Stereochemistry of Thermal Vinylcyclobutane-to-Cyclohexene Rearrangements of *cis*-(1*S*,2*R*)- and *trans*-(1*S*,2*S*)-1-(*E*)-Propenyl-2-methylcyclobutanes

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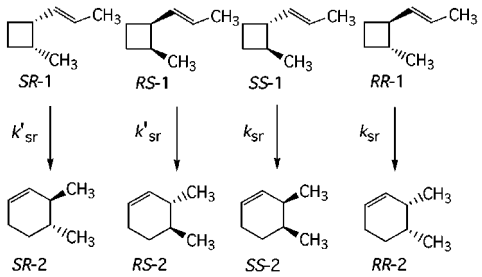
The thermal vinylcyclopropane-to-cyclopentene and vinylcyclobutane-to-cyclohexene rearrangements—among the simplest of [1,3] carbon sigmatropic shifts—have been known for some 40 years.[1,2] Stereochemical information on the isomerizations of substituted vinylcyclopropane hydrocarbons has been gained for a variety of systems,[3−5] and these experimental findings and extensive theoretical work[6] have provided considerable insight on the reactions. They are stereochemically promiscuous but not random, and appear to involve short-lived conformationally flexible (2*Z*)-pentene-1,5-diyl diradicals traversing relative flat transition regions under dynamic control.

Curiously enough, no parallel stereochemical studies on conversions of simple substituted vinylcyclobutane hydrocarbons-to-cyclohexenes have been reported.[7] Prior work with vinylcyclopropane-to-cyclopentene isomerizations[5] and with cyclohexene−vinylcyclobutane interconversions and fragmentations[8] piqued our curiosity about the stereochemical aspects of vinylcyclobutane-to-cyclohexene reactions and engendered a willingness to engage in the experimental challenges that detailed investigations of reaction stereochemistry would provide.

Stereochemically well-defined reactants, such as *cis*-(1*S*,2*R*)- and *trans*-(1*S*,2*S*)-1-(*E*)-propenyl-2-methylcyclobutane (***SR*-1** and ***SS*-1**), may each through [1,3] shifts of C2 give four distinct 3,4-dimethylcyclohexenes. The correspondences between reactant and product defined by stereochemically explicit rate constants as exemplified in Scheme 1 may be readily extended to the full 4 × 4 correlation matrix. For instance ***SR*-1** gives ***RS*-2** through rate constant k'_{ai}, ***SS*-2** through k'_{si}, and ***RR*-2** through k'_{ar}. The first-order rate constants k'_{mn} (for cis reactants) and k_{mn} (for trans reactants) are coded with subscripts indicative of overall migration

Scheme 1



with suprafacial (*s*) or antarafacial (*a*) utilization of the allylic unit, and retention (*r*) or inversion (*i*) at the migrating carbon; they do not connote mechanistic implications.

An experimental effort to decipher reaction stereochemisry would have to face complexities associated with other reactions. The vinylcyclobutanes **1** would be expected to suffer thermal stereomutations,[9] various fragmentations, and other isomerizations in competition with conversions to 3,4-dimethylcyclohexenes. Any of the four possible stereoisomers **2** could be formed from any one of the four isomers of **1**, each having time-dependent concentrations. Thus the kinetic situation as well as the analytical requirements might prove daunting.

The present report outlines experiments solving this problem in reaction stereochemistry. The overall objective, to provide a rigorous experimental definiton of reaction stereochemistry for the thermal vinylcyclobutane-to-cyclohexene isomerizations of the geometrically unconstrained hydrocarbons ***SR*-1** and ***SS*-1**, was approached in stages.

