Thermolysis of (1*R*,2*R*)-1,2-Dideuteriocyclobutane. An Application of Vibrational Circular Dichroism to Kinetic Analysis

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Abstract: The relative rates of geometric isomerization to racemization have been studied for the title compound by using a combination of infrared (IR) and vibrational circular dichroism (VCD) spectroscopies, respectively. The results are interpreted with a kinetic and mechanistic scheme which parallels that used by Berson, Pedersen, and Carpenter on a similar study of chiral cyclopropane-d_2 thermolysis. Relative rates of isomerization to stereomutation of 1.5 ± 0.4 were obtained which can be interpreted to be consistent with a mechanism best described by random methylene rotation in tetramethylene-d_2. This is the first application of VCD to kinetic analysis, and the advantages of IR techniques over the more usually employed UV spectroscopies to this type of basic mechanistic problem are illustrated.

One of the basic problems in determination of reaction mechanisms for simple molecules of fundamental interest is that of finding a suitable kinetic marker for monitoring the various possible pathways. In order to understand such a reaction and adequately compare it to theoretical predictions, these markers must not significantly affect the electronic structure of the molecule studied. For this reason, isotopic substituents have long been considered to be ideal. Unfortunately, their lack of perturbation on the molecular electronic structure also makes electronic (UV) spectroscopy somewhat insensitive to their presence or configuration. Since UV spectra are, in general, the most sensitive way of detecting molecular change, this is a major problem for kinetic studies using isotopic substitution.

Indeed, there are other methods available to address this problem; and, in this paper, we wish to point out the advantages of one of these, infrared (IR) spectroscopy, and particularly one of its new variants, vibrational circular dichroism (VCD). The detection method of choice for isotopically oriented kinetic studies should be sensitive to change in nuclear mass or other properties. The change involved may often be quite subtle. For reactions in which the initial and final states are functionally equivalent, rearrangement of otherwise identical substituents over the molecular framework can be followed by isotopic labelling only if the interactions between the substituents are altered significantly compared to the resolution and sensitivity of the detection scheme. Here vibrational spectroscopy, IR and Raman, has a clear advantage since change in nuclear mass, particularly in the case of H → D, results in a large change in the coupling of local vibrations and thus in the properties (frequency and intensity) of the resultant normal modes.

Additionally, stereomutation of isotopically substituted molecules can result in "interaction-equivalent" variants that differ only by optical isomerization. While such changes can be detected by UV optical rotation methods, the specific rotations of molecules made chiral only by nuclear mass variation can be quite small; and, thus, such studies would demand very large samples for kinetic analysis. We and others have shown that VCD, on the other hand, gives spectra as intense for isotopically produced chirality as for that resulting from the more typical chemical perturbations.[1,2] This difference in sensitivity, in large part, is due to the isotopic mass variation having a significant effect on the "vibrational chirality" while having little effect on the electronic structure.

In this paper, we present the first application of VCD to kinetic analysis. The example problem we have chosen is the thermolysis of (1*R*,2*R*)-cyclobutane-*1,2*-d_2 and analysis of the relative yields of ethylene (fractionation), (1*R*,2*S*)-cyclobutane-*1,2*-d_2 (isomerization), and (1*S*,2*S*)-cyclobutane-*1,2*-d_2 (racemization). As will be discussed below, the relative rates of these processes can be interpreted in terms of the various possible detailed mechanisms of the thermolysis reaction.

Mechanistic Background

Cyclopropane and cyclobutane are believed to stereomutate by way of biradicals.[3,4] Trimethylene, first proposed to explain the ring opening isomerization of cyclopropane to propylene,[4] has also been used to explain the geometric isomerism of *trans*-cyclopropane-*1,2*-d_2.[5] Of the four distinct stereochemical possibilities which have been considered (single,[6,7] double,[6] and triple methylene rotation in cyclopropane and random terminal methylene rotation in trimethylene),[8,9] double methylene rotation has been reported to explain the stereomutation of cyclopropane-d_2 in a seminal study by Berson and Pedersen.[10] Their study examined the relative rates of geometric isomerization to stereomutation of optically active *trans*-1,2-dideuteriocyclopropane. Double methylene rotation has not been found to dominate the stereomutation of substituted monocyclic cyclopropanes.[3,11]

