Thermodynamic, Spectroscopic, and Computational Evidence for the Irreversible Conversion of β- to α-Endosulfan

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Previous studies have provided unequivocal evidence for the symmetry of β-endosulfan and the corresponding asymmetry of α-endosulfan; the conversion of β-endosulfan to α-endosulfan was identified. In this study, evidence from differential scanning calorimetry (DSC) and nuclear magnetic resonance (NMR) experiments combined with computational chemistry calculations was used to propose a molecular mechanism for the corresponding conformational changes that occur in this process. DSC and NMR data of mixtures indicated that both isomers can influence the conformer populations in the solid, solution, and vapor phase. Computational chemistry demonstrated that the relative S═O configuration between α- and β-isomers can be the intermediate state through which the conformations of α- and β-isomers affect each other. Furthermore, calculations for mixtures indicated that the asymmetrical conformation of the sulfite in α-endosulfan can induce asymmetry in β-endosulfan, and conversion to α-endosulfan occurs from this transition state.

Keywords: *α- and β-endosulfan; conformation; NMR; volatility; eutectic mixture; computational chemistry*

INTRODUCTION

Endosulfan (1,4,5,6,7,7-hexachloro-5-norbornene-2,3-dimethanol cyclic sulfite) is a broad-spectrum organochlorine insecticide typically applied as a 7:3 α-:β-isomeric mixture (Figure 1) to cereals, fruits, vegetables, and cotton. The fate and transport of endosulfan is of particular interest because it is highly toxic to certain aquatic organisms (*1*−*3*). The fates of the α- and β-forms vary, and the observed ratio of isomers depends on the physical state of environmental compartments. The α-isomer is predominant in air samples (*4*−*7*), the β-form is favored in rain samples (*8*−*10*), and the α-isomer is more abundant in snow (*11*). Furthermore, some researchers have observed substantial conversion of the β-isomer to the α-isomer and little concomitant conversion of the α-isomer to the β-isomer (*12*−*15*).

Recently we provided evidence demonstrating that the β-isomer does convert to the α-isomer but that the reverse does not occur under the same conditions (*16*). Furthermore, nuclear magnetic resonance spectroscopy (NMR) and X-ray crystallography proved that the α-isomer exists as an equimolar mixture of asymmetrical isomers in the solid and solution states, whereas the β-isomer exists only as a single symmetrical isomer (*16*). A mechanism is required to explain why the reverse reaction does not occur. Here we propose a reaction pathway in which asymmetrical end products form from the symmetrical starting material and present as evidence both physical and spectral data and computational chemistry calculations.

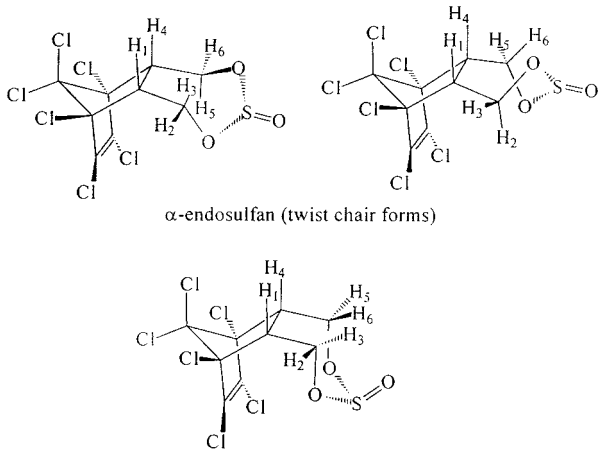

Figure 1. Structures of α- and β-endosulfan.

MATERIALS AND METHODS

Chemicals. β-Endosulfan (99.8% β-; 0.2% α-) and α-endosulfan (100%) were obtained from ChemServices (West Chester, PA). Deuterated solvents were obtained from Sigma Chemical (St. Louis, MO).

