The dark green crystals of **3** were sensitive to moisture but were stable up to 240 °C under argon. Their mass spectrum (EI, 373 K) confirmed the presence of $NPMe_3$ ligands, showing a pattern of peaks consistent with isotope distributions as calculated for tetrameric units and their fragment ions. Therefore μ_3-$NPMe_3$ units and a cubane-type molecular structure with Ni and N atoms in alternating corners are the most likely.

Formation of phosphorane–imido ligand under photochemical conditions suggests the existence of a nitrene intermediate. Such a reaction has been previously proposed to explain the photochemical reactivity of azido complexes.[17,18] Thus the chemistry of this azido Ni complex presents an interesting parallel with the chemistry of the related diazo complex. In both cases, there is formation of an electrophilic species: a carbene or nitrene, which reacts with PMe_3 giving rise to ylide-type adducts.

These results could be indicative of an interesting parallel between the chemistry of this low-valent-metal nitrene and that of the related carbene. Work is now in progress in that direction.

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Supplementary Material Available: Tables 1–4 containing crystal data for $(\mu_3\text{-NH})(\mu_3\text{-NPMe}_3)(\text{NiClPMe}_3)_3$, positional parameters and their estimated standard deviations, bond distances, and bond angles (5 pages); Table 5 containing observed and calculated structure factor amplitudes (18 pages). Ordering information is given on any current masthead page.

(17) Basolo, F. *J. Indian Chem. Soc.* **1977**, *54*, 6.
(18) Poznyak, A. L.; Pavlovski, V. I. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 789–796.

Chiral Pathways in the Thermal Rearrangement of 3,7-Dimethylene-1-ethyltricyclo[4.1.0.0^{2,4}]heptane to 2,5-Dimethylene-3-ethylbicyclo[4.1.0]hept-3-ene. Decyclization of a Pair of 2,2′-Linked Methylenecyclopropanes Avoids a Symmetrical 2,5-Dimethylenecyclohept-3-ene-1,6-diyl Biradical Intermediate

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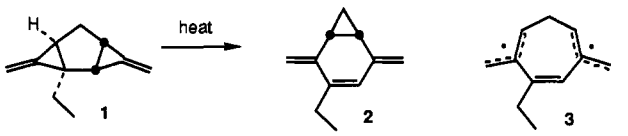
Thermal rearrangement of a 2,2′-linked di(methylenecyclopropyl) to a 1,4-dimethylenecyclohex-2-ene presents subtle problems in the description of the covalency changes. Do the two rings cleave simultaneously or sequentially? Is a disjoint[1] 2,5-dimethylenecyclohept-3-ene-1,6-diyl biradical an intermediate? This paper reports a rare example[2] of this rearrangement and the first examination of the mechanistic questions by the use of a stereochemical probe.

The tricyclic 2,2′-linked di(methylenecyclopropyl) **1** was synthesized in five steps from the known[3] 6-chloro-6-methylbicyclo[3.1.0]hexan-2-one. Heating **1** in the gas phase[4] caused clean rearrangement to 2,5-dimethylene-3-ethylbicyclo[4.1.0]-hept-3-ene (**2**). An Arrhenius treatment of the first-order rate constants (k) determined at seven temperatures spanning the range 132–180 °C gave the equation log (k in s^{-1}) = (13.9 ± 0.4) − (35900 ± 800)/2.3RT cal/mol.[5,6]



Plausibly, one might postulate the vinylogous tetramethyleneethane **3** as the key intermediate in the rearrangement. A test for such an achiral species would employ enantiomerically enriched **1**[7-9] as the reactant, from which product **2**, although chiral, necessarily would be racemic if formed via **3**. Reaction mixtures from separate pyrolyses of either enantiomer of **1** (85.6% ee in one enantiomer and 79.3% in the other) were analyzed enantiospecifically on a 50-m 2,3,6-tri-*O*-methyl-β-cyclodextrin (10% in OV-1701) fused silica capillary gas chromatography (GC) column.[10] Recovered from partial conversion, reactant **1** had essentially undiminished ee. Product **2** was *partially* but incompletely racemized. The ee of the product was independent of the duration of pyrolysis but varied monotonically with reaction temperature. Temperatures (and percentage of original reactant ee retained) were as follows: 115.0 °C (54.6%); 140.3 °C (52.4%); 159.7 °C (50.4%); 177.0 °C (48.6%); 195.6 °C (46.0%); 208.0 °C (43.8%). The slope of an Arrhenius plot of the ratio of the rate constants k_1 and k_2 for the competitive formation of the two product enantiomers gives the value of 1120 ± 230 cal/mol for the difference in activation enthalpy between these two processes.