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Tetramethylene has similarly been proposed as an intermediate in the thermal fragmentation of cyclobutane to ethylene and in the slower geometrical isomerization of 1,2-dideuteriocyclobutane.[12-14] Santilli and Dervan have demonstrated that thermal decomposition of *cis*-tetrahydropyridazine-*3,4-d*$_2$ provides a useful route to examine the potential energy surface of tetramethylene.[12] In this work, the relative rates of rotation, cleavage, and ring closure in *cis*-1,2-dideuteriotetramethylene were determined. Similar studies on substituted tetrahydropyridazines have shown these compounds to be excellent sources of other stereospecifically labeled 1,4-biradicals.[14]

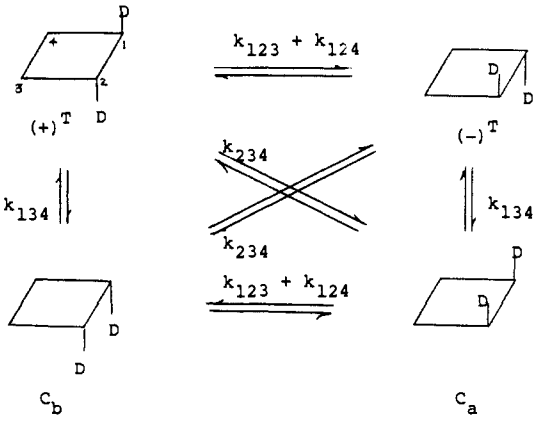
Thermochemical estimates by Benson et al.[9] of the potential surface characteristics for trimethylene and tetramethylene are comparable, suggesting similar stereochemical behavior. A potential well of approximately 2–8 kcal/mol has been estimated for tetramethylene.[3,9] Experimental results reported for the thermal decompositions of *cis*-tetrahydropyridazine-d_2 and *cis*- and *trans*-cyclobutane-d_2 are consistent with torsional barriers which are competitive with thermal fragmentation of recombination of tetramethylene.[12,13]

Theoretical calculations on tetramethylene have focused primarily on whether or not tetramethylene is an intermediate in the thermolysis[15-19] and have generally avoided the issue of stereomutation in the diradical. The results appear to be very dependent on the type of calculation used. Extended Hückel calculations by Hoffmann et al.[15] describe tetramethylene as having a flat hypersurface with no local minima. Segal[16] later concluded from ab initio calculations (SCF at STO-3G level + CI) that two minima could be located, corresponding to the gauche and trans conformations. Most recently Doubleday et al.[17] reported the gauche minimum to be an artifact of the STO-3G basis set and, using a split valence 3-21G basis set and full CI, essentially reproduced Hoffmann's original results as far as the potential energy surface is concerned. The authors did conclude that tetramethylene was a likely intermediate if entropic factors were also considered. Comparison of the theoretical calculations performed on both trimethylene and tetramethylene reveals substantial differences between the two.

We here report the results of our experiments on cyclobutane which are in the same spirit as the analysis reported by Berson and Pedersen for cyclopropane stereomutations.[10] As in their study, the relative rates of isomerization, k_i, and racemization, k_A, permit a qualitative decision between the various possible rotational mechanisms in the thermolysis of (1*R*,2*R*)-1,2-dideuteriocyclobutane. A large difference in our two studies involves the first use of VCD to determine the rate constant for loss of chirality, k_A, during the course of the reaction. Consequently, we were able to follow the stereomutation using an initial sample of (1*R*,2*R*)-cyclobutane-*1,2-d*$_2$ 1–2 orders of magnitude smaller than that used in the cyclopropane study.

Phenomenologically, the stereochemical consequence of single and [1,2]-double methylene rotation in chiral *trans*-cyclobutane-*1,2-d*$_2$ and random terminal methylene rotation in tetramethylene are identical with the same processes occurring in chiral *trans*-cyclopropane-*1,2-d*$_2$. Therefore, the kinetic expressions for these processes as derived by Berson, Pedersen, and Carpenter[10] are also applicable here.

