BAL, Aldrich, 14 mL of a 1 M solution in hexane). A small aliquot of the reaction mixture was quenched with MeOH and analyzed by GC to check for incomplete reduction products. After the addition, 14 mL of HPLC grade MeOH was added at such a rate that the reaction temperature never rose above −96 °C. The mixture was then allowed to warm to room temperature. The resulting white globular solid was filtered off and rigorously washed with 300 mL of ether. The ethereal solution was concentrated, and two layers formed. After being allowed to stand refrigerated at 4 °C for 5 days, the layers coalesced, resulting in an oil that was 70% enriched in the dialdehyde *rac*-**11**-$^{13}C,d_3$ (GC estimate: 0.53 g, 84% yield): ^{1}H NMR δ 1.37 (s, 0.5 H), 1.93 (s, 0.5 H), 2.53 (residual m, 0.05 H), 9.35 (s, 2 H); ^{13}C NMR δ 14.03 (t).

Cyclopropane-*1*-^{13}C-*trans*-*2,3*-d_2 (*rac*-1-$^{13}C,d_3$). The reagent Rh(PPh$_3$)$_3$Cl (8.09 g), freshly vacuum-distilled 1,2-dichloropropane (50 mL), and the crude dialdehyde reaction product described immediately above (*rac*-**11**-$^{13}C,d_3$, 0.29 g, 2.8 mmol) were allowed to react according to the procedure described above. The cyclopropane product *rac*-**1**-$^{13}C,d_3$ (50 mg, 38% yield) was isolated in pure form by preparative GC: mass spectrum *m/e* 47 (3.3), 46 (M, 100), 45 (80.4), 44 (58.2), 43 (34.4), 42 (55.5), 41 (45.9); IR 3090, 3061, 3045, 2272, 2155, 1075, 825, 750 cm^{-1}.

(+)-(*S,S*)-Cyclopropane-*trans*-1,2-dicarboxaldehyde-*3*-^{13}C-*1,2,3*-d_3 ((2*S*,3*S*)-11-$^{13}C,d_3$). According to the procedure for the reduction of *rac*-**2**-$^{13}C,d_3$, (2*S*,3*S*)-**2**-$^{13}C,d_3$ (0.98 g, 6.0 mmol) gave (2*S*,3*S*)-**11**-$^{13}C,d_3$ (0.49 g, 80% crude yield): ^{1}H NMR δ 1.37 (s, 0.5 H), 1.93 (s, 0.5 H), 2.57 (residual d, 0.08 H), 9.35 (s, 1 H); ^{13}C NMR δ 14.01 (t).

(−)-(*R,R*)-Cyclopropane-*trans*-1,2-dicarboxaldehyde-*3*-^{13}C-*1,2,3*-d_3 ((2*R*,3*R*)-11-$^{13}C,d_3$). According to the procedure for the reduction of *rac*-**2**-$^{13}C,d_3$, (2*R*,3*R*)-**2**-$^{13}C,d_3$ (0.5 g, 3.1 mmol) gave (2*R*,3*R*)-**11**-$^{13}C,d_3$ (0.23 g, 74% crude yield): ^{1}H NMR δ 1.37 (s, 0.5 H), 1.93 (s, 0.5 H), 2.57 (residual d, 0.08 H), 9.35 (s, 1 H); ^{13}C NMR δ 14.01 (t).

(2*S*,3*S*)-Cyclopropane-*1*-$^{13}C,d$-*trans*-*2,3*-d_2 ((2*S*,3*S*)-1-$^{13}C,d_3$). According to the procedure for the production of *rac*-**1**-$^{13}C,d_3$, (2*S*,3*S*)-**11**-$^{13}C,d_3$ (0.144 g, 1.4 mmol) produced 23 mg (35% yield) of GC-pure (2*S*,3*S*)-**1**-$^{13}C,d_3$: mass spectrum *m/e* 47 (3.2), 46 (M, 100), 45 (80.8), 44 (57.7), 43 (32.6), 42 (52.1), 41 (43.9); IR 3090, 3061, 3045, 2272, 2155, 1075, 825, 750 cm^{-1}.

(2*R*,3*R*)-Cyclopropane-*1*-$^{13}C,d$-*trans*-*2,3*-d_2 ((2*R*,3*R*)-1-$^{13}C,d_3$). According to the procedure for the production of *rac*-**1**-$^{13}C,d_3$, (2*R*,3*R*)-**11**-$^{13}C,d_3$ (0.12 g, 1.2 mmol) gave 13 mg (24% yield) of GC-pure (2*R*,3*R*)-**1**-$^{13}C,d_3$: mass spectrum *m/e* 47 (2.9), 46 (M, 100), 45 (81.8), 44 (58.5), 43 (36.6), 42 (57.4), 41 (50.9); IR 3090, 3061, 3045, 2272, 2155, 1075, 825, 750 cm^{-1}.

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Kinetics of Thermal Geometrical Isomerizations of Three Sets of Isotopically Labeled Cyclopropanes Followed by Tunable Diode Laser Spectroscopy

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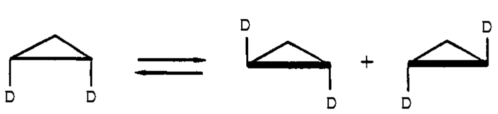
Abstract: First-order rate constants for the approach to equilibrium through thermal geometrical isomerizations have been secured using tunable diode laser spectroscopy for three sets of isotopically labeled cyclopropanes. For the cis and trans 1,2-d_2 cyclopropanes at 422.5 °C, $k_i(\mathrm{d}_2) = (13.6 \pm 0.26) \times 10^{-5}\ \mathrm{s}^{-1}$. For the syn and anti isomers of cyclopropane-*1,2,3*-d_3 at 422.5 °C, $k_i(\mathrm{d}_3) = (15.5 \pm 0.47) \times 10^{-5}\ \mathrm{s}^{-1}$. For the isomers of cyclopropane-*1*-^{13}C-*1,2,3*-d_3 at 407.0 °C, $k_i(^{13}\mathrm{C},\mathrm{d}_3) = (4.63 \pm 0.20) \times 10^{-5}\ \mathrm{s}^{-1}$. These results are compared with independent determinations of two of these rate constants based on FTIR spectroscopy, and the relative advantages and limitations of the two spectroscopic techniques are compared.