Differential Scanning Calorimetry (DSC). Approximately 1 mg of endosulfan (pure isomer or mixed) was placed in an aluminum sample pan, which was crimped together with an aluminum lid. Each lid had a small pinhole added to preclude simultaneously altering both temperature and pressure during the experiment. An empty sample pan was used as a reference. Samples were placed in the chamber of a TA Instruments model 910S differential scanning calorimeter (New Castle, DE) and equilibrated at 40.0 °C. Scans were obtained by increasing the temperature at a rate of 10.0 °C/min to 160, 220, 280, and 300 °C and held for 3 min. In some

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cases, the sample was cooled to room temperature, and the sequence was repeated several times. The pan was opened, and the contents were dissolved in ethyl acetate for gas chromatography (GC) analysis.

Gas Chromatography. GC analyses were conducted on a Hewlett-Packard 5890 gas chromatograph equipped with a 30 m (0.25 mm i.d. and 0.25 μm film thickness) Supelco SP-608 fused silica capillary column and an electron capture detector. Samples of 1.0 μL (1−10 ppm) were analyzed as follows: splitless injection with 1 min purge delay time; column head pressure of 18.2 psi; injector temperature of 270 °C; initial column temperature of 150 °C held for 1 min, ramped at 50 °C/min to 250 °C, and held for 10 min. Isomers were quantified using a standard curve obtained from a 1:1 ratio of α- to β-isomers. Attempts to separate the α-enantiomers were conducted on a BGB-172 (20% *tert*-butyldimethylsilylated β-cyclodextrin in OV-1701) 30 m column, 0.25 mm i.d. and 0.25 μm film thickness (BG Analytik AG).

NMR Spectroscopy. ^{1}H and ^{13}C NMR attached proton test (APT) experiments (*17, 18*) were conducted on a Bruker QE Plus 300 NMR spectrometer (Billerica, MA) operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C. Constant-temperature spectra were collected at 25 ± 0.3 °C in DMSO-d_6 (Aldrich, Milwaukee, WI). Chemical shifts were referenced to DMSO-d_5.

Molecular Mechanics. Semiempirical calculations were made using the program Alchemy 2000, Tripos Inc. (St. Louis, MO) and the MNDO (Minimal Neglect of Differential Orbitals) force field parameters (*19*, *20*) using MOPAC (Molecular Orbital PACkage). Calculations were energy minimized to 0.01 kcal/mol. The chlorine atoms on endosulfan were hidden only for viewing the conformers, so the relative positions among the sulfite, methine, and methylene groups in the seven-membered ring could more easily be discerned.

RESULTS AND DISCUSSION

The solution- and solid-state structures of the α-isomer of endosulfan are composed of a set of enantiomeric pairs, but the β-isomer is a single symmetrical molecule (*16*). Endosulfan consists of a seven-membered ring fused to a norbornene. The preferred conformation of cycloheptane is the asymmetrical, twist-chair; pseudorotation prevents isolation of individual asymmetrical conformers (*21*). Not all of the endosulfan seven-membered ring can participate in pseudorotation because the norbornenyl moiety maintains the two methine protons in a rigid *cis* conformation. Attempts to detect the asymmetric enantiomers of α-endosulfan in the vapor phase using a GC chiral stationary phase were unproductive. A possible explanation is that the rate of pseudorotation interconversion between enantiomers was too fast at the temperatures required for GC analysis.

Phase Transitions for Pure α- and β-Endosulfan. DSC was conducted using individual α- and β-endosulfan isomers (Figure 2). The data showed that each of the two conformers has a major phase transition in the solid state in addition to their melting point. For α-endosulfan, a sharp solid-phase transition at 108 °C and a broad liquid- to vapor-phase transition at 215 °C were observed. GC analysis of the individual α-isomer heated to 280 °C showed no conversion to β-endosulfan. For the β-isomer, three phase transition peaks were observed. The solid- to liquid-phase transition occurred at 210 °C; an even larger phase transition peak ∼5 times the area of the peak at 210 °C was observed at 151 °C, and a smaller phase transition peak at 112 °C also occurred. The first and last phase transitions are consistent with the melting points of the individual isomers. The much larger peak at 151 °C thus corresponds to a solid−solid-phase transition, that is, a change in crystal structure or crystal lattice form. Using the identical DSC procedure but stopping and holding the end temperature at 160 °C for 10 min enabled collection of the resulting material. GC analysis (Table 1) demonstrated that ∼9% of β-endosulfan converted to α-endosulfan. Under the same thermal conditions, α-endosulfan did not convert to β-endosulfan and some of the α-endosulfan evaporated.