First, methods for quantitative analyses of mixtures of all four isomers of **2** using capillary GC were developed.[10] Second, racemic samples of ***cis*-1** and ***trans*-1** were synthesized,[11] and the thermal reactions they exhibited at 275 °C were investigated.[12] Every C_8H_{14} isomer in reaction mixtures was well resolved by capillary GC; each was isolated by preparative GC and identified with the aid of authentic reference samples. Third, when attempts to resolve the enantiomers of ***cis*-1** and ***trans*-1** directly through capillary GC on columns having chiral stationary phases proved unsuccessful, an alternative tactic was developed: preparative GC gave pairs of enantiomers, which were converted (OsO_4, $NaIO_4$, dioxane, H_2O; then $LiAlH_4$, ether) on a very small scale to mixtures of the four 1-hydroxymethyl-2-methylcyclobutanes, compounds conveniently and completely separated by GC using a CycloSil B column (30% heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin in DB-1701; J&W).

Fourth, samples of the *cis*-(1*S*,2*R*)- and *trans*-(1*S*,2*S*)-isomers of 1-hydroxymethyl-2-methylcyclobutane (***SR*-3** and ***SS*-3**) of better than 99% ee were prepared[11] and assignments of absolute stereochemistry were secured through chemical interconversions and a reference compound structurally defined through X-ray crystallography.[13] These alcohols led to secure correlations of enantiomers separated by GC; on the CycloSil B column the elution order is ***RS*-3** before ***SR*-3**, and ***RR*-3** before ***SS*-3**. Fifth, the alcohols ***SR*-3** and ***SS*-3** of high ee were converted (PCC, CH_2Cl_2; then $CrCl_2$,CH_3CHI_2, THF) to the corresponding 1-pro-

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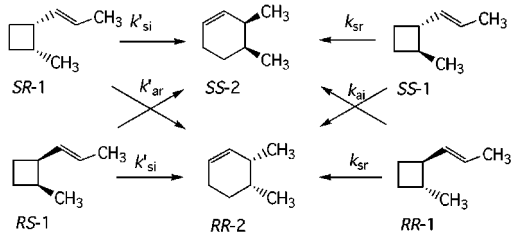
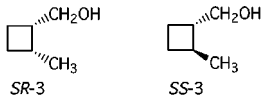
Scheme 2



penyl-2-methylcyclobutanes with about 14:1 *E*/*Z* stereoselectivity. Preparative GC then gave ***SR*-1** and ***SS*-1** for kinetic experiments.



Samples of ***SR*-1** or ***SS*-1** and cyclooctane (as internal standard) diluted with pentane (to serve as a bath gas) were heated in a gas-phase quartz static reactor at 275 °C for specified periods, then transferred to a vacuum line, condensed, and analyzed by GC. Time-dependent mol % data for sums of cis and trans enantiomers followed well the theoretically dictated kinetic forms. For thermal reactions starting from the cis isomer ***SR*-1**, ***cis*-1**(t) = 0.37 exp($-\lambda_1 t$) + 99.63 exp($-\lambda_2 t$) and ***trans*-1**(t) = 30.75 exp($-\lambda_1 t$) − 30.75 exp($-\lambda_2 t$). For reactions from ***SS*-1, *trans*-1**(t) = 89.39 exp($-\lambda_1 t$) + 10.40 exp($-\lambda_2 t$) and ***cis*-1**(t) = 6.55 exp($-\lambda_1 t$) − 6.33 exp($-\lambda_2 t$). For all four functions, $\lambda_1 = 1.84 \times 10^{-5}$ s^{-1} and $\lambda_2 = 9.02 \times 10^{-5}$ s^{-1}. These four time-dependent functions reflect ***cis*-1**,***trans*-1** equilibrations and all fragmentations, [1,3] shifts, and other isomerizations contributing to decay of (***cis*-1** + ***trans*-1**).

