CySH, etc. BSA represents the microheterogeneous preparation of bovine serum albumin; Alb–SH, the mercaptalbumin component (0–65%) in which cys-34 is present in reduced form. Other abbreviations include the following: DS = dansylsarcosine, DA = dansylamide, IS = isomer shift, QS = quadrupole splitting, Γ = Mössbauer line width, and RSH = generic thiol.

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Registry No. AuSTm, 4846-27-9; AuSCy, 74921-06-5; AuSGt, 89827-22-5; Au, 7440-57-5.

Supplementary Material Available: Fourier-filtered EXAFS spectrum of $BSA(AuSTm)_{2.65}$ and transformed spectrum of $BSA(AuSTm)_{0.44}$ (2 pages). Ordering information is given on any current masthead page.

Influence of Temperature on the Conformation of Ions Undergoing Electron Impact Induced Fragmentation

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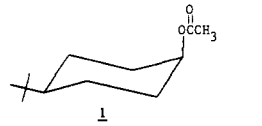
Abstract: The conformational mixture from which hydrogen abstraction occurs during the electron impact induced elimination of diethyl malonate from diethyl cyclohexylmalonate (**8**) was determined at several ion source temperatures by comparison of the mass spectra of several deuterated analogues of **8** to the mass spectra of the deuterated analogues of diethyl *trans*-4′-*tert*-butylcyclohexylmalonate (**4**) and diethyl *cis*-4′-*tert*-butylcyclohexylmalonate (**3**). It was found that the conformational distribution is closely correlated with that predicted from solution chemistry data and ion source temperature.

Mass spectroscopists have developed a variety of interesting and powerful instrumental techniques to permit study of the structure and mechanisms of fragmentation of ions after electron impact.[1] However, conceptually simpler approaches rooted in the techniques used by chemists for the study of neutrals and their reactions in more conventional environments have been less thoroughly exploited. For example, an approach frequently used in the study of conformationally mobile systems in solution is to compare their properties and behavior to conformationally immobile systems frozen into the specific conformations attainable by the mobile system. Since most cyclohexyl derivatives can exist in two chair conformations of well-defined geometry, and since accurate conformationally immobile models for these structures are available, this approach has been particularly useful when applied to the solution chemistry behavior of cyclohexyl and related systems.[2] Nevertheless, this methodology has found comparatively little application to mass spectrometric studies.

Recently, a variety of studies have suggested that this general approach might be applicable to studies of the mass spectral behavior of cyclohexyl derivatives.[3] It has been established, for example, that the McLafferty rearrangement of *cis*- and *trans*-4-*tert*-butylcyclohexyl acetate (**1** and **2**) and diethyl *cis*- and *trans*-4′-*tert*-butylcyclohexylmalonate (**3** and **4**) involve hydrogen abstraction predominantly from the most stable chair conformations and proceed with high but opposite stereochemistries.[3a,e]



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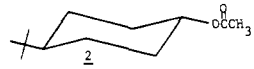

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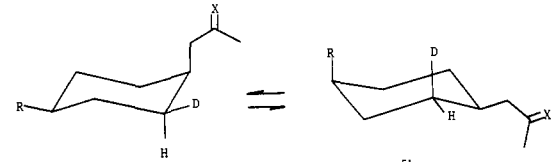
The high stereospecificities demonstrate that the 4-*tert*-butyl group effectively locks the conformation of the cyclohexyl ring prior to hydrogen abstraction and that the ring structure retains its integrity, necessary requirements for use of this technique. The observation of very predominant cis hydrogen abstraction from axial derivatives (e.g., **1** and **3**) and trans hydrogen abstraction from equatorial derivatives (e.g., **2** and **4**) provides a simple diagnostic for the stereochemistry of a reacting, conformationally mobile system. Thus, the relative amounts of cis and trans elimination from conformationally mixed systems such as **5** will



5a 5b

be revealed by the relative amounts of deuterium vs. protium elimination observed. This methodology has been used to study the mass spectral behavior of a series of 4-substituted cyclohexylmalonates and acetates,[3e] leading to the important empirical observation that the influence of structural variation on the population of fragmenting ions could be accurately predicted,

(1) See, for example: (a) Kingston, D. G. I.; Bursey, J. T.; Bursey, M. M. *Chem. Rev.* **1974**, *74*, 215–242. (b) Budzikiewicz, H.; Djerassi, C.; Williams, D. H. "Mass Spectrometry of Organic Compounds"; Holden-Day: San Francisco, CA, 1967. (c) Beynon, J. H.; Saunders, R. A.; Williams, A. E. "The Mass Spectra of Organic Molecules"; Elsevier: Amsterdam, 1968.