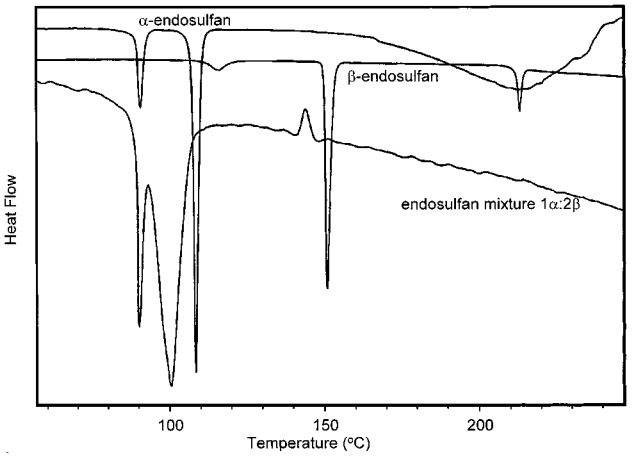

Figure 2. DSC scans of pure α- and β-endosulfan and a 1α-:2β- mixture.

Table 1. Isomeric Conversions of α- and β-Endosulfan Mixtures (Weights Calculated to Nearest 0.01 mg)

	α-endosulfan	β-endosulfan
α-endosulfan		
initial conditions	**1.00 mg (100%)**	0.00 mg (0%)
1 × 180 °C	**0.28 mg (100%)**	0.00 mg (0%)
mixture A		
initial conditions	**0.88 mg (73%)**	0.33 mg (27%)
2 × 160 °C	**0.63 mg (69%)**	0.29 mg (31%)
1 × 180 °C	**0.32 mg (63%)**	0.19 mg (37%)
β-endosulfan		
initial conditions	0.00 mg (0%)	**1.00 mg (100%)**
1 × 160 °C	0.09 mg (9%)	**0.91 mg (91%)**
mixture B		
initial conditions	0.30 mg (30%)	**0.70 mg (70%)**
3 × 220 °C	0.38 mg (38%)	**0.62 mg (62%)**
2 × 280 °C	0.63 mg (63%)	**0.37 mg (37%)**

Eutectic Mixtures and Phase Transitions. Structurally similar compounds can form a eutectic mixture. The physical properties of the mixture can be quite different from those of the pure individual components. DSC of α- and β-endosulfan mixtures showed a solid−liquid-phase transition at 88 °C. No solid−liquid-phase transition for β-endosulfan in this mixture was observed near its known melting point. A small negative peak was detected at 145 °C, consistent with the temperature of solid−solid-phase transition in β-endosulfan. Thus, the observed physical properties of β-endosulfan are neither thermodynamically nor kinetically independent of the physical properties of α-endosulfan.

Furthermore, in the solid (recondensed) phase, the identical 63% α-isomer/37% β-isomer eutectic composition was observed for both excess α-isomer (mixture A) and excess β-isomer (mixture B) (Table 1). The process by which this composition occurs is different for the two cases. From mixture A, excess α-endosulfan evaporates until the 63% α-isomer/37% β-isomer composition is achieved. Note that at 180 °C half the weight of the sample has been lost. In contrast, in mixture B the mass balance is maintained, and the final weight of α-endosulfan is larger than the initial amount.

