Communication

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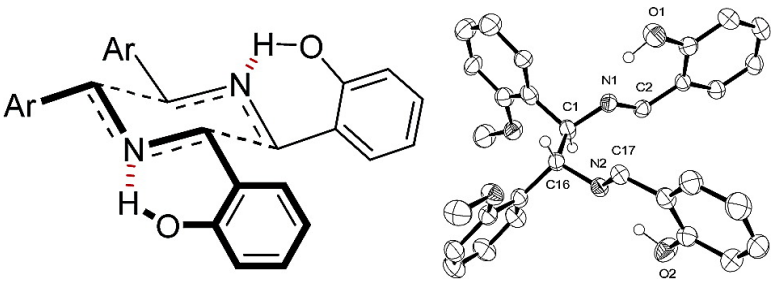

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Preorganization in Highly Enantioselective Diaza-Cope Rearrangement Reaction

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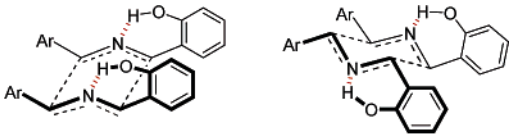
There is much current interest in developing new methods for making chiral 1,2-diamines since they are building blocks not only for stereoselective catalysts[1] but also for a variety of therapeutic agents.[2] Many interesting *meso*-1,2-diamines have been synthesized by the diaza-Cope rearrangement reaction (Scheme 1a).[3] We[4] recently showed that the success of this strategy is due in large part to resonance assisted hydrogen bonds (RAHB)[5] that dramatically shift the reaction equilibrium to one side (Scheme 1a). In RAHBs, the H-bonds are strengthened by π delocalization[5] (**2**, **4**). Here we investigate the mechanism of the rearrangement reaction for making chiral diamines (Scheme 1b).

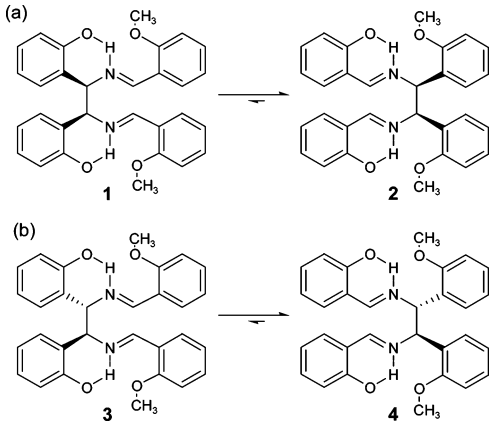
While the two reactions in Scheme 1 are obviously related, there are also striking differences. The two H-bonds in **1** are positioned to stabilize the boat-like transition state (**5**), while the two H-bonds in **3** are positioned to stabilize the chair-like transition state (**6**). If **1** were to rearrange by a chair-like transition state or **3** were to rearrange by a boat-like transition state, there could only be one internal H-bond at the transition state due to structural constraints.[6] Crystal structures[4] of **1** and **2** reveal that the two compounds are in staggered conformation (Scheme 2). Compound **1** is expected to go from a staggered conformation in the ground state to an eclipsed conformation in the transition state (**5**). In contrast, the crystal structure (Figure 1) of **4**[7] is remarkably close to the expected chair form of the six-membered ring transition state of the rearrangement reaction with all of the aryl substituents in the equatorial position (**6**). Here, both the ground state and the transition state are in staggered conformation. The two imine carbons in **4** are in close proximity to each other (<3.74 Å). It appears that the chiral diimine is highly preorganized for the rearrangement reaction while the *meso* diimine is not.