These results rule out any mechanistic pathway passing exclusively through an equilibrated achiral intermediate such as **3**. Attempts to gain access to this species by heating product **2** at higher temperatures did result in slow racemization, but the rates were erratic due to surface effects. From these data, a lower limit of 42 kcal/mol may be assigned to $\Delta G^{\ddagger}$ for this reaction.

Bond additivity[11] and strain energy[12] estimates suggest that product **2** is thermodynamically more stable than reactant **1** by ~45 kcal/mol, whereas biradical **3** lies ~33 kcal/mol above **2** but ~12 kcal/mol *below* **1**. In view of the behavior of the analogous cases of 6-methylenebicyclo[3.1.0]hex-2-ene pyrolyses (**4** → **6**),[3] where rearrangement occurs exclusively through a metastable biradical intermediate **5**, it is remarkable that the reaction pathway descending from the **1** → **2** transition state avoids the deep energy hole in the region of biradical **3**. We suggest that

(1) Borden, W. T.; Davidson, E. R. *J. Am. Chem. Soc.* **1977**, *99*, 4587.
(2) (a) We are not aware of previous examples, and no citations of the reaction are given in reference works.[2b,c] (b) Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981. (c) Berson, J. A. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Essay 5.
(3) (a) Pikulin, S.; Berson, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 8274. (b) Pikulin, S.; Berson, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 8500. (c) Berson, J. A. *Chemtracts: Organic Chemistry*, **1989**, *2*, 213.
(4) The kinetic methods and equipment used were similar to those described elsewhere: (a) Getty, S. J.; Berson, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 1652. (b) Getty, S. J.; Berson, J. A. *J. Am. Chem. Soc.*, in press.
(5) Compare the values log A = 14.26, E_a = 40400 cal/mol, for 2-methylmethylenecyclopropane: Chesick, J. P. *J. Am. Chem. Soc.* **1963**, *85*, 2720.
(6) Attempts to trap hypothetical intermediates in solution-phase reactions of **1** with neat diethyl fumarate or with maleic anhydride in triglyme were unsuccessful and gave only the rearranged hydrocarbon **2**.
(7) Synthesized from enantiomerically enriched 6-chloro-6-methylbicyclo[3.1.0]hexan-2-one, which was resolved by the sulfoximine method of Johnson and Zeller.[8,9] The relative and absolute configurations of reactant **1** and product **2** are as yet unknown but are not necessary for the conclusions of this paper. Reactant **1** was enriched in the GC later emergent enantiomer when prepared from (+) ketone and gave product enriched in the earlier emergent enantiomer of **2**.
(8) Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021.
(9) See also: Parziale, P. A.; Berson, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 1650.
(10) (a) Preparation based on work of Schurig and Nowotny[10b] and available commercially from Chrompack International BV. (b) Schurig, V.; Nowotny, H.-P. *Angew. Chem.* **1990**, *29*, 939.
(11) (a) Benson, S. W. *Thermochemical Kinetics*; Wiley: New York, 1976. (b) Benson, S. W.; O'Neal, H. E. *Kinetic Data on Gas Phase Unimolecular Reactions*; NSRDS-NBS 21; U.S. Department of Commerce: Washington, DC, 1970.
(12) Greenberg, A.; Liebman, J. F. *Strained Organic Molecules*; Academic Press: New York, 1978.