The thermal interconversion of the cis and trans isomers of cyclopropane-*1,2*-d_2 (**1** and **2**) discovered by Rabinovitch, Schlag, and Wiberg in 1958[1] involves a net epimerization of one deuteriomethylene unit. This prototypical instance of a thermal reaction which may occur by way of trimethylene diradicals has been subjected to extensive theoretical scrutiny[2] but to relatively little experimental study.



1 (*S, S*)-2 (*R, R*)-2

Since 1958, thermal epimerizations exhibited by numerous more heavily substituted cyclopropanes have been followed at various levels of completeness and rigor.[3] Yet experimental studies of isotopically labeled but otherwise unsubstituted cyclopropanes, systems of most direct relevance to theoretical efforts to understand this fundamental type of thermal reaction, have been few, indeed.

Thermal interconversions of **1** and racemic **2**, each prepared from cyclopropane through stereoselective reductions, have been

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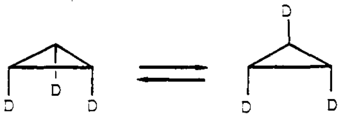
followed over a range of pressures and temperatures,[1,4,5] and an independently synthesized sample of (+)-(*S*,*S*)-**2** has been isomerized at 422.5 °C.[6] Infrared spectroscopic analyses based on a strong absorption due to the cis isomer at 11.83 μ (845 cm^{-1}) have been used to estimate the relative proportions of the two geometrical isomers in thermal reaction mixtures.[1,4-6] Kinetic work[6] with (+)-(*S*,*S*)-**2** provided, as well, the rate constant for overall racemization $k_\alpha(d_2)$ in an effort to make distinctions between one-center and two-center epimerization processes having rate constants k_j and k_j and, thus, to discriminate among various mechanistic possibilities.[7]

All of these pioneering studies of cyclopropane-*1,2-d*$_2$ stereomutations had to cope with very substantial synthetic and analytical challenges, which may partially explain why these investigations were not continued to a definitive mechanistic conclusion. Only recently, after a 15-year hiatus, has additional kinetic and analytical work relevant to the thermal stereomutations of simple isotopically labeled cyclopropanes been reported.[8-13] This renewed study was prompted both by an awareness that the fundamental mechanistically significant discrimination for these isomerizations, the relative importance of one-center and two-center epimerization paths,[7] remained undefined experimentally and by a curiosity as to whether other isotopically substituted cyclopropanes or novel analytical techniques might contribute usefully toward a solultion of this challenging problem.

Of the 15 possible deuteriated analogs of cyclopropane[14]—three pairs of enantiomers and nine achiral molecules—five are evidently not suited for this particular purpose, since they are structurally incapable of showing epimerization reactions: the d$_1$, 1,1-d$_2$, 1,1,2,2-d$_4$, d$_5$, and d$_6$ systems. The 1,2,3-d$_3$ isomers offer the possibility of following geometric iomerizations between two achiral meso forms, the syn and anti isomers (**3** and **4**).

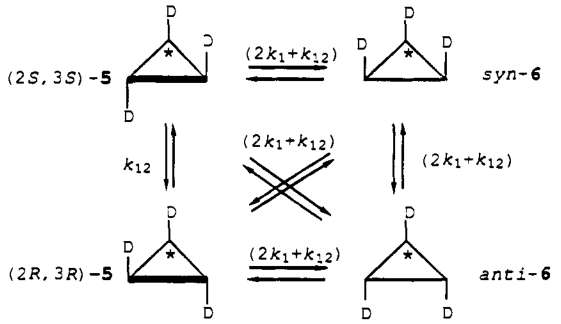


syn-**3** anti-**4**

The 1,1,2-d$_3$ isomers would permit one to follow an enantiomerization process in the absence of any geometrical isomerization. The 1,1,2,3-d$_4$ cyclopropanes, like the 1,2-d$_2$ cyclopropanes, could show both enantiomerization and geometrical isomerization reactions.

While only the three 1,2-d$_2$ cyclopropanes have been utilized before to follow thermal stereomutations,[1,4-6] several, but not all, of the other deuterated cyclopropanes have been prepared and used for mechanistic or spectroscopic investigations.[8-13,15-17]

Scheme I. Thermal Isomerizations among the Four Isomers of Cyclopropane-*1*-^{13}*C*-*1,2,3-d*$_3$



Of the many possible cyclopropanes substituted with one carbon-13 atom and one or more deuterium atoms—we count 35 possibilities—those that could not exhibit thermal stereomutations or that would give no kinetic information beyond what might be learned from studying the corresponding deuteriated cyclopropanes themselves were not of immediate interest. Cyclopropane-*1*-^{13}*C*-*2,2-d*$_2$ and the three cyclopropane-*1*-^{13}*C*-*2,3-d*$_2$ isomers exemplify such molecules.

Other carbon-13 and deuterium-labeled cyclopropanes, however, were judged to offer unique opportunities insofar as they could facilitate access to kinetic information which could not be gained through investigations of any set or sets of deuteriated cyclopropanes. The chiral isomers of cyclopropane-*1*-^{13}*C*-*2-d*, for example, would at least in principle permit the determination of a first-order rate constant for racemization in the absence of any geometrical isomerization, and thus a value for $(k_1 + k_{12})$, the rate constant for epimerization at the CDH center by both one-center and two-center processes unconditioned by any β or γ secondary deuterium kinetic isotope effects, could be determined. A chiral cyclopropane-*1*-^{13}*C*-*1,2,3-d*$_3$ would permit one to measure rate constants for both racemization and geometrical isomerization and thus would give two kinetic parameters from which one could derive $k_1 = k_2 = k_3$ and $k_{12} = k_{13} = k_{23}$ (Scheme I).[11] In this scheme, the rate constants are defined on a per C–C bond basis. Thus, a one-center epimerization at C1 takes place with rate constant $2k_1$, since the epimerization could occur with either C1–C2 or C1–C3 bond cleavage.