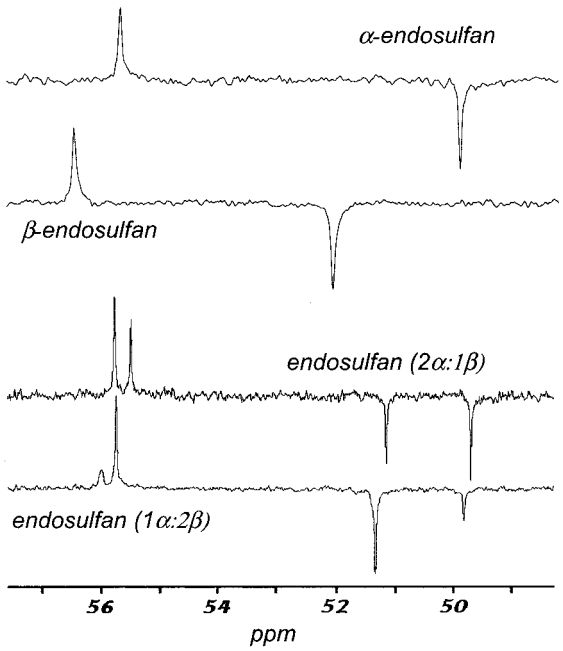

Figure 3. APT NMR spectra of pure α- and β-endosulfan and two mixtures. Methylene $\underline{C}H_2$ frequencies (~56 ppm) are up and methine $\underline{C}H$ frequencies (~51 ppm) are down.

Spectral Data. Spectroscopic evidence of the individual isomers has previously been reported (*16*). Recent NMR conformational studies have demonstrated that fundamental spectral information about conformations is often readily experimentally available only in very specific chemical environments (*22*). DSC demonstrated that the physical properties of α- and β-endosulfan are very different at a mole ratio of 2:1 from those for the pure compounds. Thus, specific changes in the chemical environment may also be occurring as a function of changes in the mole fraction of α-isomer/β-isomer. NMR experiments were conducted comparing mole ratios of 2:1 α-isomer/β-isomer with 1:2 α-isomer/β-isomer to determine whether these differences could be detected spectroscopically.

Previous reports have shown that no significant proton chemical shifts or line broadening for either isomer occurred with increasing temperature (from 25 to 160 °C) in DMSO-d_6 (*16*). This temperature range included the melting point of α-endosulfan and the solid−solid-phase transition temperature for β-endosulfan (145 °C). Unexpectedly, for both mole ratios of 2:1 and 1:2 α-isomer/β-isomer, no significant proton chemical shifts or line broadening was observed in the ^{1}H spectrum independent of solvent.

The ^{13}C NMR spectrum of endosulfan contains multiple $\underline{C}$-Cl peaks as well as $\underline{C}H$ and $\underline{C}H_2$ peaks. An APT experiment indicates the odd versus even coupling between carbon and hydrogen and gives rise to spectra where the $\underline{C}H_2$ carbons are up and the $\underline{C}H$ (and $\underline{C}H_3$) carbons are down (*17*, *18*). The APT experiment was used to investigate potential changes at these sites in the 2:1 versus the 1:2 α-isomer/β-isomer mixture.

Large differences in the predicted relative peak areas between the 2:1 and 1:2 α-isomer/β-isomer spectra were observed (Figure 3). At the 2:1 mole ratio, the $\underline{C}H_2$ peaks near 56 ppm were observed to be 6:1 α-isomer/β-isomer, not the expected 2:1; the smaller peak is also broader. This indicates that the CH_2 group on the β-isomer is less rigid in this conformation/chemical environment. The lower intensity is consistent with less efficient nuclear Overhauser enhancement (NOE) transfer from the CH_2 protons to the carbon atom at this site. The broadening is consistent with multiple and interchanging conformations at that site. In the same spectrum, a corresponding loss in intensity and broadening is not observed at the $\underline{C}H$ (~51 ppm) carbon site.

For the 1:2 α-isomer/β-isomer mole ratio, the spectrum is again quite different at the same CH_2 site. The peak areas are 2:3, but broadening is not apparent in the $\underline{C}H_2$ or the $\underline{C}H$ peaks for either isomer. The absence of peak broadening at these sites suggests that an increase in the number of multiple exchanging conformations is not occurring in the α-isomer.

Thus, spectral data confirm the thermodynamic results that the conformations and dynamics of the α- and β-isomers are not independent of each other. Moreover, the interactions are not symmetrical because 1:2 and 2:1 mole ratios did not afford the same results. Computational chemistry was used to investigate the conformational changes to explain the thermal and spectroscopic data.

