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Quantitative Analyses of Mixtures of 2-Deuterio-1-vinylcyclobutanes

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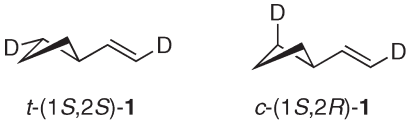
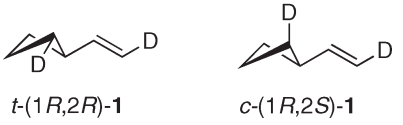
Making distinctions between two stereoisomers characterized by diastereotopic deuterium atoms can ordinarily be achieved using standard NMR spectroscopic methods. Mixtures of stereoisomers having both diastereotopic and enantiotopic deuterium labels, however, may be difficult to analyze quantitatively. The present work introduces a simple way to gain quantitative analyses of mixtures of the four stereoisomeric 2-deuterio-1-vinylcyclobutanes, an essential prerequisite to establishing the stereochemical characteristics of the thermal stereomutations of vinylcyclobutane and its structural isomerizations to cyclohexene. The unconventional NMR method introduced and validated in this work will likely prove convenient and generally applicable to related stereochemical investigations.

Introduction

Projected kinetic studies based on stereoisomers of deuterium-labeled vinylcyclobutanes **1** prompted a search for adequate quantitative analytical methods. An applicable analytical capacity would need to track the four stereoisomers during gas-phase thermal reactions as they evolved from a single structure toward equilibrium among all four. The thermal stereomutations could be followed quantitatively even as each individual vinylcyclobutane isomer reacted as well through competitive fragmentations and structural isomerizations.



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



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

Similar thermal reactions have been followed in stereochemical and kinetic detail for vinylcyclobutanes stereochemically labeled with larger substituents such as methyl and cyano, structures more susceptible to analyses through chiral capillary GC or other well established methods.[1] The deuterium-labeled vinylcyclobutanes *t*-(1*S*,2*S*)-**1**, *c*-(1*S*,2*R*)-**1**, *t*-(1*R*,2*R*)-**1**, and *c*-(1*R*,2*S*)-**1** could lead to uncovering the stereochemical and kinetic characteristics of the thermal reactions of the parent hydrocarbon, vinylcyclobutane, and thereby provide the best comparisons with theory-based efforts to probe the mechanistic subtleties at play. Thorough stereochemical and kinetic work on the parent hydrocarbon, labeled only with deuterium substituents, would facilitate attaining these objectives.

One anticipates the involvement of short-lived diradical intermediates of considerable conformational flexibility and dynamic complexities separating each specific chiral isomer of vinylcyclobutane and its formation of three isomeric vinylcyclobutanes and a mixture of seven d_2-labeled cyclohexenes. The time-dependent mixtures of vinylcyclobutanes and cyclohexenes would define the stereochemical landscape and reflect the dynamic alternatives.

Theory-based attempts to model the thermal chemistry of vinylcyclobutanes and the anticipated fragmentations, stereomutations, and [1,3] sigmatropic carbon shifts might well determine relevant potential energy conformational contours and enable calculations of reaction dynamics over the transition region. Ambitious initial efforts toward these objectives have been sketched, but they have not yet been well advanced.[2] An experimentally grounded description of the mechanistic paths involved could complement and

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illuminate theoretically derived understandings of the complex reactions involved, but adequate experimental data are simply lacking.

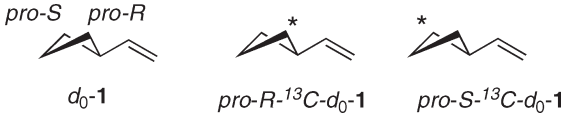
A novel method to ascertain relative concentrations of each of the four 3,4-d_2-cyclohexenes in mixtures including the three 3,6-d_2-cyclohexenes has been found and validated, thus opening a path toward uncovering the stereochemical and dynamic characteristics of thermal reactions of vinylcyclobutane.[3] The second analytical requisite, a suitable method to determine quantitatively the time-dependent relative concentrations of the four isomers of **1**, remained an elusive pursuit.

A variety of imaginable techniques, ranging from vibrational circular dichroism infrared spectroscopy to established NMR spectroscopic techniques applied to enantiomeric structures[4,5] involving chiral lanthanide shift reagents, chiral solvents, and chiral structural modifications prior to NMR analyses, as well as more sophisticated NMR approaches exploiting chiral liquid crystal solvents, were considered. Most were attempted, and each proved unsuccessful. All of these options work well in many instances but not always. Our attempts to apply chiral liquid crystal solvents were particularly frustrating, insofar as confidence in the method and appreciation for its impressive capabilities dependent on chemical shift anisotropies, dipolar couplings, and quadrupolar splittings[6−8] were not matched in our laboratory with sufficiently dexterous skills. The technical necessities required for preparing the lyotropic system poly-γ-benzyl-L-glutamate of the right average molecular weight in CH_2Cl_2 or another solvent, repeated centrifugations, ~20 times, of samples in sealed dual-head tubes in both directions to achieve complete dissolution of polymer and dispersion of the sample throughout the gel, setting suitable transversal relaxation times and an optimal spinning rate, or none at all, and other experimental prerequisites were simply not realized.