This paper reports determinations of first-order rate constants for the approach to equilibrium through thermal geometrical isomerizations in three sets of isotopically labeled cyclopropanes: between the two geometrically distinct isomers of cyclopropane-*1,2-d*$_2$ **1** and **2**, between the syn and anti forms of cyclopropane-*1,2,3-d*$_3$ **3** and **4**, and between the chiral and achiral isomers of cyclopropane-*1*-^{13}*C*-*1,2,3-d*$_3$, the two enantiomers of **5**, and the two meso isomers **6**. These determinations have been based on a comparatively novel analytical method, that of tunable diode laser spectroscopy.

The tunable diode laser (TDL) spectroscopic method is seen to be both reliable, as judged by independent measurements of two of these rate constants using more conventional FTIR spectroscopic methods, and highly sensitive, thus offering substantial advantages when only limited amounts of subtly different isotopically distinct isomers must be analyzed.

Experimental Section

Materials. The isotopically labeled cyclopropanes (±)-**2**, (+)-(*S*,*S*)-**2**, (−)-(*R*,*R*)-**2**, (±)-**5**, (2*S*,3*S*)-**5**, and (2*R*,3*R*)-**5** were synthesized from

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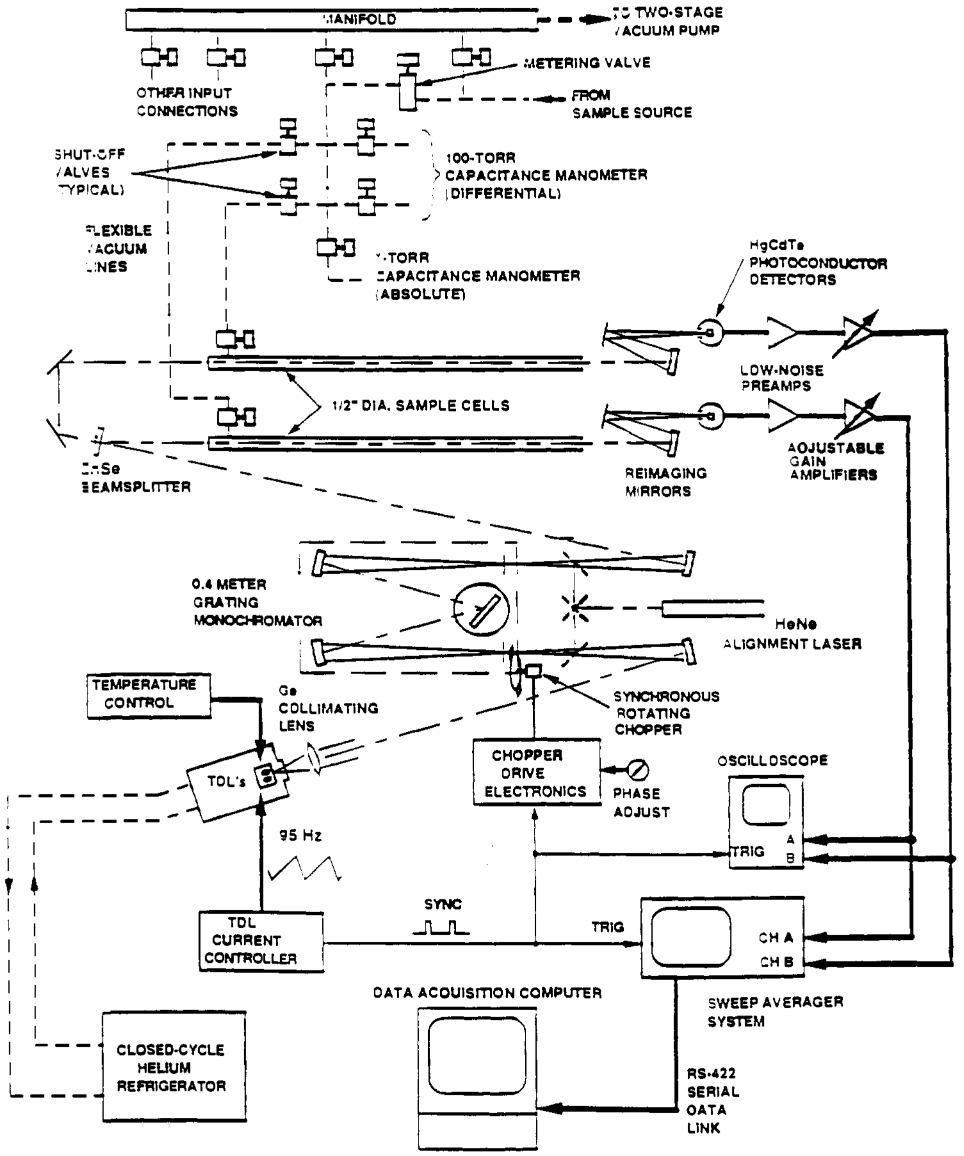

Figure 1. Schematic layout of the tunable diode laser (TDL) infrared absorption spectrometer.

simple starting materials as outlined elsewhere.[8,11] The cyclopropanes **1**, **3**, **4**, and a second sample of (±)-**2** were prepared from 3-(ethoxycarbonyl)cyclopropene (or 3-deuterio-3-(ethoxycarbonyl)cyclopropene) through reduction with $LiAlH_4$ (or $LiAlD_4$), quenching of the reduction reaction with water (or D_2O),[18] conversion of the primary alcohol function to an aldehyde (or deuterio aldehyde), and decarbonylation using $Rh(Ph_3)_3Cl$. Each of these labeled cyclopropanes was thoroughly purified by preparative gas chromatography using a 6.4-mm × 3.7-m aluminum column containing 20% SE-30 on 60/80-mesh Chromosorb W NAW that had been treated with hexamethyldisilazane and employing a Varian Aerograph A90-P3 instrument equipped with an eight-port value assembly for transferring cyclopropane samples to the injection port. The cyclopropanes were analyzed for purity using a Hewlett-Packard (HP) 5790 instrument equipped with dual flame ionization detectors and dual HP 3392A reporting integrators, employing two 0.2-mm i.d. 25-m ultraperformance fused silica capillary CG columns of different polarity, a cross-linked dimethyl silicone column and a cross-linked 5% phenyl methyl silicone column, connected to a single injection port through a two-holed graphite ferrule. They were analyzed for isotopic content and stereochemical integrity through Fourier transform infrared (FTIR) spectroscopy, tunable diode laser (TDL) spectroscopy, mass spectrometry, and NMR spectroscopic analyses of synthetic precursors. Each was estimated to have from 96 to 99% deuterium at each labeled carbon atom. The quadruply labeled cyclopropanes were prepared from barium carbonate-^{13}C (98.7% ^{13}C, Isotec Inc.).