Scheme I. Triple Methylene Rotation in (1*R*,2*R*)-Cyclobutane-*1,2-d*$_2$[a]



$$k_{123} = k_{124} = k_{234} = k_{134}$$

[a] Scheme modeled from double methylene rotation of 1,2-dideuteriocyclopropane.

Table I. Ratios of Rate Constants, Isomerization to Stereomutation, for (1*R*,2*R*)-Cyclobutane-*1,2-d*$_2$

origin of stereomutation	k_i/k_A[a]
single methylene rotation	2.0
double [1,3]-methylene rotation	2.0
random intermediate	1.5
double [1,2]-methylene rotation	1.0
triple methylene rotation	0.666
quadruple methylene rotation	0

[a] Derived from the rate expressions given in ref 8b, ignoring isotope effects.

In addition, chiral cyclobutane-d_2 has several other pathways available for stereomutation. The most obvious include [1,3]-double methylene rotation, triple methylene rotation, and quadruple methylene rotation. Although we are not aware of any theoretical or experimental justification for consideration of these processes, we include them here for completeness. [1,3]-Double methylene rotation in cyclobutane-*1,2-d*$_2$ is phenomenologically equivalent to single methylene rotation in cyclopropane-*1,2-d*$_2$. Quadruple methylene rotation in cyclobutane-*1,2-d*$_2$ is likewise equivalent to triple methylene rotation in cyclopropane-*1,2-d*$_2$. Hence, the relevant kinetic expressions can also be adapted from the cyclopropane work.[10]

A kinetic expression for the relative rates of isomerization and loss of optical activity by triple methylene rotation in cyclobutane-d_2 can be derived from the rate expressions for double methylene rotation in the corresponding cyclopropane. When the same terminology employed by Berson et al. to describe potential isotope effects associated with double methylene rotation in cyclopropane-d_2 is used, k'' (designated as $k_{123} + k_{124}$ in Scheme I) and k' (k_{134}, k_{234} in Scheme I) refer to processes in which triple methylene rotation in cyclobutane-d_2 results in rotation of both CHD groups and only a single CHD group, respectively. The following relationship between rate constants for isomerization and stereomutation was previously derived (see ref 10b, Scheme VII)

$$k_i/k_\alpha = 4k'/2(k'' + k')$$

where k_α referred to loss of optical activity measured as optical rotation (vide infra). Triple methylene rotation which results in rotation of both CHD groups to produce enantiomerization in Scheme I is statistically favored over rotation of a single CHD group to produce C_a or C_b by a factor of 2. Substitution of this condition ($k'' = 2k'$) into the equation above gives $k_i/k_\alpha = 2/3$.

The consequences of all the above mechanisms in terms of k_i/k_A are given in Table I. Here it is important to note that the

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measured rate constants are defined by using[10]

$$k_i t = -\ln \frac{(T - C)}{(T - C)_0}$$

and

$$k_A t = -\ln (\Delta T/\Delta T_0)$$

where T is the fraction trans, C is the fraction cis, ΔT is the difference in $T(+)$ and $T(-)$ (i.e., (1R,2R) - (1S,2S)), and the subscript 0 implies the initial state. In our experiments, $\Delta T/\Delta T_0$ is measured by $(\Delta A/A)/(\Delta A/A)_0$ for a particular VCD and IR band and is equivalent to the α/α_0 as measured by Berson et al.[10] Ratioing to absorbance eliminates the need to correctly account for concentration (or pressure) and path length variation to correct ΔA to $\Delta\epsilon$ for these small samples. [By using the same cell for all the gas-phase samples one could also use $(\Delta A/P)/(\Delta A/P)_0$, provided that the sample pressure, P, can be accurately determined or calibrated.]

Experimental Section

Synthesis. The synthesis of optically active 1,2-dideuteriocyclobutane as well as those of the dl and cis forms has previously been reported.[13,20] Before thermolysis all samples were purified by preparative gas chromatography. The resultant samples of (1S,2S)- and (1R,2R)-1,2-dideuteriocyclobutane consisted of 83.3% d_2, 14.8% d_1, and 1.8% d_0. This analysis was arrived at by calculating the expected mass spectrum of the 100% d_2 species by using the observed mass spectra of cyclobutane and cyclobutane-d_8 at 70 eV in the parent ion region. Loss of hydrogen/deuterium was treated statistically and corrected for isotope effects. This analysis can be compared to the deuterium distribution reported earlier[20] for succinic-d_2 anhydride (84.5% d_2, 14% d_1, 1% d_0) which was derived from the same precursor as the chiral cyclobutane-d_2.