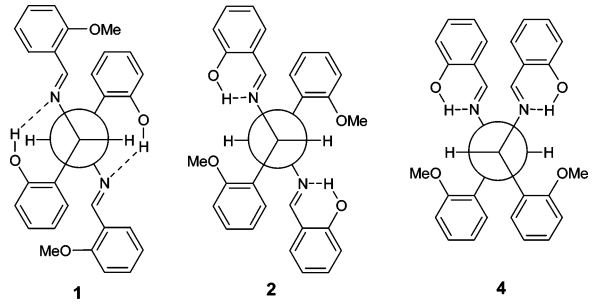
5 **6**

To further probe the extent of preorganization in the rearrangement reactions, we measured the activation entropy for the rearrangement of the *meso* diimine ($\Delta S^{\ddagger} = -24$ cal/mol/K) and the chiral diimine ($\Delta S^{\ddagger} = -6$ cal/mol/K).[8] Consistent with the above interpretation of the crystal data, the entropic barrier ($-T\Delta S^{\ddagger}$) is much greater for the *meso* diimine rearrangement (7.0 kcal/mol at 25 °C) than for the chiral diimine rearrangement (1.8 kcal/mol at 25 °C). Based on the entropic barrier alone, the chiral diimine is expected to be about 6000 times more reactive than the *meso* diimine. This is a substantial difference in reactivity given that the two reactions are so closely related. The enthalpic barrier is slightly greater for the chiral diimine rearrangement ($\Delta H^{\ddagger} = 21.7$ kcal/mol) than for the *meso* diimine rearrangement ($\Delta H^{\ddagger} = 18.1$ kcal/mol). Overall, the rate constant for the chiral diimine rearrangement reaction ($k = 6.4 \times 10^{-4}$ s^{-1}) is about 30 times greater than that for the *meso* diimine rearrangement reaction ($k = 2.0 \times 10^{-5}$ s^{-1}) at 50 °C.

Scheme 1



Scheme 2



The crystal structure of **4** shows that the chiral diimine rearrangement reaction takes place with inversion of stereochemistry. Thus the final diimine has the opposite configuration as the starting diimine. The inversion of stereochemistry can also be confirmed by circular dichroism (CD) spectroscopy (Figure 2). The CD spectrum of **4** formed from the rearrangement of (*R*,*R*)-**3** is identical in magnitude but opposite in sign to that of (*R*,*R*)-**4** directly synthesized from the corresponding (*R*,*R*)-diamine with 2 equiv of salicylaldehyde. CD spectroscopy can also be used for the purpose of assigning the absolute configuration of the diimine. Bisignate sign due to exciton coupling of the two hydroxyphenyl rings in **4** is observed around its UV maximum at 320 nm. According to the exciton coupling analysis,[9] the negative Cotton effect at 332 nm

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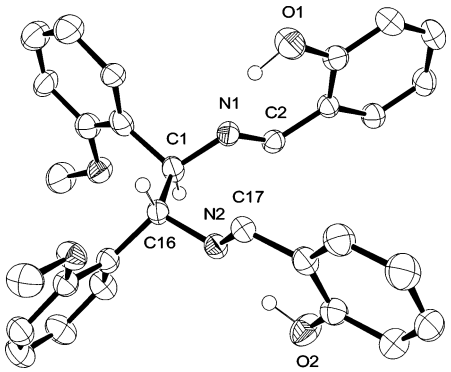


Figure 1. ORTEP diagrams of **4** with 30% probability thermal ellipsoids. All the nonpolar hydrogens except the ones at C1 and C16 are omitted for clarity. Selected interatomic distances (Å): O1···N1, 2.600; N1···C2, 1.279; C2···C17, 3.739.

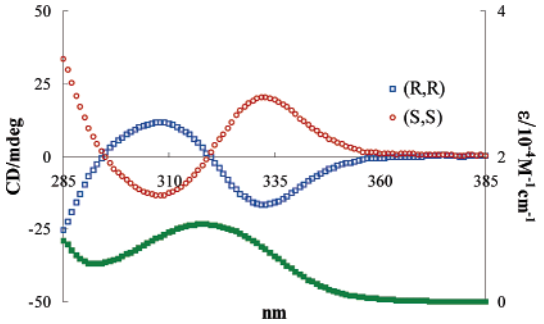
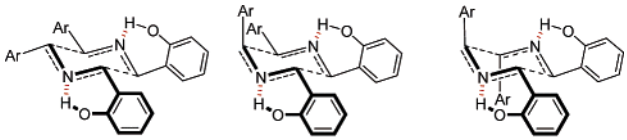


Figure 2. Circular dichroism spectra of (*R*,*R*)-**4** (open square) and (*S*,*S*)-**4** (open circle) and their UV−vis spectrum (filled square), where CD intensities of **4** are measured in tetrahydrofuran at 25 °C (80 μM, 1 cm cell in path length).

followed by the positive Cotton effect at 308 nm is consistent with (*R*,*R*)-**4**.[10] Similarly, the positive Cotton effect at 332 nm followed by the negative Cotton effect at 308 nm is consistent with (*S*,*S*)-**4**.