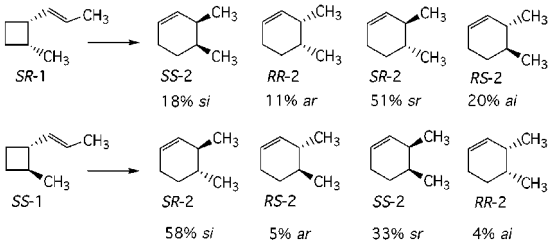
At any time t, the rate of formation of cis product is d(***cis*-2**)/dt = d(***SS*-2** + ***RR*-2**)/dt = (k'_{si} + k'_{ar})(***SR*-1** + ***RS*-1**) + (k_{sr} + k_{ai})(***SS*-1** + ***RR*-1**). Integration provides (***SS*-2** + ***RR*-2**)(t) = (k'_{si} + k'_{ar})$\int$(***SR*-1** + ***RS*-1**)dt + (k_{sr} + k_{ai})$\int$(***SS*-1** + ***RR*-1**)dt. This and the similar expression for ***trans*-2**(t) = (***SR*-2** + ***RS*-2**)(t) and the time-dependent GC-determined values of ***cis*-2** and ***trans*-2** led through least-squares optimizations to the rate constants (k'_{si} + k'_{ar}) = 2.19 × 10^{-6} s^{-1}, (k'_{sr} + k'_{ai}) = 5.34 × 10^{-6} s^{-1}, (k_{sr} + k_{ai}) = 1.45 × 10^{-6} s^{-1}, and (k_{si} + k_{ar}) = 2.44 × 10^{-6} s^{-1}.

The time-dependent values of (***SR*-1** − ***RS*-1**) and (***SS*-1** − ***RR*-1**) starting from either ***SR*-1** or ***SS*-1** were, as the relevant kinetic expressions require, well modeled as a sum of two exponential terms. For reactions starting from ***SR*-1**, (***SR*-1** − ***RS*-1**)(t) = 1.27 exp($-\lambda_3 t$) + 97.73 exp($-\lambda_4 t$) and (***SS*-1** − ***RR*-1**)(t) = 4.37 exp($-\lambda_3 t$) − 4.37 exp($-\lambda_4 t$). For reactions starting from ***SS*-1**, (***SS*-1** − ***RR*-1**)(t) = 89.44 exp($-\lambda_3 t$) + 9.35 exp($-\lambda_4 t$), where $\lambda_3 = 2.20 \times 10^{-5}$ s^{-1} and $\lambda_4 = 10.57 \times 10^{-5}$ s^{-1}, and (***SR*-1** − ***RS*-1**)(t) = 0 to within experimental uncertainties.

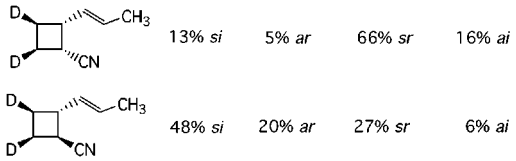
These functions and time-dependent GC-determined values for (***SS*-2** - ***RR*-2**) and for (***SR*-2** − ***RS*-2**) then provided the rate constants (k'_{si} − k'_{ar}) = 0.57 × 10^{-6} s^{-1}, (k'_{sr} − k'_{ai}) = 2.41 × 10^{-6} s^{-1}, (k_{sr} − k_{ai}) = 1.12 × 10^{-6} s^{-1}, and (k_{si} − k_{ar}) = 2.08 × 10^{-6} s^{-1} from simple linear plots based on the exact integrated kinetic expressions. The kinetic situation for the formation of *cis*-3,4-dimethylcyclohexenes illustrates the analysis (Scheme 2).