Thermolysis. The thermolysis experiments were conducted in sealed 5-mL Pyrex ampules at an initial pressure estimated to be approximately 2×10^5 Pa and at a temperature of 420 ± 1 °C for periods up to 8 h. The samples were then transferred to a vacuum line where the ethylene and cyclobutane were separated. In experiments with chiral samples, the cyclobutane-d_2 was recovered and purified by preparative gas chromatography on a squalene column at room temperature. Ethylene was the only product detected during the first half-life, and mass balance exceeded 96%. More substantial amounts of other products were obtained at longer reaction times and were shown to arise from secondary reactions of ethylene. The gas chromatographic retention times of these products were different from that of cyclobutane on the column used.

Geometrical Isomerism. The cis-trans composition of cyclobutane-d_2 was determined by gas-phase infrared analysis in the 500–600-cm^{-1} region as previously described on a Perkin-Elmer 521 infrared spectrophotometer.[13] The cis-trans compositions of cyclobutane-d_2 recovered after chromatography of the pyrolysis samples were established by comparisons with data from known mixtures of *cis*- and optically active *trans*-dideuteriocyclobutanes. The isomer composition is believed known to an accuracy of ±3%. *cis*-Cyclobutane-*1,2-d*$_2$ prepared from diethyl maleate analyzed as 10.3% d_3, 77.6% d_2, 10.9% d_1, and 1.2% d_0. The cis compound used for calibration mixtures was corrected for the isotopic distributions noted above.[21]

Measurement of Optical Purity. The optical purity of (1R,2R)-1,2-dideuteriocyclobutane is believed to be high (98.5%) as judged by the observed rotation of the chiral precursor (+)-2,3-dibromo-2,3-dideuteriobutane-1,4-diol and the (2S,3S)-dideuteriosuccinic acid which was derived from this precursor.[20] Both chiral succinic-d_2 acid and cyclobutane-d_2 were prepared from a common precursor in a sequence of reactions not directly involving the chiral centers.

The optical purity as a function of the thermolysis of (1R,2R)-cyclobutane-*1,2-d*$_2$ was measured by VCD with use of the instrument constructed at UIC which has previously been described in detail.[1,22] Each sample consisted of ca. 15 mg and was studied in the gas phase. Due to error involved in measuring the mass of such small quantities of gas-phase sample, we determined anisotropy ratios, $\Delta A/A$ (ΔA is the differential absorption, and A is the total absorption of left and right circularly polarized radiation), as a measure of the optical activity of each thermolysis sample. (Subsequent analysis of each pyrolysis sample showed its absorbance to be within 5% of that of a pure sample at the same pressure as monitored with a capacitance manometer.) The residual activity was then set equal to $(\Delta A/A)/(\Delta A/A)_0$ where $(\Delta A/A)_0$ is the anisotropy of the starting (1R,2R) compound, which was assumed to be optically pure. The C–H stretching region was chosen for monitoring the reaction because it has a significantly higher oscillator strength than the C–D stretching or the mid-IR regions. This allowed detection of VCD for smaller amounts of sample with good signal-to-noise ratio. Additionally, our instrument proved to be more stable in this region as opposed to longer wavelength regions. Detailed analyses of the VCD of the C–H stretch and mid-IR regions have been presented separately.[1,23]

