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Facilitating the Cope Rearrangement by Partial Protonation: Implications for Synthesis and Biosynthesis

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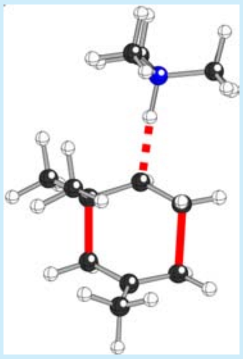
S Supporting Information

ABSTRACT: The theoretical investigation of concerted and stepwise Cope rearrangements of natural products led to the prediction that some concerted Cope rearrangements can be promoted by noncovalent association of their transition state structures with ammonium cations.



Isolation of the antimycobacterial terpenoid benzoquinone globiferin (**1**) from the roots of *Cordia globifera* was described in 2009.[1] Along with **1**, researchers found cordiachromes B and C (**2** and **6**) and cordiaquinol C (**4**, R = H). Kittakoop and co-workers transformed **1** to **2** and **3** to **4** under thermal conditions, showing that interconversion via Cope reaction ([3,3]-sigmatropic shift) is feasible at elevated temperatures,[1] consistent with previous work on Cope reactions of germacrenes and germacranolides.[2] The conversion of **4** (R = Ac) to the reduced analogue of **6** was also accomplished in the presence of HCl in methanol. This network of transformations inspired us to examine the biosynthesis of these compounds using theoretical tools (several density functional theory [DFT] methods[3]) to assess the viability of various interconversion mechanisms.

Not surprisingly, computed barriers (B3LYP/6-31G(d)[3d−f]) for the thermal **1** → **2** and **3** → **4** Cope rearrangements were too high for biological feasibility: 33−44 kcal/mol for all geometric isomers of **1** and **3**, in the gas phase, toluene, or methanol (see the Supporting Information for details). In principle, **2** could also be obtained from **1** via protonation/cyclization to form **5** (which would also lead to **6**; Scheme 1), followed by fragmentation/deprotonation, a process that could perhaps be promoted by an acid at the active site of an enzyme.[4] We suspected that protonation would likely be concerted with cyclization, consistent with previous theoretical work on terpene-forming carbocation cyclizations and rearrangements and recent proposals in the literature.[5] Along these lines, a transition state structure for protonation of **1** by NH_4^+ was found to connect **1**·NH_4^+ to **5**·NH_3 without any intervening minima on the potential energy surface. Ammonium was used in these calculations because it is simple but also because it is a reasonable mimic of lysine (and other biological amines).

We also examined Me_3NH^+ as a promoter. To our surprise, we found that this acid promotes a concerted Cope rearrangement with a predicted barrier (gas phase) of only 24 kcal/mol (Figure 1)! While lowering of barriers for hetero-Cope (e.g., Claisen) rearrangements through noncovalent interactions has been described,[6] such effects have been small. Moreover, although interaction of the "face" of a Cope transition state structure with some metal cations or Lewis acids has been shown to lower barriers,[7] we know of no examples (experimental or theoretical) of acceleration of a concerted [3,3]-sigmatropic shift of a hydrocarbon through hydrogen bonding (here, the X−H···π variety) to the carbon framework.

The generality of this mode of rate acceleration was explored using differently substituted ammonium ions—NH_4^+, $Me_2NH_2^+$, and Me_3NH^+—and truncated versions of **1** (Scheme 2). Replacement of the quinone of **1** with a simple (*Z*) C═C π-bond leads to **7**. Interestingly, the conversion of **7** to **8** is predicted to be stepwise with NH_4^+ and $Me_2NH_2^+$ but concerted with Me_3NH^+, suggesting that trisubstitution is necessary to avoid a stepwise pathway. This observation can be rationalized on steric grounds; a bulky ammonium ion has trouble achieving the geometry needed for full proton transfer. Alternatively, one could argue for a polarizability effect—more substituted ammonium ions are less acidic (at least in the gas phase)[8]—or a dispersion effect—more favorable dispersion interactions are expected with more alkyl groups.[9] M06-2X/6-31+G(d,p) calculations (which outperform B3LYP calculations