All kinetic runs were done in the gas phase with pentane as a bath gas and total pressures ranging from 680 to 690 Torr in a well-seasoned 252-mL Pyrex reactor. Temperature was maintained to ±0.1 °C with the aid of a Bailey Instruments 253 precision temperature controller and was measured with a HP 3474A digital display unit and a HP 2802A platinum resistance thermometer inserted in the aluminum heating block surrounding the Pyrex bulb to within a few millimeters of the wall of the Pyrex reactor. Following the reactions, mixtures of the labeled cyclopropanes were isolated in pure form by preparative gas chromatography and analyzed spectroscopically.

Tunable Diode Laser Spectroscopic Instrumentation and Methods. Only the essential design features of the tunable diode laser (TDL) infrared absorption spectrometer[19-21] will be discussed here. A schematic diagram of the system used is shown Figure 1. The light source is a highly monochromatic (frequency spread of a few megahertz) lead salt diode laser enclosed in an evacuated chamber, which is cooled to $T > 10$ K by a closed-cycle helium refrigerator. Given the narrow emission profile of the TDL, an inherent resolution of 10^{-5} cm^{-1} is obtained. The narrow line width also greatly enhances system sensitivity over that of a wider bandwidth instrument, as all the light intensity is concentrated in the narrow absorption lines of the sample molecule and none is wasted on regions where the sample is transparent. The transmitted laser intensity can be measured to an accuracy of 1 part in 10^5, enabling quantitative measurements of weak (less than 1% absorbing) vibration–

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rotation transitions of deuteriated cyclopropane samples smaller than 1 mg.

A spectral region is scanned by first fixing the TDL temperature at a desired value between 10 and 100 K. This establishes the index of refraction of the lead salt and provides a coarse adjustment of the lasing wavelength. A sawtooth current ramp is then applied across the diode junction, which induces the lasing action and causes the diode to scan repeatedly over a defined spectral interval of up to 0.1 cm^{-1}. The IR light emitted from the diode is passed through a 0.4-m grating monochromator to ensure that a single longitudinal mode of oscillation is transmitted through the system. The monochromator also serves as a means of determining the output frequency of the diode to ±1 cm^{-1}. The light beam is then split 70% T/30% R by a ZnSe beam splitter and passed through two carefully matched sample cells constructed of heavy-wall glass tubing. The cells are capped with BaF_2 or KRS-5 windows which are tilted 10 degrees off axis to spoil any etalon effects in the beam path. Pairs of cells used in this study are 1.27 cm × 70.0 cm and 1.27 cm × 120.0 cm. For analyses of very weak absorption features, both pairs of cells are used in series to produce path lengths of 190.0 cm. After passing through the cells, the two light beams are focused on matched, AC-coupled HgCdTe detectors cooled to 77 K, the outputs of which are sampled by a two-channel sweep averager that sweeps synchronously with the current ramp. A synchronous rotating-blade chopper blocks the light beams at the beginning and end of each sweep to define an accurate zero signal level. The signal amplitudes produced by the two beams are matched by careful beam alignment and by adjustment of variable gain preamplifiers, with sample and reference cells evacuated. Spectra are acquired by making a few hundred scans (typically 300) at a scan repetition rate of 95 Hz. The sample and reference beams are scanned alternately during data acquisition, which effectively averages out gradual fluctuations in laser frequency or power. Reflecting optics are used wherever possible to eliminate refocusing as the operating wavelength is changed.

Since the earlier reports on the design and operation of the TDL spectrometer,[19-21] numerous changes and improvements have been made. In addition to the two original diodes covering wavelength segments between 950 and 1050 cm^{-1} and between 1240 and 1310 cm^{-1}, we have added another which operates within the range of 2250–2300 cm^{-1} and a monochromator grating blazed for 4.4 μm. This was needed to access strong and distinctive absorption features of the cyclopropane-*1*-^{13}C-*1,2,3*-d_3 isomers. The Tekmar Lab Master/IBM PC data acquisition system has been replaced by an EG&G/PARC Model 4203 signal averager coupled to a Macintosh Plus computer through an IEEE-422 interface. The two 14-bit buffers of the PARC signal averager allow more sample and reference scans to be acquired and averaged without data overflow, providing more accurate line intensity measurements of weak lines. The entire system has been moved onto a honeycomb optical table for mechanical rigidity, and the original optical mounts have been replaced with more rigid devices. A new diode mounting stage has been constructed within the cold head which rotates the diodes by 90 degrees from their conventional orientation; this maximizes the first-order intensity of light passed by the monochromator. Finally, a new gas sample handling system has been constructed, using bakeable stainless steel bellows valves and fittings.

With each set of isomeric cyclopropanes, a three-step data acquisition process was followed. First, absorption spectra of authentic samples of all expected isomers and possible contaminants were recorded over the range of frequencies and possible contaminants were recorded over the range of frequencies covered by our diodes. From these surveys, we selected the most intense unique absorption features of each compound. Only lines adjacent to a clear (zero absorbance) region were selected, so that accurate absorption measurements could be made. Second, we constructed a curve-of-growth (Beer's law plot) using two or more isolated features for each isomer over a range of pressures up to 1.0 Torr, to be certain that the sample absorbance scaled linearly with concentration. Before analysis, the samples were degassed at 77 K to remove any air that might have leaked into their containers (Pyrex bulbs sealed with Teflon brand stopcocks). All samples were loaded onto the cells and scanned two or more times to check the repeatability of the pressure measurements. Some samples were studied in both light paths to be certain that no biases were introduced by choice of cell. Pressures were measured to the nearest millitorr with a 1.0-Torr, temperature-stabilized MKS Baratron capacitance manometer. Comparison of line profiles at various sample pressures indicated no measurable pressure broadening up to 1 Torr. Finally, we measured the intensities of the isomers of interest in product samples from the kinetic runs relative to the intensities of the same absorption features in each of the authentic unreacted samples. Line profiles were carefully examined to be certain that no broadening had occurred due to temperature-associated TDL frequency drift during the few seconds required to superimpose the 100–300 scans; if any broadening was evident, the scans were repeated. Product samples from each time sequence were analyzed in random order. During each set of measurements, zero absorbance (I_0) spectra for both beam paths were acquired by pumping each cell and flushing twice with 10-Torr ultrapure argon. This same procedure was followed before a new sample was introduced into a cell. Fringe spectra of a 2.5-cm Ge calibration etalon were also scanned at frequent intervals, to be certain that the laser output consisted of a single mode and to provide a measurement of the range of frequency scanned on each sweep.