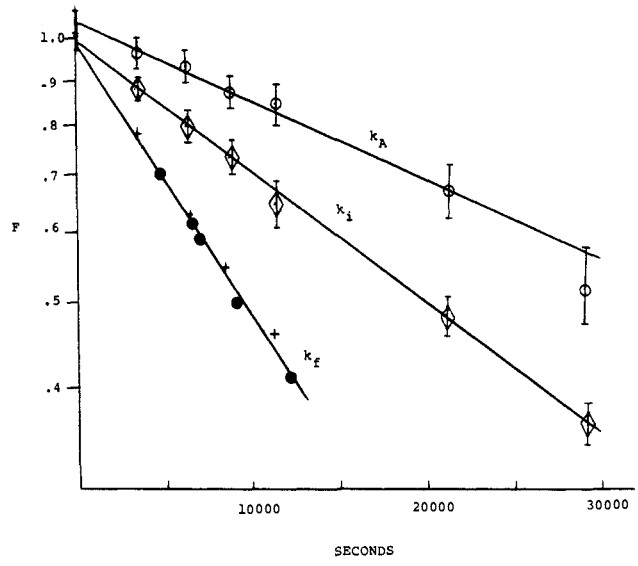

Figure 1. log plot of rates of fragmentation, isomerization, and stereomutation data of Table II. Fragmentation: solid circles, F = [cyclobutane]/[cyclobutane]$_0$; crosses, $F = [T + C]/[T + C]_0$. Isomerization: diamonds, $F = [T - C]/[T - C]_0$. Stereomutation: circles, $F = [\Delta A/A]/[\Delta A/A]_0$.

Before our undertaking of these experiments, extensive analysis of the quantitative aspects of VCD had not been attempted. Primary interest in the VCD field has been centered on qualitative spectral patterns and "order of magnitude" intensity values. In order to achieve VCD and absorption intensities reproducible to better than ±5% on our instrument and to minimize errors from drift, it was necessary to scan the thermolysis samples and standards under conditions as identical as possible. The specific protocol used included the following precautions: (a) base line and calibration curves were run before and after thermolysis sample; (b) the instrument was left "on" during the entire experimental period; (c) the VCD of the standard, pure (1R,2R)-1,2-dideuteriocyclobutane was run before and after each series of thermolysis samples studied. In the latter case, our pairs of reference $(\Delta A/A)_0$ values were self-consistent to better than 3%. All runs involved averaging of 8 scans at time constants of 10 s to achieve the signal stability needed for a 5% reliability level.

Stereochemistry of Recovered Ethylene. Thermolysis of *trans*-cyclobutane-d_2 for periods of 310, 1500, and 3000 s at 420 °C, as described above, produced samples of ethylene-d_0,d_1 and *cis*- and *trans*-ethylene-d_2. Fragmentations amounting to 2, 11, and 21% were obtained, respectively. The infrared spectra of the ethylene recovered from the samples were recorded on a PE 780 spectrophotometer equipped with a Data Station. The infrared spectra of samples obtained at 1500 and 3000 s were found to be identical, and no changes were observed in the difference spectra when these samples were further heated. Only the sample obtained after heating for 310 s was not completely equilibrated. The ethylene-d_2 recovered from this thermolysis analyzed as 54 ± 3% trans and 46 ± 3% cis. It also appeared to be slightly enriched in ethylene-d_1. *trans*-Ethylene-d_2, when heated under the same conditions for the same time intervals, produced 7, 31, and 45% cis isomer, respectively. The amount of stereomutation observed at 1500 s (~1 half-life) was used to establish an upper limit to the uncertainty in the stereochemical analysis. The *cis*-ethylene-d_2 to *trans*-ethylene-d_2 composition at 11% thermolysis is estimated at 50 ± 2%.

Results and Discussion

The thermolysis of cyclobutane was demonstrated to be a homogeneous first-order process under the reaction conditions stated

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Table II. Rates of Fragmentation, Isomerization, and Stereomutation of (1*R*,2*R*)-1,2-Dideuteriocyclobutane at 420 °C[a,b]

run no.	fragmentation[a,b] $[C+T]/[C+T]_0$	isomerization[b] $[C]/[C+T]^b$	isomerization[b] $[T-C]/[T-C]_0$	stereomutation $(\Delta A/A)/(\Delta A/A)_0$	stereomutation t (s)
1	1	0	1	1	0
2	0.76 ± 0.02	0.07 ± 0.02	0.87 ± 0.04	0.96 ± 0.05	3650
3	0.62 ± 0.02	0.11 ± 0.02	0.78 ± 0.03	0.92 ± 0.05	6366
4	0.53 ± 0.02	0.14 ± 0.02	0.72 ± 0.03	0.87 ± 0.05	8150
5	0.46 ± 0.02	0.19 ± 0.02	0.63 ± 0.03	0.84 ± 0.05	11000
6		0.26 ± 0.02	0.48 ± 0.03	0.66 ± 0.05	20900
7		0.32 ± 0.02	0.36 ± 0.04	0.51 ± 0.05	29090

	least-squares treatment[c] (−) slope × 10^5 s	intercept	correl coeff
k_f	7.2 ± 0.3[a]	0.99	0.997
k_i	3.5 ± 0.2	0.97	0.997
k_A	2.3 ± 0.4	1.05	0.991