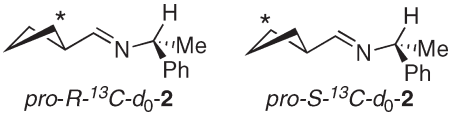
Disappointing attempts to apply reported analytical methods were followed in due course by imagining, implementing, and validating a simple technique for gaining quantitative analyses of mixtures of the isomers of **1**.

Results and Discussion

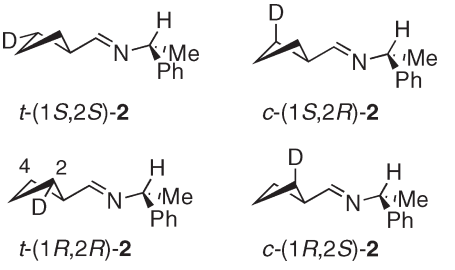
The new approach was attained through a structural modulation of the vinylcyclobutane system to provide a predictable basis for the required analyses. Unlabeled vinylcyclobutane (d_0-**1**) is prochiral, and the carbons C(2) and C(4) are distinct: the two structural alternatives, *pro-R*-^{13}C-d_0-**1** and *pro-S*-^{13}C-d_0-**1**, would be enantiomers and yet have identical ^{13}C NMR spectral absorptions. Mixtures of the two could not be analyzed quantitatively by standard NMR methods; mixtures in any proportions would appear to be identical.



A simple conversion of d_0-**1** to cyclobutanecarboxyaldehyde through an oxidative step and further through a condensation with (*R*)-α-methylbenzylamine would make the former *pro-R* and *pro-S* carbons in *pro-R*-^{13}C-d_0-**2** and *pro-S*-^{13}C-d_0-**2** structures diastereomeric. The carbon-13 labels would experience different regions of the chirotopical structural space and could be distinguished through ^{13}C NMR spectroscopy. The diastereomers could in principle register a significant chemical shift difference, $\Delta\delta$, thanks to the chirotopical influence of the imine function.



This phenomenon is well-known: linking a suitable chirotopical structure with a possible mixture of two enantiomers can often reflect the enantiomeric excess of the sample.[9] The imines d_0-**2** were prepared and analyzed in $CDCl_3$ at 75.5 MHz; the ^{13}C NMR spectrum confirmed a substantial $\Delta\delta$ value separating *pro-R* and *pro-S* atom absorptions (68 ppb). Other NMR spectra of d_0-**2** solutions recorded using 500 and 600 MHz proton frequency spectrometers and at different concentrations gave similar but not identical $\Delta\delta$ values. The $\Delta\delta$ distinction thus demonstrated would contribute as well for *d*-labeled structural analogues such as the isomers of **2**.



The distinctive CHD carbons in each of the four stereoisomers of **2** would reflect chemical shift contributions from the chirotopical influence of the imine function and also from stereochemically distinctive deuterium perturbations of carbon-13 δ values. Thus, all four isomers of **2** might be analyzed quantitatively by $^{13}C\{^1H,^2H\}$ NMR spectroscopy quite easily.

Whether *pro-R*-^{13}C-d_0-**2** or *pro-S*-^{13}C-d_0-**2** would have the more downfield carbon-13 absorption could not be predicted, but the chirotopical influence contributing to all

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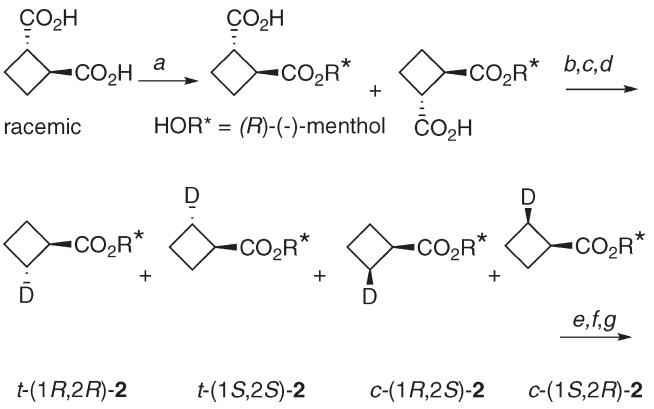
SCHEME 1. Preparation of Imines 2[a]



[a]Reagents and conditions: (a) (1*R*)-(−)-menthol, DCC, DMAP, CH_2Cl_2; (b) $SOCl_2$; (c) $BrCCl_3$, DMAP, 2-mercaptopyridine 1-oxide sodium salt; (d) Bu_3SnD, $InCl_3$, BEt_3, THF; 55% over three steps; (e) $LiAlH_4$; (f) PCC, CH_2Cl_2; (g) (*R*)-(+)-α-methylbenzylamine.