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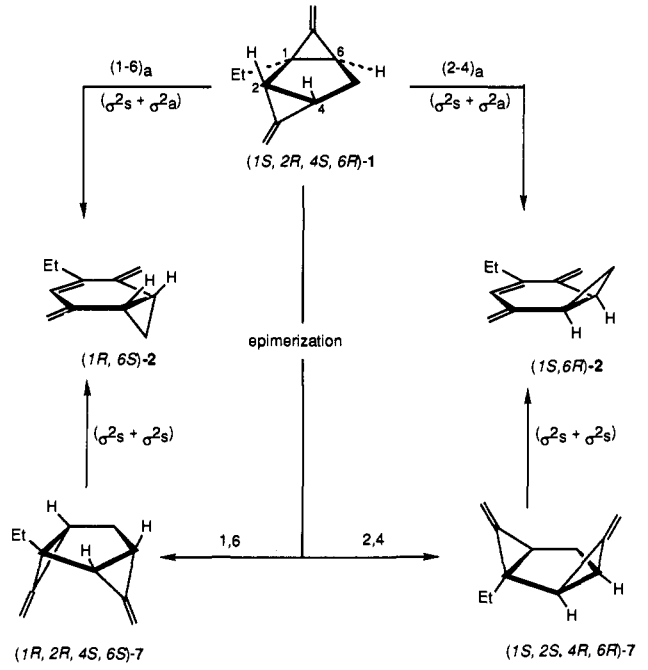
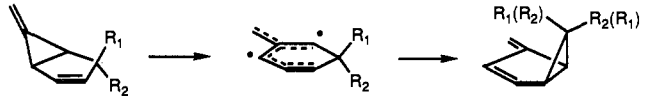
Scheme I



two mutually reinforcing factors produce the contrast in rearrangement mechanisms of **4** and **1**.



4 **5** **6**

The first is that in the hypothetical "half-planar" geometry resulting from opening of one of the methylenecyclopropane units of **1**, the orbitals of the trimethylenemethane (TMM) are out of alignment with the canted orbitals of the remaining bridge bond. Not until the exocyclic CH_2 group of the TMM unit has passed through the plane of the six-membered ring, giving a syn geometry, does overlap of the reacting orbitals become favorable. From **4**, however, formation of the TMM **5** directly generates a fully planar carbon skeleton with good overlap of the p orbitals.

The second is that the geometry of **1** holds the bent bridge bond orbitals in a nearly perpendicular relationship conducive to an orbital symmetry allowed ($\sigma^2s + \sigma^2a$) cycloaddition, which would produce the observed cis fusion of the rings and a cis endocyclic double bond in the product **2** (Scheme I). For this mechanism, two competing allowed ($\sigma^2s + \sigma^2a$) reactions passing over diastereomeric transition states to enantiomeric products are expected, in accord with the observed partially racemized **2**. Which σ-bond prefers to participate antarafacially will determine the dominant enantiomeric configuration of **2** in the product.

Alternatively, double epimerizations of reactant **1** at the two bridge bond sites could give the enantiomers of the (at present unknown) syn tricyclic compound **7** at unequal rates, which eventually in formally forbidden ($\sigma^2s + \sigma^2s$) reactions would give the enantiomers of **2** in unequal amounts.[13]

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for support of this research.

Supplementary Material Available: Details of synthesis and characterization of reactant **1** and product **2** (5 pages). Ordering information is given on any current masthead page.

(13) A subtly different pathway would involve conversion of the syn biradical derived from **1** directly to **2** *before* cyclization to **7**. The formal reaction **7** → **2** might also proceed through the same biradical. Note that a hypothetical alternative ($\sigma^2s + \sigma^2s$) reaction from anti reactant **1** not only would be formally forbidden but also would lead to a much more strained, trans-fused rearrangement product.

Proton–Proton Overhauser Effects of Receptor-Bound Cyclosporin A Observed with the Use of a Heteronuclear-Resolved Half-Filter Experiment

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This communication presents a novel combination of the use of isotope labels, heteronuclear NMR[1] correlation spectroscopy, and heteronuclear editing[2-4] for structure determinations[5] of receptor-bound bioactive molecules. The new experiment complements homonuclear 2D ^1H NMR with an $X(\omega_1,\omega_2)$-double-half-filter (X is usually ^{13}C or ^{15}N) that yields subspectra containing exclusively intramolecular cross peaks between different hydrogen atoms of the isotope-labeled ligand molecule in the complex or the unlabeled receptor molecule, respectively.[2,4,6] Limitations for the use of the latter, homonuclear 2D NMR experiment may arise with increasing size of the individual molecules in the complex, when there is spectral overlap even in the edited subspectra. The presently introduced *heteronuclear-resolved half-filter experiment* alleviates the aforementioned limitations for the isotope-labeled component in the complex. A practical application is described with studies of fully ^{13}C labeled cyclosporin A (CsA) (MW 1265) bound to unlabeled cyclophilin (MW 17900). CsA is an immunosuppressive cyclic undecapeptide that has found widespread use in the treatment of allograft rejection following organ transplantations.[7] The protein cyclophilin is the presumed cellular receptor of CsA.[8]