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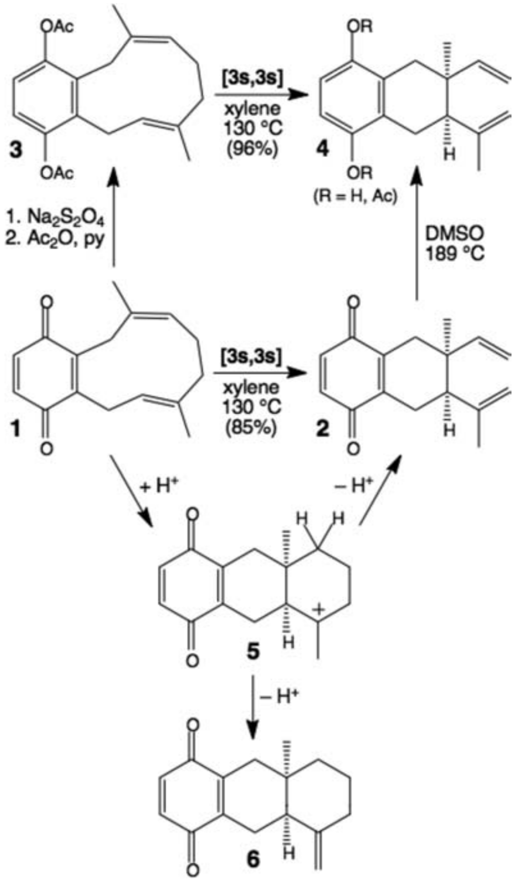
Scheme 1. Reactions that Interconvert Globiferin (1), Cordiachromes B and C (2 and 6), and Cordiaquinol C (4, R = H)



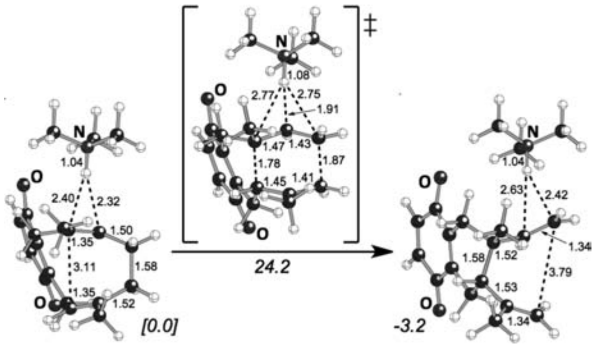
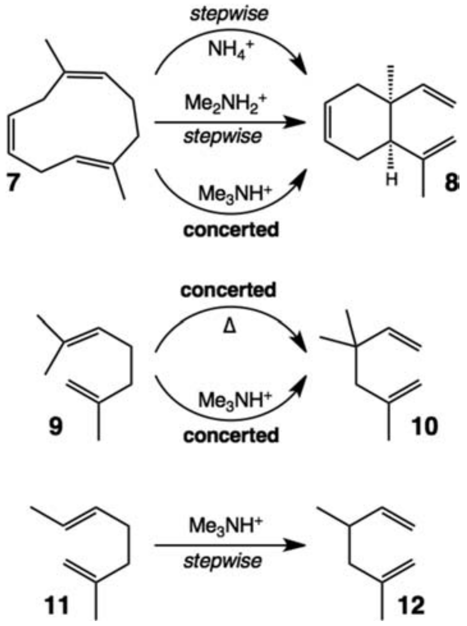


Figure 1. Conversion of **1** to **2** in the presence of Me_3NH^+. Free energies in italics, selected distances in angstroms (B3LYP/6-31G(d)).

when dispersion is involved;[3a] see also the Supporting Information for CAM-B3LYP results[3b]) predict that the barrier for rearrangement of 7 is 30.4/30.6 kcal/mol (electronic/free energy), while the comparable uncatalyzed Cope rearrangement has a barrier of 36.5/38.0 kcal/mol at the same level, a large predicted rate acceleration. Intensified hydrogen bonding at a transition state structure was previously suggested by Radom and co-workers as a means to accelerate migrations of functional groups in enzymatic radical reactions and termed "partial proton transfer"; their calculations indicated similar rate enhancements.[10]

Scheme 2. Model Systems Examined and Mechanisms Predicted for Their Rearrangements



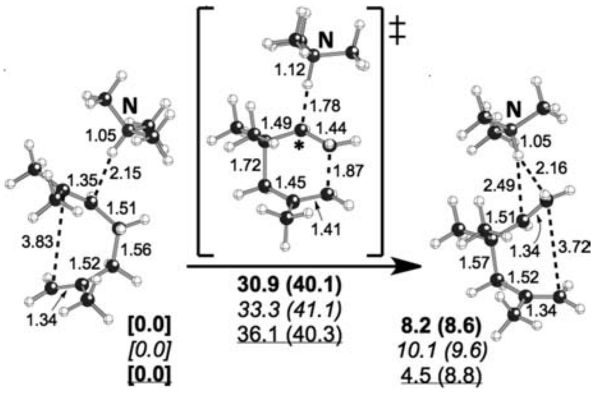


Figure 2. Rearrangement of **9** to **10**. Selected distances in angstroms (B3LYP/6-31G(d)). B3LYP/6-31G(d) ZPE-corrected electronic energies in bold, B3LYP/6-31G(d) free energies in italics, SMD-(water)-M06-2X/6-31+G(d,p)//B3LYP/6-31G(d) single-point energies underlined. Energies for ammonium-free reactions in parentheses.[14]

