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Thermal Isomerizations of 2-*d*-1-(*E*)-Propenylcyclobutanes to 4-*d*-3-Methylcyclohexenes

John E. Baldwin* and Jean-Marie Fedé

Department of Chemistry, Syracuse University, Syracuse, New York 13244

Received January 3, 2006; E-mail: jbaldwin@syr.edu

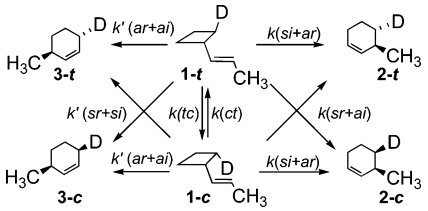
Thermal stereomutations of isotopically labeled cyclopropanes, structural isomerizations of 2,3,2′-d_3-labeled vinylcyclopropanes to 3,4,5-d_3-labeled cyclopentenes, and degenerate isomerizations of 4- and 6-*d*-bicyclo[3.1.0]hex-2-enes have been probed in great detail through kinetic and stereochemical investigations,[1−3] computational efforts to define potential energy surfaces,[4−6] and quasiclassical dynamic trajectory simulations.[7−9] In all three cases, fair agreements between experimentally defined reaction stereochemistry and stereochemical inferences from the trajectory simulations have been attained. The mechanistic model for all three of these families of reactions features short-lived diradical intermediates. Inertial effects are reflected in product ratios, to some degree, for completely random stereochemical outcomes are not observed.[10] During passage from entry onto a nearly flat energy plateau, a caldera,[11] to one of several possible exit channels leading to stereochemically distinct products, conformational changes of diradical intermediates are dictated by distributions of energy among various vibrational modes and their phase relationships. Initial conditions in individual molecules as they enter a transition region may give different stereochemical outcomes; observable outcomes may be matched by the statistical composite of many hundred or thousand computationally followed individual trajectories.

The stereochemical characteristics of thermal isomerizations shown by two sets of *cis*- and *trans*-2-substituted-1-(*E*)-propenylcyclobutanes have recently been determined.[12,13] In all four instances, all four possible stereochemically distinct [1,3] carbon shift products were formed under kinetic control. Balances between isomeric 4-substituted-3-methylcyclohexene products advantaged the more thermochemically stable trans diastereomers in every case. When "allowed" (*si* + *ar*) products were trans, they were favored; when (*si* + *ar*) paths led to cis products, the "forbidden" (*sr* + *ai*) outcomes, affording trans products, were dominant.[12,13] Rationalizations based on orbital symmetry theory and concerted reaction profiles cannot account for these experimental findings, nor are these mechanistic assumptions consistent with the best theory currently available for stationary point structures and energies on the potential energy surface for vinylcyclobutane thermal reactions.[14]

Before experimentally based stereochemical findings, a calculationally defined and analytically expressed potential energy surface, and quasiclassical dynamic trajectory simulations may be brought to bear on vinylcyclobutane-to-cyclohexene isomerizations, much needs to be done. A system without an intrinsic thermochemical bias for some products needs to be prepared and its thermal stereochemistry uncovered. For such a system, the symmetry characteristics of the high-energy plateau on the potential energy surface, the caldera, would lead to a relatively simple analytical definition of the surface and more tractable dynamics calculations.

We have initiated stereochemical studies on the thermal reactions of racemic 2-*d*-1-(*E*)-propenylcyclobutanes and are preparing for

Scheme 1



related work starting with (1*R*,2*R*)-2-*d*-1-(*E*)-propenylcyclobutane and (1*R*,2*R*)-2-*d*-1-(2′-(*E*)-*d*-ethenyl)cyclobutane. The experimental challenges posed by such systems are substantially more daunting than those encountered with the 2-methyl-1-(*E*)-propenylcyclopropanes, for neither capillary GC nor "chiral" GC, analytical mainstays in the earlier work,[12] can serve similar functions. All determinations of diastereomeric and enantiomeric relationships in starting materials and [1,3] carbon shift products would need to be secured spectroscopically. Only one complete stereochemical study of [1,3] carbon shifts in vinylcycloalkanes[2] has uncovered stereochemical outcomes when the migrating carbon was substituted with one H and one D.[15]