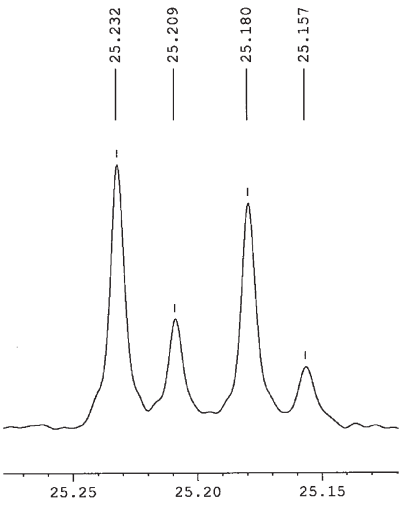


FIGURE 1. $^{13}C\{^1H,^2H\}$ absorptions of a mixture of isomers **2** in the CHD region.

^{13}C absorptions for isomers of **2** could be counted on to be consistent. Both this phenomenon and stereochemical-dependent deuterium perturbations of ^{13}C chemical shifts could be anticipated. Experimental evidence, then, could lead to secure assignments of ^{13}C absorptions to specific isomers of **2**.

A sample of a mixture of all four *d*-labeled isomers of **2** was made so that the hypothetical path to a successful stereochemical analysis might be surveyed. The synthetic steps leading to the desired uneven mixture of the four isomeric structures of **2** are outlined in Scheme 1.

The formation of the monoester from the trans diacid (*a*) took place with a very modest diastereoselective outcome. The three-step reaction sequence (*b*−*d*) afforded mixtures favoring *trans*-bromo and *trans*-deuterio substituents at C(2), for in each case a cyclobutyl radical was involved as an intermediate and reacted preferentially to give trans diastereomers from atom-donor coreactants, $BrCCl_3$ leading to the bromides and Bu_3SnD to 2-*d*-cyclobutanecarboxylic esters.

The mixture of menthyl esters was converted to the imines **2** as outlined (*e*−*g*) without stereochemical modifications. When the mixture of isomers **2** was studied by $^{13}C\{^1H,^2H\}$ NMR spectroscopy with broadband decoupling of both proton and deuterium spins,[3] a pattern of four absorptions for CHD carbons was observed, and the peaks were easily assigned, provisionally. The spectral features of importance portrayed in the upfield CHD four-peak pattern observed (Figure 1) gave relative intensities left to right of 37, 19, 33, and 11%. The absorptions in the four-line pattern at δ 25.232 and 25.180, the first and third, together accounting for 70% of relative intensity, were tentatively assigned to trans isomers. The less intense absorptions at δ 25.209 and 25.157 were ascribed to the cis isomers. If any one peak could be surely assigned to a specific stereoisomer of **2**, all of the assignments would follow. That one initial assignment could not be made unambiguously without further information.

The chemical shifts of CHD methylene carbons flanking the imine function in isomers of **2** would be influenced by deuterium perturbations of carbon-13 δ values, a stereochemically very informative and long-established effect well described by Günther,[10] Berger,[11] and others.[12] For "frozen" chair-conformation cyclohexane, for instance, ax D and eq D substituents lead to upfield ^{13}C $^1\Delta$ chemical shift perturbations (over one bond) of 444.9 and 398.4 ppb, respectively,[10] a significant difference of 46.5 ppb. A qualitatively similar distinction would be expected for the isomers of **2**. A structure having a pseudoaxial D would be expected to have a larger upfield perturbation than a pseudoequatorial D isomer.

All CHD carbons in isomers of **2** were well upfield from absorptions associated with CH_2 methylene carbons; the observed $^3\Delta$ deuterium perturbations of chemical shifts were appreciably smaller, as expected.[10] The downfield peaks are contributed by $^{13}C(4)H_2$ nuclei experiencing $^3\Delta$ perturbations of chemical shifts provided by deuterium substituents at C(2)HD as well as differential shielding from chirotopical influences of the imine function. For 4-*d*-*tert*-butylcyclohexanes the axial and equatorial deuterium substituents contribute upfield shifts of δ by 14.7 and 37.7 ppb, respectively, a difference of 23 ppb. In isomers characterized by a pseudoequatorial versus a pseudoaxial C(2)HD deuterium the $^3\Delta$ difference at $^{13}C(4)H_2$ would be expected to have similar net upfield δ shifts. The first and second and the third and fourth absorptions in Figure 2 are separated by 24 ppb. The spacings between absorptions in Figure 2 for $^{13}C(2)HD$ peaks match those shown in Figure 1, though the figures record slightly different chemical shift reference settings.