[a] The following rate data for fragmentation of cyclobutane-d_0 were also obtained ([cyclobutane]/[cyclobutane]^0, t (s)): 0.69 ± 0.02, 4760; 0.61 ± 0.02, 6565; 0.58 ± 0.02, 7085; 0.48 ± 0.02, 8953; 0.40 ± 0.02, 12150. Least-squares treatment of these data gives a rate constant, k_f, of (7.69 ± 0.2) × 10^{-5} s^{-1}. [b] T = the fraction of (1*R*,2*R*)-cyclobutane-*1,2*-d_2. C = the fraction of *cis*-cyclobutane-d_2. [c] The least-squares calculations were performed prior to rounding the data off to two significant figures for inclusion in this table.

above by measuring the rate constant for fragmentation over 1.5 half-lives. Values of $k_f = (7.7 \pm 0.2) \times 10^{-5}$ and $(7.2 \pm 0.3) \times 10^{-5}$ s^{-1} were obtained by least-squares analysis for cyclobutane-d_0 and chiral cyclobutane-d_2, respectively. These data are given in Table II and are graphically presented in Figure 1 with solid circles and crosses for d_0 and d_2, respectively. The thermolysis of cyclobutane as a function of both pressure and temperature has been examined by several groups.[9b,24] The temperature dependence of the thermolysis reaction has been reported by Genaux, Kern, and Walters[24] for the temperature range 420–467 °C. The high pressure rate constant is given by

$$\log k = 15.6 - 62500/(2.306RT)$$

which gives a value for k_f of 7.9×10^{-5} s^{-1} at 420 °C. A least-squares treatment of all available rate data for cyclobutane thermolysis has also been reported.[9b] The rate constant, k_f, calculated from the least-squares data is 7.5×10^{-5} s^{-1} (420 °C). Our data clearly agree well with these results; hence, we conclude that the thermolysis of cyclobutane under our experimental conditions is a homogeneous process.

Thermolysis of (1*R*,2*R*)-*1,2*-dideuteriocyclobutane at 420 °C for periods of time sufficient to fragment up to 90% of the initial cyclobutane gave the isomerization ($[T-C]/[T-C]_0$) and racemization ($[\Delta A/A]/[\Delta A/A]_0$) results shown in Figure 1 (diamonds and circles, respectively) and Table II. It is clear from the figure that the empirical rate constants for racemization, k_A, and isomerization, k_i, are much smaller than that for fragmentation. Additionally, k_A is significantly smaller than k_i thus immediately eliminating the quadruple, triple, and double [1,2]-methylene rotation mechanisms as being dominant in the thermolysis process (Table I). Least-squares treatment of the data in Table II gives values for the corresponding rate constants, k_i and k_A, of $(3.5 \pm 0.2) \times 10^{-5}$ and $(2.3 \pm 0.4) \times 10^{-5}$ s^{-1}, respectively, corresponding to $k_i/k_A = 1.5 \pm 0.4$.

Comparison of the results for fragmentation, isomerization, and stereomutation, presented in Figure 1, reveals more deviation from linearity for the VCD data, $\Delta A/A$, than for that of isomerization or fragmentation. We have looked for possible systematic sources of error, and of those considered (below), none explains the deviations better than the intrinsic random error in the VCD intensity measurements. Consistent with this assumption is the fact that the least-squares line corresponding to the k_A (above) easily passes through the error bars on Figure 1.

