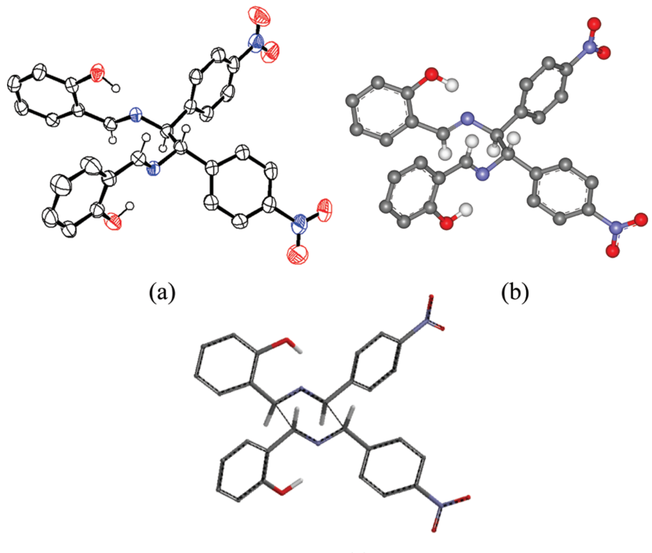


FIGURE 7. Crystal and computed structures. (a) Crystal and (b) computed structures of a rearranged diimine. (c) Computed transition state structure leading to the rearranged diimines in part a.

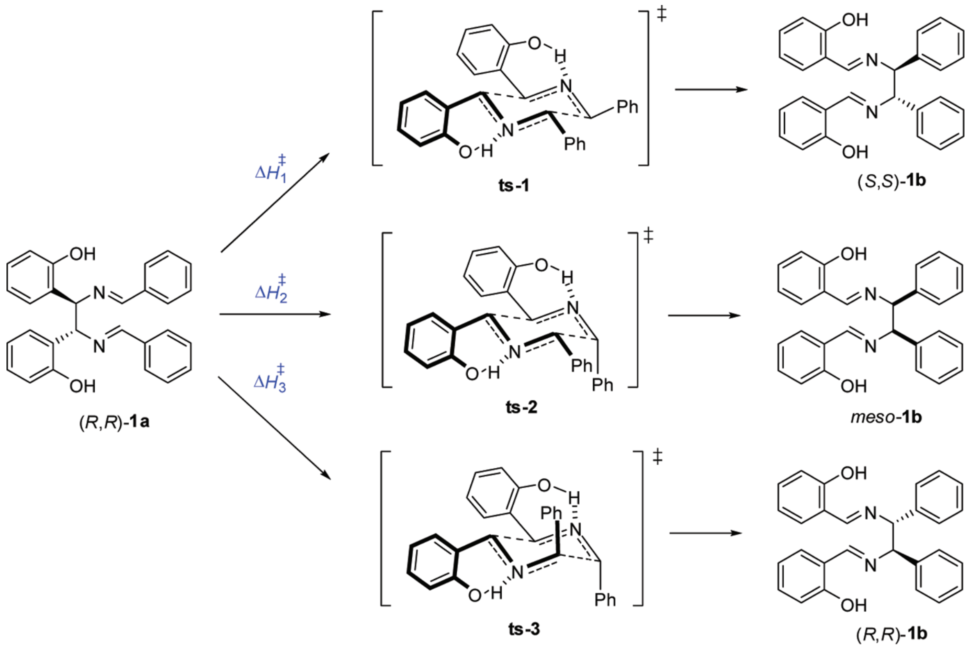
While 4-hpen is more useful than 2-hpen for making some vicinal diamines, only 2-hpen can be used for making 1,2-alkyl-substituted vicinal diamines.

In summarizing the thermodynamic effect, both DFT computation and ^{1}H NMR data show that the effects of weak forces on the diaza-Cope rearrangement are essentially additive (Figure 6). Both experiment and computation show that the oxyanion effect (rearrangement of **4a**) is the greatest followed by the RAHB, steric (mesityl), and electronic (dimethylamino) effects for the diaza-Cope rearrangement. Conjugation effect (Scheme 2e) is also significant for the rearrangement. The agreement between experiment and computation is remarkable considering the variety of weak forces involved.