To outline the logic of the assignments, one might assume temporarily that the most intense absorption at δ 25.232 seen in Figure 1 may be assigned to isomer *t*-(1*S*,2*S*)-**2**. Then the third absorption would correspond to *t*-(1*R*,2*R*)-**2**. The differences between the two trans and the two cis isomers

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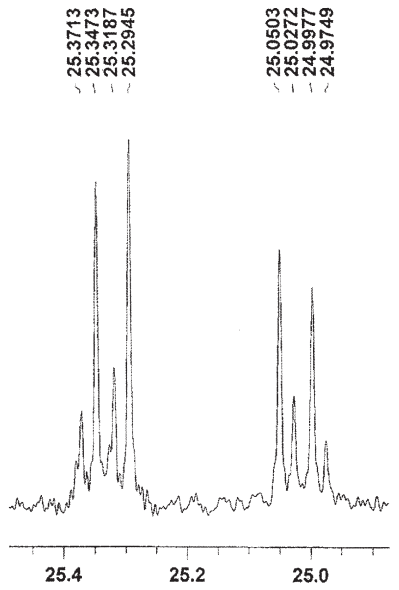


FIGURE 2. $^{13}C\{^{1}H,^{2}H\}$ absorptions observed for a mixture of the four isomers of **2** in the upfield C(2)HD and the downfield $C(4)H_2$ regions.

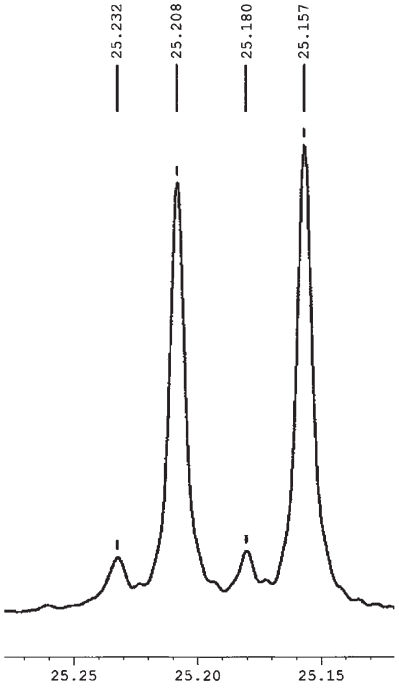
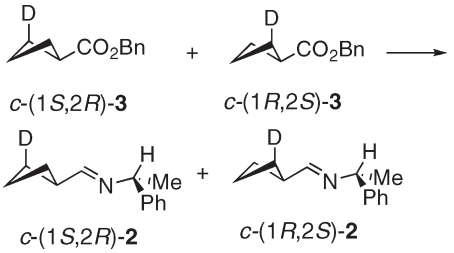


FIGURE 3. Pattern for $^{13}C\{^{1}H,^{2}H\}$ NMR absorptions for C(2)HD carbons for all four isomers of **2** prepared from a racemic mixture of *c*-(1*S*,2*R*)-**3** and *c*-(1*R*,2*S*)-**3**; the isomers of **2** from left to right are *t*-(1*S*,2*S*)-**2**, *c*-(1*S*,2*R*)-**2**, *t*-(1*R*,2*R*)-**2**, and *c*-(1*R*,2*S*)-**2**.

in Figure 1 were identical, 52 ppb, a consequence of the difference in chemical shift influences contributed by the chirotopical influence of the imine substituent. The shifts between the first two absorptions at δ 25.232 and 25.209 and the pair at 25.180 and 25.157 were both 23 ppb, favoring the upfield chemical shift perturbation by the pseudoaxial substituent, as in the cyclohexane prototype. Thus, the second absorption, at 25.209 ppm, might be tentatively assigned to *c*-(1*S*,2*R*)-**2**, shifted upfield by the trans to cis change (an "eq D" to an "ax D" substituent change) while the relatively deshielded position of the *pro-S*-$^{13}C(2)HD$ group remained constant. The last absorption, the weakest and the most upfield of the four, would be assigned to *c*-(1*R*,2*S*)-**2**; it would be shifted upfield by an "ax D" and by being located at the position most shielded preferentially by the chirotopical imine function, as in *pro-R*-^{13}C-d_0-**2**.

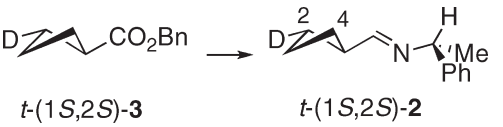
Thus, the proof of principle of this approach to gaining quantitative analytical assessments of mixtures of the set of four deuterium-labeled stereoisomers **1** and of **2** was secured, but the specific structural assignments were based only on a tentative assumption. A rigorous assignment of absolute stereochemistry linking specific isomers of **2** with specific ^{13}C absorptions required additional experimental evidence.

Two reference compounds at hand[13] were used to prepare mixtures of different ratios of isomers of **2**. A racemic sample of benzyl *c*-2-*d*-cyclobutanecarboxylate (*c*-(1*S*,2*R*)-**3** and *c*-(1*R*,2*S*)-**3**) was converted through a LAH reduction, a PCC oxidation, and a condensation with (*R*)-α-methylbenzylamine to give a mixture of *c*-(1*S*,2*R*)-**2** and *c*-(1*R*,2*S*)-**2**. The precursor racemic ester was examined by ^{2}H NMR and found to be a mixture of 94.2% cis (δ = 2.329)/5.8% trans (δ = 2.222) isomers.