One possible problem in using $\Delta A/A$ as a measure of loss of optical activity is that *cis*-cyclobutane-*1,2*-d_2 has a higher ϵ at the frequency used for analysis (2958 cm^{-1}) than does trans by ~3%. Correction for this would make only a negligible change in the results especially considering the relatively low amount of cis in most samples. Second, in principle, there is a possibility of some nonlinearity in our instrument leading to non-Beer's law like behavior in the VCD. We checked this with well-characterized mixtures of *d*- and *l*-camphors[25] and found only a slight deviation (~3%) of $(\Delta A/A)/(\Delta A/A)_0$ from expected values which lies in the range of our reproducibility errors. Similarly, we tested the possibility that the time constant which we have used distorted the observed line shapes such that systematic error was introduced. Indeed, a 10-s time constant slightly distorts the VCD band shapes as compared to those obtained with a 3-s time constant under the scanning conditions used for the thermolysis samples. The resultant error would tend to artificially decrease the ΔA values for larger as compared to smaller signals. Correcting for this, in turn, would slightly decrease the values in Table II and hence decrease k_A but would *not* make the data more linear. No such corrections were made to the final data because they lie within our ±5% reproducibility range.

The rate constants k_i and k_A are apparent rate constants for isomerization and racemization since they do not correct for the portion of stereomutated cyclobutane-d_2 which fragments. A direct comparison of rate constants k_i and k_A is meaningful only if the fragmentation process is independent of both stereochemistry and deuterium substitution. Results reported previously on the ethylene composition from the thermolysis of cyclobutane-*1,1,2,2*-d_4[26] and *cis*- and *trans*-cyclobutane-*1,2*-d_2[13] confirm that this condition is satisfied. The statistical distribution of isotopically substituted ethylenes obtained in each case was characteristic of nondiscriminant cleavage of the cyclobutane ring. In addition, the intermolecular kinetic isotope effect reported for cyclobutane-d_8, $k_H/k_D = 1.44$ (420 °C),[27] suggests a secondary deuterium isotope effect (k_H/k_D) of roughly 1.05 per deuterium (geometric mean).[28] At 90% fragmentation, using $k_H/k_D \sim 1.1$ for d_2, the isotopic distribution of the recovered (1*R*,2*R*)-cyclobutane-*1,2*-d_2 can be calculated to be 85% d_2, 13.5% d_1, and 1.5% d_0 compared to an initial composition of 83.3% d_2, 14.8% d_1, and 1.8% d_0. We conclude from this analysis that the extent of isotopic fractionation which has occurred during the portion of the reaction monitored is small in comparison to experimental error. The resulting errors introduced into evaluations of k_i and k_A were therefore neglected. Contributions of d_1 and d_0 to the IR absorbance and VCD normalization would be expected to effectively cancel since they remain nearly constant in proportion.

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(28) The intermolecular kinetic isotope effect k_H/k_D of 1.10 is estimated from the geometric mean of k_H/k_D 1.44 for cyclobutane-d_8. This value can be compared to the measured value of 1.07 ± 0.05 reported for cyclobutane/(1*R*,2*R*)-cyclobutane-*1,2*-d_2 in Table II.

A comparison of the first-order rate constants for isomerization and stereomutation in Table II results in a k_i/k_A value of 1.5 ± 0.4. This value, when compared to the theoretical expectations of each mechanism listed in Table I, agrees best with that expected for random methylene rotation in tetramethylene. The experimental uncertainty in the k_i/k_A value is, of course, quite limiting in terms of interpretation. Various mixed mechanisms could be proposed that would yield k_i/k_A within these error bars. At this time, nothing in our data eliminates consideration of a mixture of two or more of the processes listed in Table I. However, *if* only a single process were to be involved, then the experimental results would be consistent with the random intermediate mechanism. This is in general agreement with the results of many other mechanistic studies of cyclobutane thermolysis, including studies on non-isotopically substituted systems.[3,12-14,24,29]

It is instructive to compare the ratio of fragmentation to isomerization observed in this study to that reported for *cis*-tetramethylene-*1,2*-d_2 in the thermolysis of *cis*-tetrahydropyridazine-*3,4*-d_2.[12] Our k_f and k_i values cannot be compared directly since this would require knowledge of the amount of cis isomer which fragments. However, it is possible to estimate fragmentation to isomerization values by comparing the amount of (1*R*,2*R*)-cyclobutane-*1,2*-d_2 which fragments to that which isomerizes, c_f/c_i, at short reaction times. If we ignore isotope effects and correct for the statistical factor (4/3)[13] which favors fragmentation over isomerization of tetramethylene-d_2, a c_f/c_i value of 3.4 ± 2 (420 °C) results from our study. This compares to a c_f/c_i value of 5 ± 0.5 (439 °C) obtained from the thermolysis of *cis*-tetrahydropyridazine-*3,4*-d_2.[12]