Stereospecificity

Chiral HPLC, CD spectroscopy, crystallography, and DFT computational data all show that the diaza-Cope rearrangements take place with a high degree of stereospecificity. Meso diimines rearrange to give meso diimines while chiral diimines rearranges to give chiral diimines. All of the weak

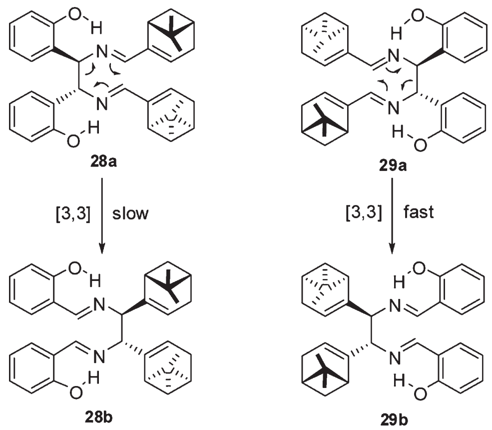
SCHEME 11. Calculated Activation Enthalpies for Possible Chairlike Transition States (**ts**)



	$\Delta H^{\ddagger}$ (kcal/mol)[a]	$\Delta H^{\ddagger} - \Delta H_1^{\ddagger}$
ts-1	15.4	-
ts-2	23.1	7.7
ts-3	30.7	15.3

[a] DFT at the B3LYP / 6-31G(d) level

SCHEME 12. Diastereoselective DCR



forces in Scheme 2 can be used to drive the diaza-Cope rearrangement to completion with excellent stereospecificity. In all cases, the configurations of the product diimines are opposite to those of the starting diimines. The stereospecific transfer of chirality from the starting diimines to the product diimines can be understood in terms of the diimine and transition state structures. The computed global minimum structures of the diimines closely match the corresponding crystal structures (Figure 7). Furthermore, the computed structures of the six-membered ring, chairlike transition state with all equatorial substituents resemble the crystal structure of the corresponding starting diimine (Figure 7). The stereospecific rearrangement of **1a** is discussed below as a representative example for weak force directed diaza-Cope rearrangement (Scheme 2).

In order to understand the origin of the stereospecificity for rearrangement of **1a**, three chairlike transition states for the diaza-Cope rearrangement may be considered (Scheme 11).[5] Among these structures, **ts-1** is expected to be the most stable since all aryl substituents are in pseudo-equatorial positions. DFT computation shows that **ts-1** is more stable than **ts-2** and **ts-3** by about 7.7 and 15.3 kcal/mol, respectively. Thus one phenyl group in the pseudo-axial position (**ts-2**) should result in about 4×10^5-fold decrease in the rate of rearrangement at 25 °C. Reaction of (*R*,*R*)-**1a** through **ts-1** is expected to produce (*S*,*S*)-**1b**. In contrast, reaction of (*R*,*R*)-**1a** through **ts-2** or **ts-3** is expected to produce *meso*-**1b** or (*R*,*R*)-**1b**, respectively (Scheme 11). Thus DFT computation indicates that the rearrangement should take place by **ts-1** with apparent inversion of stereochemistry.

The diaza-Cope rearrangement has been shown to be highly diastereoselective[47] in addition to being highly stereospecific. Racemic hpen reacts with (*R*)-myrtenal to give **28a** and **29b** (Scheme 12). The initial diimine **29a** rearranges rapidly to give **29b**, whereas the initial diimine **28a** does not rearrange under the same conditions to any appreciable extent. It appears that steric effect prevents facile rearrangement of diimine **28a**.

Conclusion

The diaza-Cope rearrangement provides a rare opportunity to study the effects of many fundamental weak forces on a chemical reaction. It is rather unusual that the equilibrium constant of a single reaction can be so cleanly controlled by so many different weak forces (Scheme 2). It is also fortuitous that the effects of these weak forces can be investigated in detail by experiment and by computation. We find that the anion effect is the strongest for the diaza-Cope rearrangement (10.9 kcal/mol) followed by the RAHB effect (7.1 kcal/mol), the steric effect (5.7 kcal/mol), the conjugation effect (5.5 kcal/mol), and the electronic effect (3.2 kcal/mol). The additive nature of the effects of the weak forces can be demonstrated by computation and by experiment. DFT computation provides a powerful tool for not only rationalizing but also predicting the effects of the weak forces. The diaza-Cope rearrangement provides a platform not only for studying the interplay of fundamental weak forces in a chemical reaction but also for synthesizing a wide variety of chiral diamines that are considered as privileged structures for making stereoselective catalysts and therapeutic agents.

Financial support of this research by NSERC is gratefully acknowledged.

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FOOTNOTES

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