To gain some insight into the origin of stereoselectivity of the rearrangement reaction (Scheme 1), three possible transition states (**7**, **8**, **9**) for the reaction were considered. Transition state **7** is expected to be the most stable since all four substituents are in the equatorial position. In the case of the chair form of phenyl cyclohexane, the phenyl group is more stable in the equatorial position than in the axial position by about 3.0 kcal/mol.[11] Thus (*S*,*S*)-**3** should give mainly (*R*,*R*)-**4** through transition state **7** with negligible amounts of the *meso* diimine (by **8**) and even less of the *S*,*S*-enantiomer (by **9**). The two internal hydrogen bonds in **7** are expected to gain in strength as they progress from regular hydrogen bonds to RAHBs during the course of the rearrangement reaction. The hydrogen bonds should be stronger at the transition state than in the starting material and strongest in the product. Thus the hydrogen bonds should speed up the rearrangement reaction and also drive the stereoselective reaction to completion.

The enantioselectivity of the rearrangement reaction was determined by chiral HPLC. (*S*,*S*)-**3** gave (*R*,*R*)-**4** in quantitative yield with no observable loss in enantiopurity (>99.8% ee). Similarly, (*R*,*R*)-**3** gave (*S*,*S*)-**4** in quantitative yield with no loss in enantiopurity.[12] On the basis of this result, we expect **7** to be more stable than **9** by at least 4.0 kcal/mol. Since **8** is expected to be more stable than **9**, there is a greater chance of forming the *meso* diimine than the wrong enantiomer from the rearrangement reaction. However, even the *meso* diimine was below the detection limit of the HPLC. Thus the enantioselectivity of the chiral diimine rearrangement reaction is exceptionally high.



In summary, crystallographic and activation entropy data indicate a high degree of preorganization for the diazo-Cope rearrangement of the chiral diimine but not for that of the *meso* diimine. The rearrangement of the chiral diimine takes place with inversion of stereochemistry as supported by crystallography and CD spectroscopy. ^{1}H NMR and chromatographic analyses show that the rearrangement reaction takes place with quantitative yield and with exceptional enantioselectivity.

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Supporting Information Available: Experimental procedure and characterization details, including HPLC chromatogram for **4** (PDF), X-ray structural data for **4** (CIF), and kinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) See **IIa** and **IIb** in: Gilli, P.; Bertolasi, V.; Ferretti, V.; Gilli, G. *J. Am. Chem. Soc.* **2000**, *122*, 10405−10417.

(6) Even without any H-bonds, *meso* diimines are expected to rearrange by boat-like transition states and chiral diimines are expected to rearrange by chair-like transition states. (a) Vögtle, F.; Goldschmitt, E. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 767−768. (b) Vögtle, F.; Goldschmitt, E. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 480−482.

(7) Crystal structure of **4**: $C_{30}H_{28}N_2O_4$, M_w = 480.54, yellowish crystal 0.20 × 0.10 × 0.06 mm^3, triclinic *P*1, *a* = 9.2775(7) Å, *b* =10.3554(8) Å, *c* = 13.6763(8) Å; α = 85.718(4)°, β = 73.325(4)°, γ = 83.745(4)°; *V* = 1249.87(15) Å^3, *Z* = 2, ρ_{calcd} = 1.277 Mg/m^3, μ(Mo$_{K\alpha}$, 0.71073) = 0.085 mm^{-1}, $2\theta_{max}$ = 55.08; 11 660 measured reflections, of which 5065 were unique. The structure was solved by direct methods and refined by full-matrix least squares calculations with SHELX-97. The final *R*1 = 0.0645, *wR*2 = 0.1580 ($I > 2\sigma(I)$); *R*1 = 0.1462, *wR*2 = 0.2010 (all data); measurements, Nonius SMART CCD equipped with a graphite crystal incident-beam monochromator *L*p.

(8) To slow the rearrangement reactions of chiral diimines, the *o*-methoxy substituents were replaced with *p*-dimethylamino substituents.

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(12) CHIRALCEL OD-H, 10% *i*-PrOH in hexane, 0.8 mL/min, 7.5 min for (*R*,*R*)-**4** and 10.2 min for (*S*,*S*)-**4**.

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