Absorption features of the 1,2-d_2 cyclopropanes were measured for reference samples of **1**, racemic **2**, (+)-(*S*,*S*)-**2**, and a mixture of **1** and **2** produced by heating a sample of racemic **2** for 1800 min (more than 20 half-lives) at 422.5 °C. To determine the purity of the unreacted materials, absorption features of cyclopropane, cyclopropane-d_1, **3**, and **4** were also recorded. Except for small (1-4%) concentrations of cyclopropane-d_1, the only contaminant identified in any cyclopropane-d_2 reactant was the only isomer: 7.24% **2** in **1** and 5.47% **1** in the sample of racemic **2**. The TDL analyses of product samples showed the same levels of cyclopropane-d_1 that were found in the unreacted samples, and no identifiable features of **3** or **4**; this was true even for the 1800-min equilibrium burn. Thus, it was concluded that intermolecular H/D isotope exchange reactions could not have occurred at rates sufficient to affect the results of this study. Independent FTIR analyses[10] (Nicolet 7199, 2048 scans at 2-cm^{-1} resolution) of 4.5-mg samples of unreacted **1** at 1038.4 cm^{-1}) and chiral **2** (at 1043.7 cm^{-1}) indicated 7.2% trans contaminant in the unreacted cis isomer and 5.4% cis in the chiral trans starting material, in agreement with the TDL spectroscopy results. Mass spectrometric analyses of the unreacted samples supported the conclusions reached from TDL spectra: except for the possibility of traces of cyclopropane-d_1, which would be difficult to quantify, no contaminants were observed, and thermal reaction product mixtures showed no evidence of **3** or **4**.

Analysis of the 1,2,3-d_3 cyclopropanes followed similar procedures. The TDL, FTIR, and MS analyses of unreacted samples of both **3** and **4** showed no contaminents other than small amounts of **1** and **2**. No increases in concentrations of **1** or **2** were found in any of the reacted samples.

The only quadruply labeled cyclopropane available for characterization was the reactant (2*S*,3*S*)-**5**. Upon analysis of both unreacted and heated samples, some spectral features were found which decreased with increasing time of heating, reaching 50% of I_0 at 5700 min; these were assigned to structure **5**. Other features were found which grew with time of heating; these were attributed to the meso product. While it could not be determined which features were associated with the syn and with the anti forms of **6** because no authentic samples were at hand, this limitation is of no consequence, since the two geometric isomers would be produced at equal rates. The spectral lines used in the analysis were determined not to be features of **1**, **2**, **3**, **4**, or cyclopropane-d_1.

Results

For the 1,2-d_2 cyclopropanes, $k_i(d_2)$, the first-order rate constant for the approach to equilibrium between **1** and (±)-**2**, is the sum of the forward and the reverse rate constants. Experimentally, the rate constant may be secured by fitting observed concentration versus time data to the expression given in eq 1; the same expression is equally suited for data based on either cis or trans starting material.

$$([\mathbf{1}(t)] - [\mathbf{2}(t)])/([\mathbf{1}(0)] - [\mathbf{2}(0)]) = \exp(-k_i(d_2)t) \quad (1)$$

In terms of the mechanistically significant rate constants k_j and k_{jl} and with K_{eq} taken to be 1, $k_i(d_2)$ is equal to 4 $(k_1 + k_1' + k_{13})$; here k_1 is the rate constant for one-center epimerization at C1 when C1–C2 breaks, and k_1' is the rate constant for one-center epimerization at C1 when C1–C3 breaks. By symmetry $k_1 = k_2$, $k_1' = k_2'$, and $k_{13} = k_{23}$. Or, one may let $k = k_1' + k_{13}$, and thus express $k_i(d_2)$ as $4(k_1 + k)$.[10]

Analyses of reaction mixtures by TDL spectroscopy were based on distinctive absorption features shown by the two isomers near 1026 cm^{-1} (Figure 2). The stacked plot display in Figure 2 shows both unreacted cis and trans isomers, an equilibrium mixture of the two, and four kinetic samples. The concentration data of Table I, based on three different starting materials and ten thermal reaction mixtures from kinetic runs at 422.5 °C, gave through a nonlinear least-squares treatment[22] $k_i(d_2) = (13.6 \pm 0.26) \times$

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[22] SAS Institute Inc., Cary, NC 27511; the uncertainities given are 1 × σ.

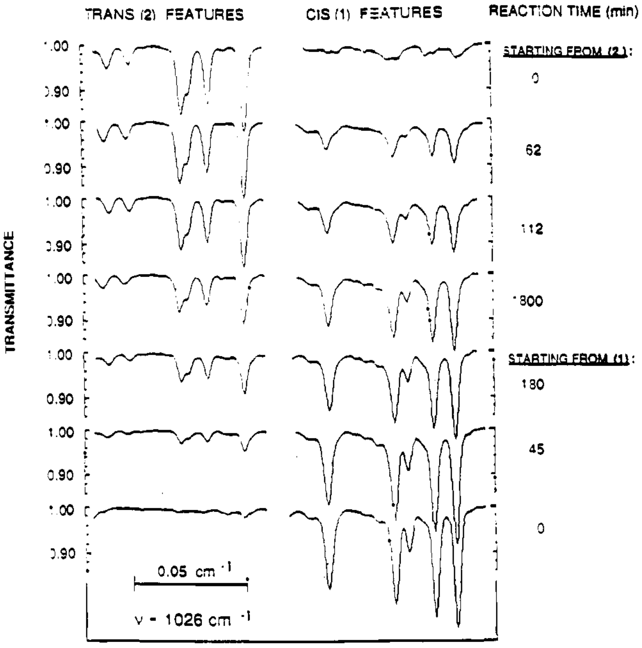


Figure 2. TDL spectra of less than 1 mg of 1,2-d_2 cyclopropanes in the gas phase as a function of thermolysis reaction times at 422.5 °C. The spectral features represent individual vibrational–rotational transitions of the respective isomers near 1026 cm^{-1}.