When *trans*-2-*d*-1-(*E*)-propenylcyclobutane (**1-*t***) is heated, it interconverts with its cis form (**1-*c***); both diastereomers give *cis*- and *trans*-4-*d*-3-methylcyclohexenes and *cis*- and *trans*-6-*d*-3-methylcyclohexenes (Scheme 1), as well as various fragmentation products. Reliable analytical data for the time evolution of isomeric racemic 2-*d*-1-(*E*)-propenylcyclobutanes and 4-*d*-3-methylcyclohexenes could be used to deconvolute the data to secure rate constants $k(tc) = k(ct)$, $k(si + ar)$, and $k(sr + ai)$. These rate constants involve reactions initiated by C1−C2 bond cleavages; when C1−C4 is broken and **3-*t*** and **3-*c*** are eventually formed, $k'(ar + ai)$ and $k'(sr + si)$ reflect the product ratio.

The synthetic prerequisites posed by this projected investigation have been addressed successfully through a reaction sequence starting with racemic *trans*-1,2-cyclobutanedicarboxylic acid. Its monoethyl ester[16] acid chloride[17] was reduced using *n*-Bu_3SnD and $(Ph_3P)_4Pd$);[18] the deuterioaldehyde formed was decarbonylated[19] to give ethyl *trans*-2-*d*-cyclobutanecarboxylate. Utilizing a stereochemically controlled Horner−Wittig protocol,[20] the *d*-labeled ester was converted to a 1:1 mixture of crystalline diastereomeric *syn*-2-diphenylphosphinoyl-1-cyclobutylpropane-1-ols (^{2}H NMR δ 1.89 and 1.66). A hydride-promoted elimination of diphenylphosphinic acid at 50 °C afforded **1-*t***, together with some **1-*c*** (**1-*t*:1-*c*** ≈ 88:12).[21]

Gas-phase kinetic runs at 276.1 °C with methylcyclohexane as an internal standard and pentane as a bath gas were followed by capillary GC. They provided mol % concentration versus time profiles for (**1-*t*** + **1-*c***) and all *d*-labeled 3-methylcyclohexene products. The rate constant for disappearance of starting material, $k(f) + k(1,3)$, was 1.03×10^{-5} s^{-1}. Here $k(f)$ is the rate constant for fragmentation to ethylenes and 1,3-pentadienes; $k(1,3)$ is $k(si$

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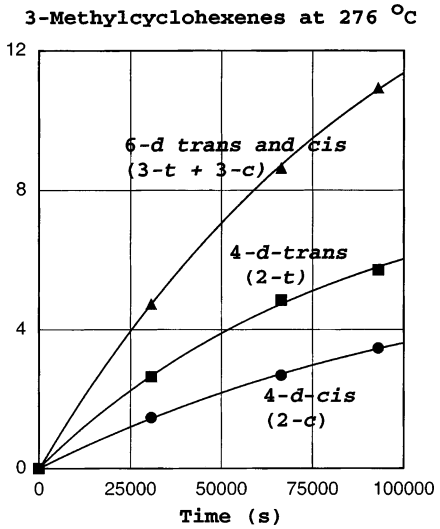

Figure 1. Formation of (**3-*c*** + **3-*t***), **2-*t***, and **2-*c*** from **1-*t*** (*t*) and **1-*c*** (*t*).

+ *ar* + *sr* + *ai*) + *k*′(*si* + *ar* + *sr* + *ai*), the sum of all rate constants for [1,3] carbon shifts shown in Scheme 1. The value for *k*(1,3) was 3.36×10^{-6} s^{-1}, and thus *k*(f) = 6.9×10^{-6} s^{-1}.