Computational Chemistry of Stable Energy Conformers and Their Transitions. Heats of formation for the conformations of endosulfan (Figure 4) were determined using MNDO calculations. The calculations correspond to the energies at room temperature of single diffuse molecules in the vapor phase. The norbornene portion of endosulfan is hidden in each of the figures to draw attention to the conformational changes within the seven-membered aliphatic ring structure. Within the seven-membered ring, only the two CH_2 groups and the sulfite group can change conformation.

The symmetrical isomers (1a, 1b) are consistent with β-endosulfan structure in the vapor phase. The sulfur is tetrahedral and includes a lone pair of electrons, which can fully exchange with the S═O moiety (1a to 1b). Both isomers are present simultaneously and in equilibrium with one another. This conformational change at the sulfite group from up to down causes no calculated change in the relative conformation of either CH_2 group and is consistent with previous experimental solution-state NMR results for pure β-endosulfan: as the temperature increased, no significant changes in the CH_2 conformation were observed.

No experimental evidence for the second symmetrical isomer (2a, 2b) was found. Although the energy of formation of these structures by MNDO calculations (Table 2) is within 1−2 kcal/mol of the corresponding other two symmetrical isomers (1a and 2a; 1b and 2b), conversion of 1a to 2a is precluded. Any symmetrical intermediate conformation creates enormous strain on the ring. From MNDO calculations, conformations in which both methylene groups are symmetrically intermediate between the 1a and 2a occur only with the addition of nearly 100 kcal/mol of energy. Bond dissociation energies for a carbon−carbon bond are ~80 kcal/mol (*23*).

The tetrahedral sulfur in 1a is very sterically hindered; the S═O cannot move left or right. The only conformational change available in 1a is that the S═O group can move down (forming 1b). Stable asymmetrical conformations can occur only from the higher energy 1b form. From there, the S═O group can move left to form 3a or right to form 3b. In 3a, the CH_2 group on the right moves slightly inward, the oxygen on the left moves slightly upward, and the CH_2 group on the left moves significantly downward, inducing asymmetry.

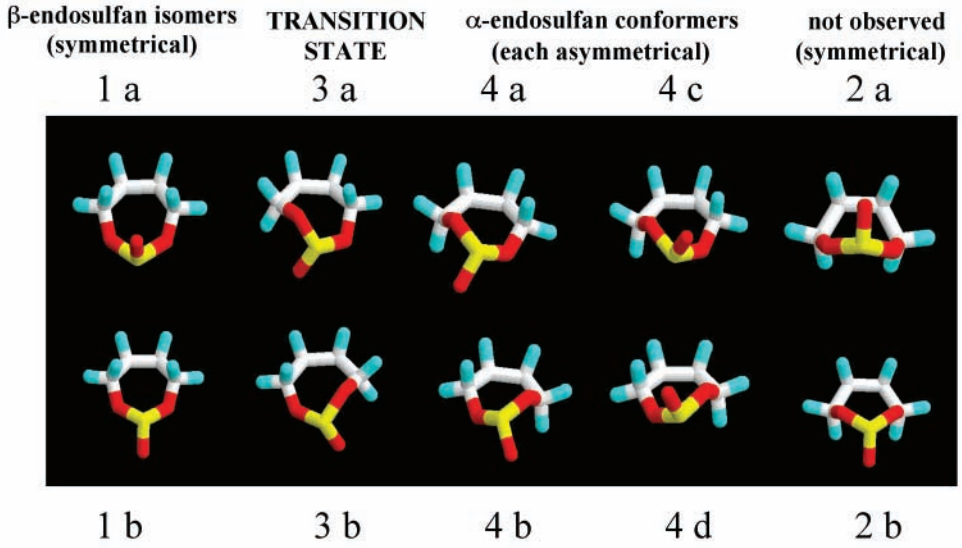

Figure 4. Computational chemistry molecular structure of stable endosulfan conformers. Carbon-chlorine atoms are hidden. (Carbon = white; hydrogen = blue; oxygen = red; sulfur = yellow.)