The presently used heteronuclear-resolved half-filter experiment consists of a ^1H NOE relayed [^{13}C,^1H] COSY measurement recorded with a $^{13}C(\omega_2)$-half-filter (Figure 1). The delay τ_1 for coherence transfer is chosen as $\tau_1 = 1/[2[^1J(^{13}C,^1H)]]$ or slightly shorter, and the delay τ_2 in the half-filter element[2] is set to $\tau_2 = 1/[^1J(^{13}C,^1H)]$. The π pulses are always in the middle of the respective time period. The $\pi(^1H)$ pulse in the middle of the mixing time prevents the unwanted evolution of heteronuclear antiphase magnetization present at the beginning of the mixing time into in-phase magnetization. Two data sets are recorded with and without application of the $\pi(^{13}C)$ editing pulse. The spectrum obtained as the difference of these two recordings (*^{13}C-selected subspectrum*) contains exclusively NOEs between different ^{13}C-bound protons. The sum spectrum (*^{13}C-filtered subspectrum*) exhibits only NOEs between ^{13}C-bound and ^{12}C-bound protons.

We applied the experiment of Figure 1 to a complex containing one molecule each of 99% ^{13}C-labeled CsA and unlabeled cyclophilin. To collect the data for a three-dimensional structure determination of CsA bound to cyclophilin,[9] we used primarily 2D [^1H,^1H] NOESY with a ^{13}C-double-half-filter.[6] In the subspectrum that contains the intramolecular ^1H–^1H NOEs of the ^{13}C-labeled CsA, some of these NOEs could not be unambiguously

(1) Abbreviations and symbols used: NMR, nuclear magnetic resonance; NOE, nuclear Overhauser enhancement; 2D, two-dimensional; 3D, three-dimensional; NOESY, 2D NOE spectroscopy; COSY, 2D correlated spectroscopy; ppm, parts per million; CsA, cyclosporin A; MeVal, *N*-methylvaline; MeLeu, *N*-methylleucine.

(2) Otting, G.; Wüthrich, K. *Q. Rev. Biophys.* **1990**, *23*, 39–96.
(3) Otting, G.; Senn, H.; Wagner, G.; Wüthrich, K. *J. Magn. Reson.* **1986**, *70*, 500–505. Fesik, S. W.; Gampe, R. T., Jr.; Rockway, T. W. *J. Magn. Reson.* **1987**, *74*, 366–371. McIntosh, L. P.; Dahlquist, F. W.; Redfield, A. G. *J. Biomol. Struct. Dyn.* **1987**, *5*, 21–34. Bax, A.; Weiss, M. *J. Magn. Reson.* **1987**, *71*, 571–575. Griffey, R. H.; Redfield, A. G. *Q. Rev. Biophys.* **1987**, *19*, 51–82.
(4) Otting, G.; Wüthrich, K. *J. Magn. Reson.* **1989**, *85*, 586–594.
(5) Wüthrich, K. *NMR of Proteins and Nucleic Acids*; Wiley: New York, 1986.
(6) Wider, G.; Weber, C.; Traber, R.; Widmer, H.; Wüthrich, K. *J. Am. Chem. Soc.* **1990**, *112*, 9015–9016.
(7) Kahan, B. D., Ed. *Cyclosporin*; Grune and Stratten: Philadelphia, 1988.
(8) Handschuhmacher, R. E.; Harding, M. W.; Rice, J.; Drugge, R. J. *Science* **1984**, *226*, 544–547.
(9) Weber, C.; Wider, G.; von Freyberg, B.; Traber, R.; Braun, W.; Widmer, H.; Wüthrich, K. *Biochemistry*, in press.

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