The thermal reaction product mixtures were separated by preparative GC, and ^{2}H NMR spectra were obtained. The **3-*t*** and **3-*c*** isomers could not be distinguished (δ 1.945), but the other pairs of diastereomers were readily quantified (**1-*t***, δ 2.08; **1-*c***, δ 1.82; **2-*t***, δ 1.78; **2-*c***, δ 1.18). The first-order decay of the difference in mol % concentrations of **1-*t*** and **1-*c***, corresponding to 2*k*(*tc*) + *k*(f) + *k*(1,3), was 1.87×10^{-5} s^{-1}, and hence *k*(*tc*) = 0.42×10^{-5} s^{-1}. The time-dependent mol % concentrations of **1-*t*** and **1-*c*** depend on the rate constants *k*(f) + *k*(1,3) and 2*k*(*tc*) + *k*(f) + *k*(1,3), and on the initial concentrations of **1-*t*** and **1-*c***, 88.35 and 11.65, respectively. The integrated solutions of the pair of differential equations appropriate to the kinetic situation are [**1-*t*** (*t*)] = 38.35 exp($-\lambda_1 t$) + 50 exp($-\lambda_2 t$) and [**1-*c*** (*t*)] = −38.35 exp($-\lambda_1 t$) + 50 exp($-\lambda_2 t$), where $\lambda_1 = 1.87 \times 10^{-5}$ s^{-1} and $\lambda_2 = 1.03 \times 10^{-5}$ s^{-1}.

From these equations, one can easily calculate the weighted average concentrations of **1-*t*** and **1-*c*** over any time period and then derive the relative importance of the rate constants *k*(*si* + *ar*) versus *k*(*sr* + *ai*) using the ^{2}H NMR data. The data analysis based on three kinetic runs revealed a significant k_H/k_D effect on ring cleavage leading to methylcyclohexene products, *k*′(*si* + *ar* + *sr* + *ai*)/*k*(*si* + *ar* + *sr* + *ai*) = 1.16 ± 0.02, and to a *k*(*si* + *ar*):*k*(*sr* + *ai*) proportion of (72±1):(28±1). Figure 1 shows kinetic plots for the formation of **2-*t***, **2-*c***, and (**3-*c*** + **3-*t***) based on the eqs 1 and 2 and the rate constants *k*(1,3) = 3.36×10^{-6} s^{-1}, *k*′(*si* + *ar* + *sr* + *ai*) = 1.81×10^{-6} s^{-1}, *k*(*si* + *ar*) = 1.12×10^{-6} s^{-1}, and *k*(*sr* + *ai*) = 4.3×10^{-7} s^{-1}.

This vinylcyclobutane-to-cyclohexene isomerization is less complicated by kinetically competitive stereomutations of starting material than reactions of *d*-labeled vinylcyclopropanes.[15] Once a C1−C2 bond is cleaved, there is a much higher likelihood of fragmentation or a [1,3] shift outcome than reformation of a vinylcyclobutane structure. The kinetic advantage of (*si* + *ar*) over (*sr* + *ai*) outcomes is more pronounced than is the case for vinylcyclopropane, where the balance is 53:47.[15] It is slightly larger than the preference found in [1,3] shifts from the trans isomer of 2-methyl-1-(*E*)-propenylcyclobutane, 63:37.[12]

A detailed understanding of the fundamental determinants of reaction stereochemistry for the isomerizations of 2-*d*-1-(*E*)-propenylcyclobutanes to 4-*d*-3-methylcyclohexenes must await a full stereochemical dissection of the [1,3] shift outcomes, and theoretical work, including dynamics calculations, to model reaction trajectories across the caldera. The work required will be demanding, but it is surely feasible.

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Supporting Information Available: Synthetic scheme, ^{1}H chemical shift assignments for 3-methylcyclohexene, tables of kinetic data, kinetic plots, and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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