The sample of the imine isomers of **2** derived from the racemic cis ester exhibited the expected strong $^{13}C\{^{1}H,^{2}H\}$ NMR absorptions (Figure 3) for the second and fourth peaks found in Figure 1 and in the upfield pattern in Figure 2. The $\Delta\delta$ between the two cis peaks was 51 ppb; the δ values were 25.232, 25.208, 25.180, and 25.157 ppm. The relative peak areas were 7, 41, 7, and 45%.

c-(1*R*,2*S*)-2-Benzyloxycarbonylcyclobutanecarboxylic acid of high ee was secured expeditiously following Bolm and coworkers through a highly asymmetric addition of benzyl alcohol to *cis*-1,2-cyclobutanedicarboxylic anhydride, facilitated by quinidine at −55 °C .[14] The (1*R*,2*S*) acid ester was employed to prepare *t*-(1*S*,2*S*)-**3**;[13] according to ^{2}H NMR spectroscopy, the *t*-(1*S*,2*S*)-**3** made through a sequence of steps was 5.3% cis (δ = 2.334) and 94.7% trans (δ = 2.225).



The imine *t*-(1*S*,2*S*)-**2** was prepared from the stereochemically related ester *t*-(1*S*,2*S*)-**3**, and it together with other

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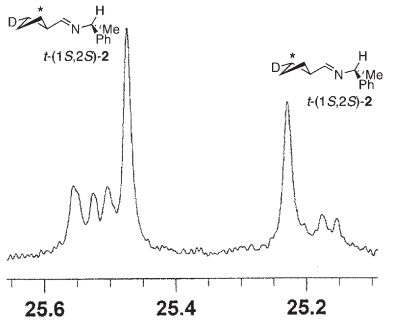

FIGURE 4. $^{13}C\{^{1}H,^{2}H\}$ absorptions of a mixture of the four isomers of **2** rich in *t*-(1*S*,2*S*)-**2**, in the upfield CHD and the downfield CH_2 regions.

isomers of **2** were identified by $^{13}C\{^{1}H,^{2}H\}$ NMR (Figure 4). The dominant peak, peak 1 from left to right in the upfield pattern, confirmed the *t*-(1*S*,2S)-**2** absolute stereochemistry of its structure.

The $^{13}C\{^{1}H,^{2}H\}$ NMR spectrum obtained for *t*-(1*S*,2*S*)-**2** together with the other three isomers identified it as the first absorption from the left of the four-peak upfield $^{13}C(2)HD$ pattern. Reductions of absolute stereochemical control during the preparation of *t*-(1*S*,2*S*)-**2** from *t*-(1*S*,2*S*)-**3** were anticipated to be modest, though some could well have intervened. But the absolute stereochemical finding was unambiguous. With the absolute stereochemistry assignment for peak 1 secured, all other assignments followed.

The second peak was upfield by 23 ppb, a switch from an "eq D" to an "ax D" substituent, so the absorption is for *c*-(1*S*,2*R*)-**2**. The third and fourth peaks are further upfield, for the chirotopical influence of the imine function comes into play as an additional factor; the third and fourth absorptions are each upfield from the first and second peaks respectively by 52 ± 1 ppb. The chirotopical influence favors stronger shielding for *pro-R*-$^{13}C(2)HD$ than for *pro-S*-$^{13}C(2)HD$. Isomer *c*-(1*R*,2*S*)-**2** has the most upfield $^{13}C\{^{1}H,^{2}H\}$ absorption, for it has an "ax D" substituent in the magnetic environment which provides the best shielding by the chiral imine function, at *pro-R*-$^{13}C(2)HD$. The four absorptions, from left to right, are for *t*-(1*S*,2*S*)-**2**, *c*-(1*S*,2*R*)-**2**, *t*-(1*R*,2*R*)-**2**, and *c*-(1*R*,2*S*)-**2**, as most clearly shown in Figure 1.

The downfield pattern in Figure 2, left to right, may be assigned to *c*-(1*R*,2*S*)-**2**, *t*-(1*R*,2*R*)-**2**, *c*-(1*S*,2*R*)-**2**, and *t*-(1*S*,2*S*)-**2**. Peak 4 is *t*-(1*S*,2*S*)-**2**, obviously, from the dominant absorption characteristic of the authentic sample (Figure 4). Peak 3 is downfield from peak 4 by 24 ppb, corresponding to the change of stereochemistry at C(2), from a pseudoequatorial D to a pseudoaxial D for the cis isomer *c*-(1*S*,2*R*)-**2**. Peak 1 (*c*-(1*R*,2*S*)-**2**) is similarly downfield from peak 2 by 24 ppb (Figure 2). The gaps between the two cis and the two trans isomers (52 and 53 ppb, Figure 2) reflect the relatively deshielded position of *pro-S*-$C(4)H_2$ in peaks 1 and 2 versus *pro-R*-$C(4)H_2$ dispositions in peaks 3 and 4. The same $^{3}\Delta$ perturbation difference separating peak 2 from 1, and peak 4 from 3, follows from the larger upfield $^{3}\Delta\ \delta$ perturbation afforded by a pseudoequatorial D substituent.