The stereochemical composition of ethylene-d_2 obtained from tetrahydropyridazine-d_2 thermolysis is also only qualitatively in agreement with the results obtained from thermolysis of *cis*- and *trans*-cyclobutane-*1,2*-d_2. Dervan and Santilli[12] report 56.3% *cis*- and 43.7% *trans*-ethylene-d_2 while we previously found the ethylene-d_2 recovered from thermolysis of *cis*- and *trans*-cyclobutane-d_2 to be completely isomerized (within our experimental error).[13] We have reported the thermolysis experiments for *trans*-cyclobutane-d_2 as described in the Experimental Section, and the infrared spectra of the recovered ethylene have been analyzed with a spectral decomposition program. The composition of the ethylene-d_2 recovered after short reaction times (1500 s, 11% fragmentation) was found to be 50 ± 2% trans and 50 ± 2% cis. The uncertainty in this value was obtained from an estimate of the amount of stereomutation possible from other processes under these conditions. This result essentially reproduces our previous findings. However, when a sample of *trans*-cyclobutane-d_2 was heated for shorter periods of time (310 s, 420 °C, 2% fragmentation), the ethylene-d_2 in the recovered ethylene sample did not appear to be completely stereorandom. A composition of 54 ± 3% *trans*- and 46 ± 3% *cis*-ethylene-d_2 was estimated from the spectra. This result offers a potential explanation of the discrepancy found in these two investigations. In our experiments, a period of 310 s is barely sufficient time for thermal equilibration of the sample. Much of the recovered ethylene under these conditions is likely to be formed at significantly lower temperatures. A temperature dependence on terminal methylene rotation would be expected, even if the terminal methylene group behaves as a free rotor. In fact, such a temperature dependence has been previously observed in other systems.[30] The thermolysis of *cis*-tetrahydropyridazine-*3,4*-d_2 was achieved by injection as a solution in benzene at 439 °C for contact times of 5 and 30 s. If the rate of thermolysis of the tetrahydropyridazine is significant at lower temperatures, the composition of the products are likely to be reflective of those lower temperatures at which the reaction rate becomes appreciable and not necessarily of the temperature at which thermal equilibration is ultimately achieved. Thus the small but significant differences in the ethylene-d_2 composition reported in these two studies may be simply due to differences in reaction temperature. Whether the differences in c_f/c_i have a similar origin is not clear at this time.

Conclusion

In summary, we find that *if* the thermal decomposition of chiral cyclobutane-d_2 can be described as proceeding through single mechanism, one utilizing a tetramethylene intermediate in a manner in which the terminal methylene groups behave stereochemically independent of each other best fits our data. This is in contrast to the reported behavior of cyclopropane-d_2 as involving a double methylene rotation. However, it is clear that this initial study contains significant uncertainty and that more work will be needed to confirm this mechanism.

Finally, a significant, but perhaps less obvious, result of this work is the demonstration that VCD based stereochemical analyses with deuterium as the chiral marker are possible with use of the same quantities of substrate (mg) as UV stereochemical analyses using more conventional markers. Except perhaps in a few cases,[20,31] electronic CD or optical rotation cannot easily be measured on these sized, isotopically chiral samples. However, the VCD we have measured is equivalent in magnitude to that reported for a variety of more conventional chiral molecules.[22] Although the time constant of the VCD measurement presently prohibits its "real-time" use in kinetics, in cases, such as this, where the reaction can be effectively quenched, VCD can provide a new and sensitive tool for the study of reactions with isotopically substituted chiral molecules. This paper has presented the first demonstration of that potential. Clearly better signal to noise ratio and stability are required for more extensive application of the technique. Such improvements may, in fact, be possible given the recent development of Fourier transform IR-VCD by Nafie and co-workers.[32]

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