Table I. Geometrical Isomerization of 1,2-d_2 Cyclopropanes at 422.5 °C, Determined by TDL Spectroscopy

time (min)	sample	% cis (exptl)	% cis (calcd)[a]
0.0	**1**	92.76	92.74
45.0	**1**	79.71	79.61
180.0	**1**	59.75	59.85
402.0	**1**	50.88	51.61
0.0	(*S*,*S*)-**2**	*b*	0.00
62.0	(*R*,*R*)-**2**	22.68	23.12
112.0	(*R*,*R*)-**2**	30.97	32.12
240.0	(*R*,*R*)-**2**	43.60	43.70
0.0	(±)-**2**	5.47	5.49
50.4	(±)-**2**	21.54	20.48
207.5	(±)-**2**	42.32	41.81
446.5	(±)-**2**	49.14	48.83

[a] Calculated from eq 1 with $k_i(d_2) = 13.6 \times 10^{-5}$ s^{-1}. [b] Not measured.

10^{-5} s^{-1}. A plot of these data with the calculated theoretical time dependence of the function of eq 1 is shown in Figure 3. An independent measure of this rate constant by FTIR, based on three product mixtures from (−)-(*R*,*R*)-**2** as well as starting material and the equilibrium mixture, gave $k_i(d_2) = (13.3 \pm 0.22) \times 10^{-5}$ s^{-1}.[10]

For the 1,2,3-d_3 cyclopropanes, the equilibrium constant [**4**]/[**3**] is 3, neglecting any small equilibrium deuterium isotope effect, and $k_i(d_3)$ is equal to the sum of the forward and reverse reactions; in terms of the rate constants k_j and k_{ij}, $k_i(d_3) = 4(2k_1 + k_{12})$, or $8k_1 + 4k_{12}$. Here, k_1 is the rate constant for one-center epimerization at C1 when *either* C1–C2 or C1–C3 breaks; thanks to the C_{3v} symmetry of the syn isomer **3** and $K_{eq} = 3$, each C–C bond would give rise to trimethylene diradicals at equal rates, and $k_i(d_3)$, therefore, depends on only two mechanistic rate constants.

Experimentally, $k_i(d_3)$ is calculated from concentration versus time data starting from the syn isomer **3** using eq 2, an expression

$$(4[3(t)] - 1)/(4[3(0)] - 1) = \exp(-k_i(d_3)t) \qquad (2)$$

easily derived for this case of reversible first-order reactions.[23]

The TDL spectra obtained for the separate isomers **3** and **4**, a thermal equilibrium mixture, and four reaction mixtures are shown in Figure 4. Spectral features A and B were taken as characteristic of the syn isomer **3**, while features C and D were taken as proportionate to the anti isomer **4**. The relative concentration implications from the observed spectra depend upon the pair of features selected for comparisons: all four binary combinations are presented in Table II. While estimated concentrations of **3** at short times are lower when feature D is used than when it is not, all four of the pairs of spectral features may be fit well with a common value of $k_i(d_3)$ (Table II). It may be that the low intensity of feature D in the starting material is due to a low concentration of another component in the synthetic sample. The nonlinear least-squares treatment of the data for thermal isomerizations at 422.5 °C gave $k_i(d_3) = (15.5 \pm 0.47) \times 10^{-5}$ s^{-1}.

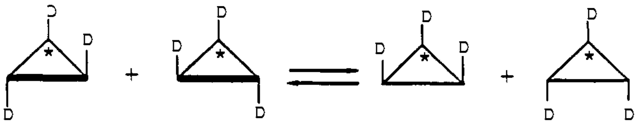
Table II. Isomeric Composition of Product Mixtures from the Geometrical Isomerization of Cyclopropane-*syn-1,2,3-d_3* (**3**) at 422.5 °C, Determined by TDL Spectroscopy

time (min)	features[a]	% syn (exptl)	% syn (calcd)[b]
0.0	AC	94.0	93.16
32.0	AC	74.12	75.62
262.8	AC	32.14	30.92
402.0	AC	26.85	26.26
0.00	BD	89.4	88.62
32.0	BD	71.16	72.25
262.8	BD	31.66	30.53
402.0	BD	26.84	26.52
0.00	BC	93.9	93.06
32.0	BC	74.21	75.55
262.8	BC	33.08	30.91
402.0	BC	27.16	26.62
0.0	AD	89.3	88.52
32.0	AD	71.07	72.17
262.8	AD	30.74	30.52
402.0	AD	25.33	26.51

[a] Spectral features identified in Figure 4. [b] Calculated from the least-squares fit to eq 2, $(4[3(t)] - 1)/(4[3(0)] - 1) = 0.988 \exp(-(15.5 \times 10^{-5}\ s^{-1})t)$, with 3(0) = % syn isomer at time = 0, as experimentally estimated for each combination of spectral features.

Every effort was made to make certain that $k_i(d_2)$ and $k_i(d_3)$ kinetic runs were conducted at the same temperature; both sets of isomers were subjected to thermal isomerizations alternately and randomly in the constant temperature kinetic bath. A d_2 sample was introduced and allowed to react, followed by a d_3 sample, and so on. The thermolysis time for each kinetic sample was not in a regular ascending or descending order. Equilibrium samples in each case were secured through reactions lasting 1800 min, more than 20 half-lives.

For the ^{13}C,d_3-labeled isomers, the kinetic situation may be treated as a reversible interconversion between the sum of the two chiral forms ([(2*S*,3*S*)-**5**] + [(2*R*,3*R*)-**5**] = [**5**]) and the sum of the two meso isomers ([*syn*-**6**] + [*anti*-**6**] = [**6**]), with an equilibrium constant of 1.