Another way to present the chemical shift perturbation contributions by pseudoaxial versus pseudoequatorial D substituents at C(2)HD, and the relative perturbations associated with *pro-R*- versus *pro-S*-^{13}C atoms, can be summarized using a tabular scheme. The chemical shift perturbations associated with the two options available for each influence are shown in Table 1. The two structural aspects each providing two possible upfield chemical shift perturbations for $^{13}C(2)HD$ in stereoisomers of **2** combine to determine the four distinct chemical shifts exhibited in $^{13}C\{^{1}H,^{2}H\}$ spectra.

TABLE 1. Upfield Perturbations of $^{13}C(2)$ Chemical Shifts for the Four Stereoisomers of 2-*d*-1-Cyclobutanecarboxyaldehyde (*R*)-α-Methylbenzylimines 2

isomer	$^{13}C(2)$-D Eq (rel ppb)	$^{13}C(2)$-D Ax (rel ppb)	*pro-S*-^{13}C (rel ppb)	*pro-R*-^{13}C (rel ppb)	sum (rel ppb)[a]
t-(1*S*,2*S*)-**2**	0		0		0
c-(1*S*,2*R*)-**2**		23	0		23
t-(1*R*,2*R*)-**2**	0			52	52
c-(1*R*,2*S*)-**2**		23		52	75

[a]The relative chemical shifts for these absorptions in Figures 1, 2, and 3, left to right, are 0, 23 or 24, 52, and 75 ppb.

The contributions of these chemical shift perturbations recorded by $^{13}C\{^{1}H,^{2}H\}$ NMR spectroscopy are not strictly comparable to those affording stereochemically informative spectra for mixtures of isomeric 3,4-d_2-cyclohexenes in the presence of 3,6-d_2-cyclohexenes.[3] In both cases, structural adjustments were employed to convert hydrocarbons potentially formed through thermal reactions of deuterium-labeled vinylcyclobutanes to deuterium-labeled cycloalkanes retaining all the relevant stereochemical information encoded in thermal reaction products, and the cycloalkane derivatives in each case were conformationally restricted so that stereochemical options at CHD elements within a ring could be readily identified, yet the chemical shift perturbations in the two instances depended on different structural influences.

In the 3,4-d_2-cyclohexenes and the derivatives employed to gain access to the stereochemical information required, the chemical shift perturbations were provided by $^{1}\Delta$ CHD and $^{2}\Delta$ CHD contributions combining in four possible ways, characteristic of the four possible stereochemical options. Since the information could be read by scanning four ^{13}C absorptions well separated from absorptions associated with isomers derived from 3,6-d_2-cyclohexene precursors, they could not conflagrate the requisite data deleteriously.

In analyses of mixtures of isomeric 2-*d*-1-cyclobutanecarboxyaldehyde (*R*)-α-methylbenzylimines **2** derived from deuterium-labeled vinylcyclobutanes, the $^{13}C\{^{1}H,^{2}H\}$ NMR analytical method depended on two types of chemical shift perturbations, each with two options, thus leading to four combinations each characteristic of a specific stereoisomer of **2**. The pseudoaxial versus pseudoequatorial D substituents at C(2)HD provided one alternative; the choice between *pro-R*- versus *pro-S*-$^{13}C(2)$ atoms provided the second.

Conclusions

This exploitation of $^{13}C\{^{1}H,^{2}H\}$ NMR spectroscopy will make possible realistic attempts to characterize the kinetics and stereochemistry of thermal stereomutations of *d*-labeled vinylcyclobutanes **1**, the instigating goal leading to this capability, but it is likely to be of greater importance elsewhere. For hydrocarbons, at least, the method will almost surely prove more practically useful than analyses based on chiral lanthanide chemical shift reagents, though these shift reagents are sometimes serviceable in other structural environments.

The specific chiral perturbing substituent introduced to modify vinylcyclobutane worked well, but obviously a great variety of other chiral structural modifications could be considered and utilized and possibly proved to be better. The method being introduced is not dependent on modulating a structure through introducing a specific chiral functional group. It depends on interrogating the stereochemical character of mixtures of deuterium-labeled compounds by introducing and exploiting a chirotopical influence on NMR shielding characteristics while taking advantage simultaneously of stereochemically sensitive deuterium perturbations on ^{13}C chemical shifts. The absorptions registered by $^{13}C\{^1H,^2H\}$ NMR spectroscopy provided useful analytical data quantifying relative concentrations of the stereoisomers of **1** and of **2** with considerable ease. Other applications of this novel method will surely be exercised and found to be valuable.