At any time t, d(***SS*-2** − ***RR*-2**)/dt = (k'_{si} − k'_{ar})(***SR*-1** − ***RS*-1**) + (k_{sr} - k_{ai})(***SS*-1** − ***RR*-1**). Integration provides (***SS*-2** − ***RR*-2**)(t) = (k'_{si} − k'_{ar})$\int$(***SR*-1** − ***RS*-1**)dt + (k_{sr} − k_{ai})$\int$(***SS*-1** − ***RR*-1**)dt. The integrals may be calculated for any range 0 to t, and the equation rearranged to standard $y = mx + b$ form: (***SS*-2** − ***RR*-2**)(t)/$\int$(***SS*-1** − ***RR*-1**)dt = (k'_{si} − k'_{ar})$\int$ (***SR*-1** − ***RS*-1**)dt/$\int$ (***SS*-1** − ***RR*-1**)dt + (k_{sr} − k_{ai}). Similarly, (***SR*-2** − ***RS*-2**)(t) = (k'_{sr} − k'_{ai})$\int$ (***SR*-1** − ***RS*-1**)dt + (k_{si} − k_{ar})$\int$(***SS*-1** − ***RR*-1**)dt and (***SR*-2** − ***RS*-2**)(t)/$\int$(***SS*-1** − ***RR*-1**)dt = (k'_{sr} − k'_{ai})$\int$ (***SR*-1** − ***RS*-1**)dt/$\int$ (***SS*-1** − ***RR*-1**)dt + (k_{si} − k_{ar}) serve for treating time-dependent data for reactions leading to the enantiomers of ***trans*-2**. The two slopes for the linear plots give values of (k'_{sr} − k'_{ai}) and (k'_{si} − k'_{ar}). For runs starting with ***SS*-1**, one has (***SS*-2** − ***RR*-2**)(t) = (k_{sr} − k_{ai})$\int$(***SS*-1** − ***RR*-1**)dt and (***SR*-2** − ***RS*-2**)(t) = (k_{si} − k_{ar})$\int$(***SS*-1** − ***RR*-1**)dt. The linear plots provide measures of (k_{sr} − k_{ai}) and (k_{si} − k_{ar}).

Scheme 3



Scheme 4



From the experimentally determined rate constant sums and differences one may derive all eight rate constants for distinct [1,3] carbon sigmatropic shifts, or the relative importance of the stereochemically different paths utilized by each reactant (Scheme 3, in percentage terms, ±2−3%).

Several points are worth noting. An enantiomer of ***trans*-1** reacts using the four possible paths in a pattern similar to the one uncovered in 1976 for *trans*-1-(*E*)-propenyl-2-methycyclopropane − 65% *si*, 8% *ar*, 22% *sr* and 5% *ai*.[5a] One may thus anticipate that the sorts of theoretical efforts which have provided illuminating insights for vinylcyclopropane-to-cyclopentene isomerizations[6] may be directly relevant to the similar isomerizations of vinylcyclobutanes. The stereochemical pattern for one enantiomer of ***cis*-1** is quite dissimilar, however, for the most prominent *sr* and *ai* paths seen experimentally are "forbidden" by orbital symmetry theory. The dictates of orbital symmetry for these reactions seem irrelevant. Rather, relative product stabilities and entropic factors may control reaction dynamics and stereochemical outcomes for these isomerizations.

Comparable stereochemical findings were attained by Doering and Cheng in 1989 for racemic 1-(*E*)-propenyl-2-cyanocyclobutanes labeled stereoselectively with deuterium at C3 and C4.[14] The relative importance of the various reaction modes, rounded to the nearest percent (Scheme 4), are remarkably similar. Again, the cis isomer favors "forbidden" paths; the "allowed" *si* component prominent for the trans reactant is strikingly diminished in isomerizations shown by the cis substrate.

The differences in stereochemical preferences for the 1-(*E*)-propenyl-2-methylcyclobutanes ***SR*-1** and ***SS*-1** underscore both the substantial influences the spatial dispositions of methyl substituents exert on reaction dynamics and the need for complete stereochemical information on the vinylcyclobutane-to-cyclohexene isomerizations shown by systems with only truly minimal stereochemistry-marking substituents: deuterium atoms. Such an undertaking lies in the future.

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Supporting Information Available: Four figures displaying kinetic data and derived theory-based functions (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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