(2*S*,3*S*)-**5** (2*R*,3*R*)-**5** *syn*-**6** *anti*-**6**

The corresponding function used to extract the rate constant $k_i(^{13}C,d_3)$ from experimental observations is given in eq 3.

$$([5(t)] - [6(t)])/([5(0)] - [6(0)]) = \exp(-k_i(^{13}C,d_3)t) \qquad (3)$$

Between the kinetic work on defining $k_i(d_2)$ and $k_i(d_3)$ at 422.5 °C and kinetic studies with the ^{13}C,d_3-labeled schemes, we were obliged to dismantle the kinetic bath and the associated vacuum line, relocate to a new building, and reconstruct the system. Conscious of the difficulty of reestablishing precisely the same temperature in the new configuration of heating, temperature control, and temperature monitoring components, the kinetic bulb was brought to a decidedly different temperature, 407.0 °C. While constancy of kinetic reactor temperatures used in these studies

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[23] Benson, S. W. *The Foundations of Chemical Kinetics*; McGraw-Hill: New York, 1960; pp 27–29.

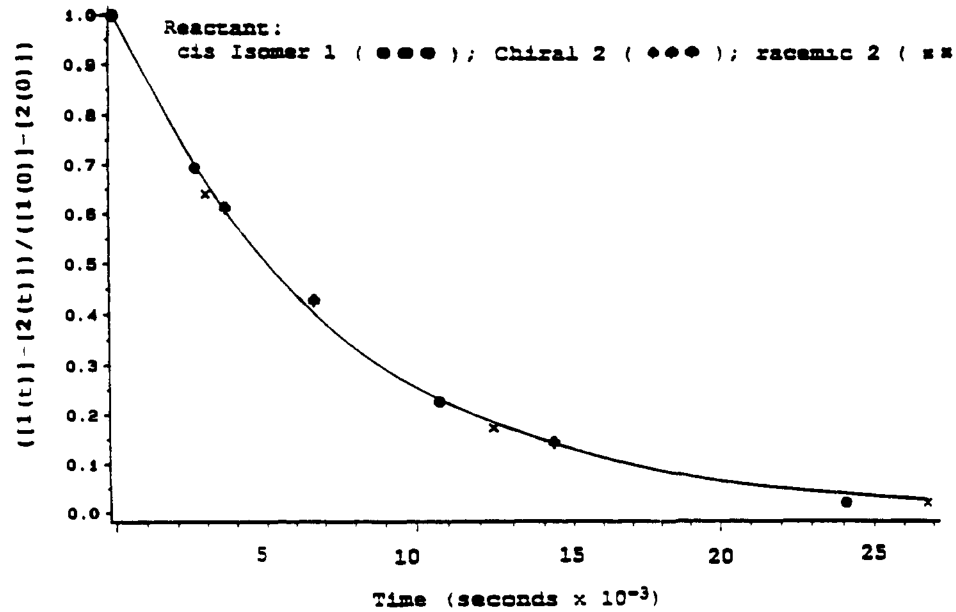

Figure 3. Nonlinear least-squares fit of TDL data (Table I) based on eq 1 and $k_i(d_2) = 13.6 \times 10^{-5}$ s^{-1}.

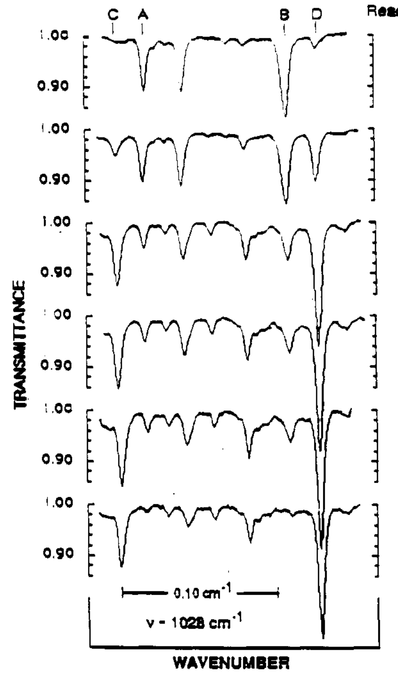

Figure 4. Gas-phase TDL spectra near 1028 cm^{-1} for the cyclopropane-*1,2,3-d*$_3$ kinetic samples from syn isomer 3 as a function of thermolysis reaction time at 422.5 °C. Spectral features A and B are assigned to the syn isomer 3, and features C and D correspond to the anti isomer 4.

was assured, it is less certain that the two temperatures were precisely 15.5 °C different.

At 407.0 °C, then, thermal isomerizations starting with (2*S*,3*S*)-**5** were followed by TDL spectroscopy employing the new diode laser emitting near 2290 cm^{-1} (Figure 5). The time = 0 trace has a higher noise factor because it was recorded in path B (30%) of the laser light) and consequently required greater amplification to match the I_0 values of the other spectra, which were all recorded in path A (70% of the light). The data are presented in numerical form in Table III. The rate constant $k_i(^{13}C,d_3)$ was found to be $(4.63 \pm 0.20) \times 10^{-5}$ s^{-1}. A parallel determination by FTIR methods based on eight reactions mixtures gave $k_i(^{13}C,d_3) = (4.59 \pm 0.09) \times 10^{-5}$ s^{-1}.[11]

Summary

The utilization of TDL spectroscopy to determine rate constants for the geometrical isomerizations of isotopically labeled cyclopropanes demonstrates its several advantages over conventional infrared spectroscopic methods: extremely high resolution over a selected, limited fractional wavenumber range, thus permitting clear quantitative distinctions between vibrational–rotational transitions associated with stereochemically different isotopically

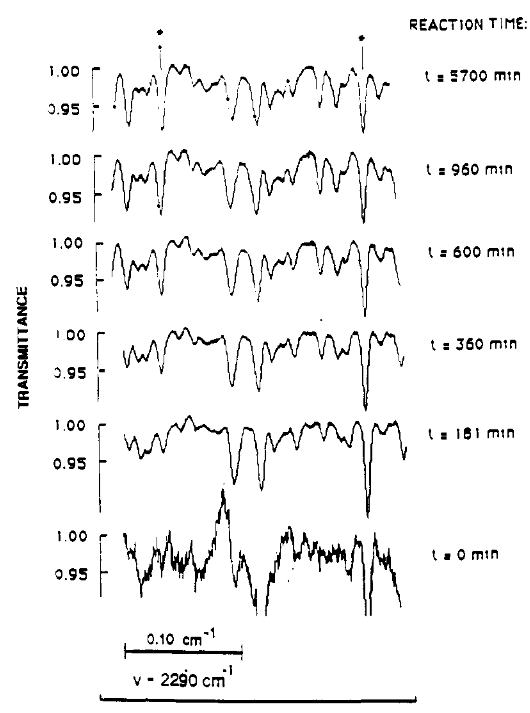

Figure 5. TDL spectra near 2290 cm^{-1} of gas-phase cyclopropane-*1*-^{13}*C,1,2,3-d*$_3$ product mixtures from (2*S*,3*S*)-**5** as a function of thermolysis reaction time at 407.0 °C.