Compound **9** is an acyclic model of **7**, removing the constraints associated with inclusion of the 1,5-hexadiene unit in a macrocycle. The thermal rearrangement of **9** is predicted to be concerted as expected, as is the Me_3NH^+ promoted rearrangement, and once again the barrier for rearrangement is lower for the latter, by up to ca. 10 kcal/mol (Figure 2; several levels of theory, in both the gas phase and water). The relative importance of electrostatic and dispersion effects in lowering this barrier was examined via the Morokuma−Ziegler energy decomposition analysis in ADF (along with calculations of dispersion contributions; B3LYP-D3/DZP single points).[11,12] First, the change in *total* electrostatic contributions to bonding in the transition state structure upon complexation is predicted to be 59 kcal/mol, while the change in dispersion contributions is only 2 kcal/mol. As expected, electrostatic interactions are much larger for the ion−molecule complex, while dispersion interactions are similar for the complexed and free transition state structures. In addition, the magnitude of electrostatic interactions *between* the ammonium and hydrocarbon fragments of the transition state structure for the conversion of **9** to **10** is predicted to be 23 kcal/mol, while that of dispersion interactions is predicted to be only 8 kcal/mol. Moreover, while dispersion interactions between the ammonium and hydrocarbon fragments are predicted to change by less than 0.5 kcal/mol *from the reactant to the transition state structure*, electrostatic interactions are predicted to strengthen by 11 kcal/mol—approximately the amount by which the rearrangement barrier is lowered upon complexation. These results are consistent with a model for rate acceleration in which electrostatic interactions between the ammonium ion and diene increase as the transition state structure, presumably a more polarized transition state structure than usually found for Cope rearrangements, is reached.[13] Note also that the carbon to which the N−H bond points in the **9** → **10** transition state structure (marked with *) is pyramidalized (sum of angles at this carbon = 343°), while the remote trisubstituted carbon adopts a carbocation-like geometry (Figure 2).

Interestingly, when one of the geminal methyl groups is removed from **9** (cf. **11** in Scheme 2; Figure 3), the stepwise mechanism is preferred again, consistent with an important role for steric clashes in preventing full proton transfer.

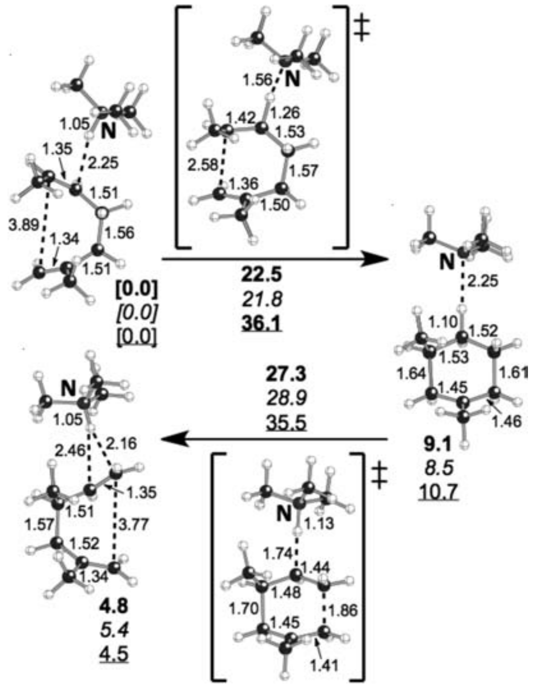


Figure 3. Rearrangement of **11** to **12**. Selected distances in angstroms (B3LYP/6-31G(d)). B3LYP/6-31G(d) ZPE-corrected electronic energies in bold, B3LYP/6-31G(d) free energies in italics, SMD-(water)-M06-2X/6-31+G(d,p)//B3LYP/6-31G(d) single-point energies underlined. Energies for ammonium-free reactions in parentheses.

The experimental implications of these results are clear. Cope reactions might be accelerated greatly in the presence of appropriate ammonium cations, be they synthetic (e.g., phase transfer catalysts) or biological (e.g., enzymes with active site ammonium ions). For example, the **9** → **10** reaction could be run in reverse with a barrier of only approximately 20 kcal/mol rather than approximately 30 kcal/mol if the magnitude of rate acceleration predicted here is borne out. Chiral ammonium ions[15] could also then be used to control absolute stereochemistry in reactions such as the **1** → **2** reaction, a reaction whose transition state structure has distinctly different convex and concave faces (Figure 1). We look forward to experimental tests of these predictions.[16]

■ ASSOCIATED CONTENT

Supporting Information

Coordinates and energies for all computed structures, IRC plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) The **9**→**10** transition state structure was also reoptimized with M06-2X/6-31+G(d,p)[3a] and CAM-B3LYP/6-31+G(d,p),[3b] and small geometric changes were found, e.g., N−H···C distances varied by <0.1 Å, partial C---C bonds varied by <0.05 Å, other distances varied by much less. See the Supporting Information for details.

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