Experimental Section

All $^{13}C\{^1H,^2H\}$ spectra were acquired at 30 °C with a 600 MHz ^1H (150.9 MHz ^{13}C frequency) NMR spectrometer, acquired by decoupling both ^1H and ^2H simultaneously using inverse-gated WALTZ16 decoupling sequences to obtain completely decoupled ^{13}C absorptions.[3]

Condensation of Cyclobutanecarboxyaldehyde with (*R*)-(+)-α-Methylbenzylamine. Cyclobutylmethanol (86 mg, 1 mmol) was added to a suspension of PCC (237 mg, 1.1 mmol) and Celite (350 mg) in CH_2Cl_2 (3 mL). The resulting black mixture was stirred for 4 h and then passed through silica gel packed in a 5-cm Pasteur pipet and eluted by 3 mL of CH_2Cl_2. (*R*)-(+)-α-Methylbenzylamine (121 mg, 1 mmol) was added to the eluate followed by about 100 mg of $MgSO_4$. The reaction mixture was allowed to stand for 1 h and then filtered, concentrated in vacuo, and redissolved in $CDCl_3$. The imine product was analyzed without further purification, since weak signals characteristic of unreacted amine did not interfere with the regions of interest. ^1H NMR ($CDCl_3$): δ 1.50 (d, 3H), 2.25−1.80 (m, 6H), 3.15 (quintet of d, 1H), 4.30 (q, 1H), 7.34 (m, 5H), 7.80 (d, 1H). ^{13}C NMR: δ 19.1, 24.9, 25.615, 25.683, 40.2, 69.6, 125.9, 126.9, 128.6, 145.4, 166.5. The CH_2 absorptions for *pro-R*-^{13}C and *pro-S*-^{13}C atoms in the d_0-**2** imine at δ 25.615 and 25.683 were confirmed through DEFT spectrum editing, though they could not be assigned.

Isomeric *t*-(1*S*,2*S*)-2, *c*-(1*S*,2*R*)-2, *t*-(1*R*,2*R*)-2, and *c*-(1*R*,2*S*)-2 (*R*)-(+)-α-Methylbenzylimines. To a solution of racemic *trans*-cyclobutane-1,2-dicarboxylic acid (2.88 g, 20 mmol), DMAP (∼ 50 mg), and (−)-menthol (3.18 g, 20.4 mmol) in CH_2Cl_2 (100 mL) was added DCC (4.54 g, 22 mmol) at 0 °C. The reaction mixture was stirred for 3 h and then filtered. The filtrate was evaporated in vacuo; the residue was redissolved in ether and filtered through a thin layer of silica gel. Ether was removed in vacuo to provide diastereomers of crude mono-menthyl *trans*-cyclobutane-1,2-dicarboxylic acids contaminated with a small amount of dimenthyl esters.

Thionyl chloride (3.7 mL, 50 mmol) was added to the crude monomenthyl esters (5.64 g, 20 mmol), and the reaction mixture was heated at reflux for 3 h. Excess $SOCl_2$ was removed under reduced pressure; the resulting acyl chloride product was used without further purification. A 100-mL round-bottomed flask was charged with mercaptopyridine *N*-oxide sodium salt (3 g, 20 mmol), DMAP (∼50 mg), and bromotrichloromethane (50 mL). The resulting suspension was heated at reflux for 2 h, and then the acyl chloride from the $SOCl_2$ reaction was added dropwise. The reaction mixture was heated at reflux overnight, cooled to rt, and concentrated under reduced pressure. The residue was redissolved in ether (100 mL); the ethereal solution was washed with 1 M HCl (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue on silica gel afforded a mixture of the four stereoisomeric menthyl 2-bromocyclobutanecarboxylates (4.11 g, 13 mmol) in 65% in overall yield. ^1H NMR ($CDCl_3$): δ 0.78 (m, 3H), 0.93 (m, 6H), 0.9−2.6 (m, 13H), 3.43 (m, 1H), 4.62 (m, 1H), 4.72 (m, 1H). ^{13}C NMR: complicated spectrum for the mixture of isomers.

Tributyltin deuteride (4.4 g, 15 mmol) was added dropwise to the solution of menthyl 2-bromocyclobutanecarboxylates (4.11 g, 13 mmol) and indium(III) chloride (155 mg, 0.7 mmol) in THF (125 mL). The reaction mixture was stirred for 3 h at rt, after which time no conversion of the starting material was observed. Triethylborane (0.5 mmol solution in THF) was then added, and the reaction mixture was stirred overnight at rt. The following morning, the mixture was heated to reflux for 2 h, all volatiles were removed under reduced pressure, and the residue was redissolved in ether (100 mL). The ethereal solution was washed with 1 M HCl (50 mL) and then with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification on silica gel afforded the four stereoisomeric (*R*)-menthyl 2-deuteriocyclobutanecarboxylates in 92% yield (2.87 g, 12 mmol). ^1H NMR ($CDCl_3$): δ 0.78 (d, J = 6.9 Hz, 3H), 0.91 (m, 6H), 2.3−0.9 (m, 13H), 3.12 (q, 1H), 4.69 (td, 1H). ^{13}C NMR: δ 16.7, 18.6, 21.1, 22.4, 23.9, 26.7, 31.8, 34.7, 38.7, 41.3, 47.5, 74.1, 175.5.