Table III. Geometric Isomerization of 1-^{13}C,1,2,3-d$_3$ Cyclopropanes Followed by TDL Spectroscopy

time (min)	**5** (%) (exptl)	**5** (%) (calcd)^a
0	100	100
181	82.2	80.6
360	67.9	68.6
600	59.1	59.5
960	53.1	53.5

^{a}Calculated from the least-squares derived expression $([\mathbf{5}(t)] - [\mathbf{6}(t)])/([\mathbf{5}(0)] - [\mathbf{6}(0)]) = 1.01 \exp(-(4.63 \times 10^{-5}\ \mathrm{s}^{-1})t)$.

labeled isomers, and high sensitivity and accuracy. For two of the three isomerizations (the two for which substantial quantities of substrates had been synthesized), excellent agreement in measured rate constants based on TDL and FTIR methods was demonstrated.

The mechanistic significance of the rate constants measured by TDL depends on related kinetic work measuring rates of racemization of chiral samples of cyclopropane-*1,2*-d_2 and cyclopropane-*1*-^{13}*C*-*1,2,3*-d_3 and on the ways in which kinetic isotope effects are estimated and interpreted. The interpretational issues are by no means simple, and they remain controversial.[24] The TDL spectroscopic methods and kinetic studies reported here should clarify this component of the experimental work on cyclopropane stereomutations. Further experimental and theoretical effort will be needed before the interpretational debate may be concluded.

Acknowledgment. We thank the National Science Foundation for support of this work at Syracuse University through CHE 87-21656 and CHE 91-00246 and at Colgate University through CHE 90-23319. We also thank Dr. Christof B. Selden for his participation in some of the synthetic work and the Research Corporation for support at Colgate University through a Cottrell College Science Grant and a William and Flora Hewlett Foundation Grant.

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Enzymatic Asymmetrization in Organic Media: Synthesis of Unnatural Glucose from Cycloheptatriene

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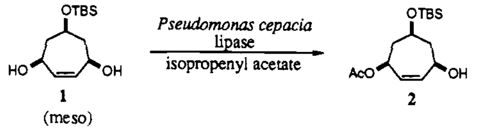
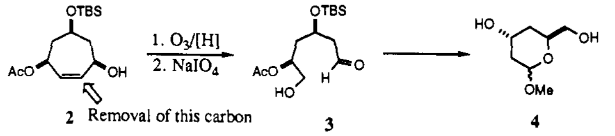
Abstract: *Pseudomonas cepacia* lipase mediated asymmetrization of a *meso*-3-*O*-protected 6-cyclohepten-1,3,5-triol using isopropenyl acetate as solvent produced optically pure monoacetate **2**. Elaboration of **2** by stereoselective oxygenation of the ring system using the Rubottom reaction, diastereoselective reduction, and osmium tetroxide catalyzed cis hydroxylation lead to cycloheptanehexaol derivative **20**. This cyclic polyol was transformed into an allylic alcohol which was subjected to ozonolysis followed by $NaIO_4$ diol cleavage to give L-glucose.

The application of enzymes in syntheses is a topic of much current interest.[1] The use of enzymes, particularly lipases, in organic media has opened the door to a wide variety of substrates unsuitable for aqueous media due to insolubility. Lipases are proving to be very useful due to their stability in organic media and their widespread commercial availability. Enzymatic reactions using prochiral and meso substrates rather than racemic mixtures can be particularly effective, as, in theory, all of the substrate may be processed to a single enantiomer.[2]

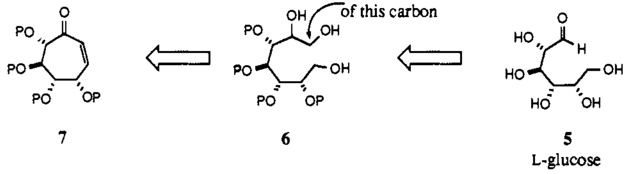
In a preliminary report, we recently described the enzymatic asymmetrization of **1** and its C-6 epimer.[3] It was shown that the products of these reactions can be transformed into all possible stereoisomers of 2,4-dideoxyhexose.[4] The efficiency of the synthesis of optically pure monoacetate **2** makes this compound an interesting starting material for the synthesis of a variety of chiral polyoxygenated targets including hexoses and heptoses. There has been much recent interest in the synthesis of unnatural sugars from noncarbohydrate sources.[5] Unnatural sugars, in general, are important as precursors for the synthesis of natural products. The synthesis of the unnatural sugar L-glucose, which has potential use as a noncaloric sweetener,[5c] is the subject of this paper.



Scheme I



Scheme II



Our previous synthesis of 2,4-dideoxyhexose **4** involved ozonolysis of **2**; subsequent reductive workup with sodium borohydride followed by sodium periodate cleavage of the resulting vicinal diol

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[1] (a) Margolin, A. L. *CHEMTECH* **1991**, 160. (b) Nakamura, K.; Takebe, Y.; Kitayama, T.; Ohno, A. *Tetrahedron Lett.* **1991**, *32*, 4941. (c) Klibanov, A. *Acc. Chem. Res.* **1990**, *23*, 114. (d) Wong, C.-H. *Science* **1989**, *244*, 1145. (e) Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695. (f) Toone, E. J.; Simon, E. S.; Bednarski, M. D.; Whitesides, G. M. *Tetrahedron* **1989**, *45*, 5365. (g) Xie, Z.-F. *Tetrahedron: Asymmetry* **1991**, *2*, 733.

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