Table 2. Heats of Formation of Stable Endosulfan Isomers

(β-) symmetrical isomers	ΔH_f (kcal/mol)	dΔH (kcal/mol)	transition states	ΔH_f (kcal/mol)	dΔH (kcal/mol)	(α-) asymmetrical isomers	ΔH_f (kcal/mol)	dΔH (kcal/mol)	endosulfan form not observed	ΔH_f (kcal/mol)
1a	−26.7		3a	−21.6		4a and 4b	−22.4		2a	−27.8
1b	−19.9		3b	−21.4		4c and 4d	−22.0		2b	−22.3
1a to 1b		6.8	3a to 4a		−0.8	4a to 4b		0		
			3b to 4b		−0.6	4a to 4c		0.4		
						4c to 4d		0		
						4d to 4b		−0.4		

Continued movement of the CH_2 group on the left fully inverts this group (the other CH_2 group is unaffected), forming α-endosulfan (4a and 4c). Mirror image asymmetry occurs when initial S=O movement is right instead of left, converting 3b into 4b and 4d.

The asymmetrical isomers (4a, 4b, 4c, and 4d) have the same heats of formation (~ -22 kcal/mol). The S=O group can flip with the lone pair of electrons (4a to 4c or 4b to 4d), requiring virtually no additional energy. Two sets of enantiomers exist, and each can interconvert freely via pseudorotation: 4a to 4b and 4c to 4d. A two-step process is required for 4a to convert to 4d (or for 4b to convert to 4c).

The calculation of free energy (ΔG) for any reaction must include the TDS component as well as the ΔH. The formation of 4a is equally as likely as that of 4b, 4c, or 4d. There are four equally populated distinct final states, each of which has physical properties very different from that of their initial state. An increase in entropy occurs with the formation of each molecule of α-isomer.

In the solid and solution states, the 2:1 α-isomer/β-isomer is favored. The structural basis for the composition could be related to the average conformation of the S=O group. In liquid and/or solution, the preferred conformation of the S=O group could be a mixture of 1a to 1b. The presence of α-endosulfan in the liquid/solution could stabilize this ratio of 1a to 1b. At lower mole ratios, for example, 1:2 α-isomer/β-isomer, each α-molecule in the conformation 4a and 4b has the capacity to induce asymmetry into every β-endosulfan in the 1b conformation. In the 2:1 α-isomer/β-isomer mixture, the combination of 4c, 4d, and 1b could be stabilizing a symmetrical S=O conformation instead of inducing its asymmetry. The chiral chemical environment could also affect the ratio of populations between 4a (and 4b) and 4c (and 4d).

Conclusions. The physical and molecular properties of β-endosulfan in the solid, solution, or vapor phase clearly depend on the relative concentration of α-endosulfan. The presence of α-endosulfan dramatically lowers the melting point and phase transition temperatures of β-endosulfan. The melting point of α-endosulfan is also lowered by β-endosulfan, which in turn decreases the energy required to volatilize α-endosulfan (relative to pure α-endosulfan). NMR demonstrates the conformation of each isomer in solution is altered by the presence of the other isomer. Computational chemistry calculations identify the conformation of the S=O group as intrinsically involved in such conformational changes. The β-endosulfan S=O is symmetrical in conformation, and the α-endosulfan S=O is asymmetrical in conformation; any α-endosulfan molecule inducing asymmetry into the seven-membered ring of β-endosulfan converts the β-isomer into the α-isomer. In contrast, the α-isomer does not convert into the β-isomer because β-endosulfan does not induce symmetry at the corresponding sites in α-endosulfan molecules.

The evidence that the β-isomer readily converts to the α-isomer must be considered when the environmental fate of endosulfan is evaluated. Understanding the mechanism responsible for these changes is essential to accurately predict the isomers that concentrate in various environmental compartments. The findings of this investigation strongly suggest that previous studies describing the half-life of endosulfan are suspect if both α- and β-isomers were not quantified.

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