To a suspension of $LiAlH_4$ (27 mg, 0.7 mmol) in dry ether (5 mL) was added menthyl 2-deuteriocyclobutylcarboxylates (120 mg, 0.5 mmol), and the reaction mixture was stirred for 1 h at rt. It was then carefully quenched and washed with 2 M HCl (2 × 3 mL), and the combined aqueous layer was extracted with ether (2 × 2 mL). The combined organic phase was washed with saturated sodium bicarbonate (3 mL), dried over $MgSO_4$, and filtered; the filtrate was evaporated under atmospheric pressure at ∼40−50 °C.

The residue was added to a suspension of PCC (237 mg, 1.1 mmol) and Celite (350 mg) in CH_2Cl_2 (3 mL). The resulting black mixture was stirred for 4 h and then passed through silica gel and condensed with (*R*)-(+)-α-methylbenzylamine (121 mg, 1 mmol) as detailed above. The reaction mixture, containing imines derived from the four stereoisomeric 2-*d*-cyclobutanecarboxaldehydes was allowed to stand for 1 h and then filtered, concentrated in vacuo, and redissolved in $CDCl_3$. The mixture of imines was analyzed by $^{13}C\{^1H,^2H\}$ NMR for absorptions characteristic of the chiral amine-derived imine; the unreacted amine did not interfere with the NMR chemical shift region of interest. The isomers *t*-(1*S*,2*S*)-**2**, *c*-(1*S*,2*R*)-**2**, *t*-(1*R*,2*R*)-**2**, and *c*-(1*R*,2*S*)-**2** were present in the relative concentrations 37, 19, 33, and 11% (Figure 1). See also Figure 2.

cis-2-*d*-Cyclobutanecarboxylates *c*-(1*S*,2*R*)-**3** and *c*-(1*R*,2*S*)-**3**, and *trans*-2-*d*-Cyclobutanecarboxylate *t*-(1*S*,2*S*)-**3** were available from another synthetic project.[13] The ^1H, ^2H, and ^{13}C NMR spectra for the racemic benzyl *cis*-2-*d*-cyclobutanecarboxylates *c*-(1*S*,2*R*)-**3** and *c*-(1*R*,2*S*)-**3** and for benzyl *trans*-(1*S*,2*S*)-2-*d*-cyclobutanecarboxylate *t*-(1*S*,2*S*)-**3** are included in the Supporting Information. The unlabeled benzyl ester of cyclobutanecarboxylic acid is a known and fully characterized compound.[15] The racemic sample of *c*-(1*S*,2*R*)-**3** and *c*-(1*R*,2*S*)-**3** was converted following the reactions used above to prepare a mixture of *t*-(1*S*,2*S*)-**2**, *c*-(1*S*,2*R*)-**2**, *t*-(1*R*,2*R*)-**2**, and *c*-(1*R*,2*S*)-**2** in the relative concentrations of 7, 41, 7, and 45%. The $^{13}C\{^1H,^2H\}$ spectrum of these absorptions is shown in Figure 3. The sample of *t*-(1*S*,2*S*)-**3** was converted following the reactions used above to prepare a mixture of *t*-(1*S*,2*S*)-**2**, *c*-(1*S*,2*R*)-**2**, *t*-(1*R*,2*R*)-**2**, and *c*-(1*R*,2*S*)-**2** rich in *t*-(1*S*,2*S*)-**2**. The most downfield absorption of the C(2)HD pattern was dominant

(15) (a) Bender, D. M.; Peterson, J. A.; McCarthy, J. R.; Gunaydin, H.; Takano, Y.; Houk, K. N. *Org. Lett.* **2008**, *10*, 509–511. (b) Hale, J. J.; Lynch, C. L.; Caldwell, C. G.; Willoughby, C. A.; Kim, D.; Shen, D.-M.; Mills, S. G.; Chapman, K. T.; Chen, L.; Gentry, A.; Maccoss, M.; Konteatis, Z. D. US 2002094989 A1, 103 pp.

(Figure 4). Another mixture of the isomers of **2** rich in *t*-(1*S*,2*S*)-**2** is shown in Figure S5 in the Supporting Information.

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Supporting Information Available: NMR spectral data for *pro*-*R*-^{13}C-d_0-**2** and *pro*-*S*-^{13}C-d_0-**2**, 2-*d*-labeled stereoisomers of benzyl cyclobutanecarboxylate ((*c*-(1*S*,2*R*)-**3** and *c*-(1*R*,2*S*)-**3**, and *t*-(1*S*,2*S*)-**3**), and a 54, 8, 12, and 26% mixture of *t*-(1*S*,2*S*)-**2**, *c*-(1*S*,2*R*)-**2**, *t*-(1*R*,2*R*)-**2**, and *c*-(1*R*,2*S*)-**2**. This material is available free of charge via the Internet at http://pubs.acs.org.