(2) Hanack, M. "Conformation Theory"; Academic Press: New York, 1965; Chapter 3.

(3) (a) Eadon, G.; Gold, P.; Bacon, E. *J. Am. Chem. Soc.* **1975**, *97*, 5184–5189. (b) Eadon, G. *Ibid.* **1976**, *98*, 7813–7819. (c) Eadon, G.; Jefson, M. *J. Org. Chem.* **1976**, *41*, 3917–3920. (d) Eadon, G. *Org. Mass Spectrom.* **1977**, *12*, 671–680. (e) Rej, R. N.; Bacon, E.; Eadon, G. *J. Am. Chem. Soc.* **1979**, *101*, 1668–1675. (f) Rej, R. N.; Taylor, C.; Eadon, G. *J. Org. Chem.* **1980**, *45*, 126–130. (g) Eadon, G.; Alonso, C.; Valente, H. *Ibid.* **1983**, *48*, 520–526. Also see: (h) Splitter, J. S.; Calvin, M. *Ibid.* **1982**, *47*, 4545–4552.

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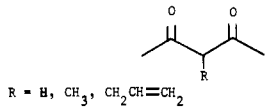
based on conformational data readily available from neutral molecules.

Solution chemists have conducted numerous studies of the influence of temperature on conformer distribution and reaction products among conformationally mobile systems. These experiments have provided data of fundamental importance to the prediction and rationalization of reactions and structure. Mass spectroscopists have also conducted numerous studies of the influence of temperature on the course and extent of electron impact induced fragmentation.[4] However, few of these have dealt with the interpretation of thermal effects in terms of the structure of rearranging ions. Larsen,[4i] for example, examined the temperature dependence of the fragmentation of several β-diketones (**6**) and,



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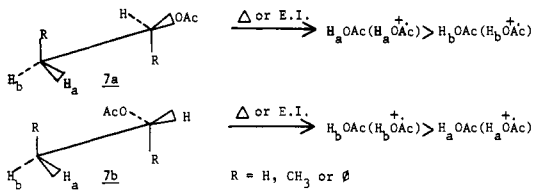
with some success, interpreted their mass spectral behavior in terms of their keto–enol content during fragmentation.

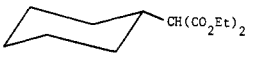
Of particular relevance to this work is a study in which the relative rates of γ-hydrogen abstraction at selected ion source temperatures were monitored in the McLafferty rearrangement of 2-butyl acetate (**7a** and **7b**).[4n] The Arrhenius dependence



observed in this system was taken as proof that the "internal temperature" of the rearranging ions is close to the temperature of the precursor neutrals which are in thermal equilibrium with the ion source walls.[5] Moreover, the preference for hydrogen abstraction corresponding to the transition state in which the methyl groups are placed into an anti orientation, similar to the corresponding thermally induced elimination, elegantly supports the concept that in this case the structure of the rearranging ions is not grossly distorted with respect to the precursor neutral.

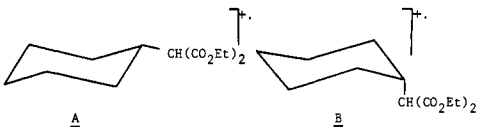
These results, in conjunction with studies already described which demonstrate that diethyl cyclohexylmalonates fragment predominantly from chair conformations and that the conformation can be deduced from the behavior of stereospecifically labeled compounds, support the study of the temperature dependence of the electron impact induced behavior of these compounds. Since the relevant chair conformations are well defined and separated by significant energy barriers,[6] any temperature dependence observed may be relatable to a specific conformation, and quantitative comparisons between predicted and observed behavior are possible.

The conformationally mobile system chosen for the study is diethyl cyclohexylmalonate (**8**). As already discussed, the electron impact induced behavior of this compound at constant temperature



8

has already been studied and is entirely consistent with hydrogen abstraction from a mixture of the two possible chair conformers. The related conformationally immobile systems, diethyl *trans*-4′-*tert*-butylcyclohexylmalonate (**4**) and diethyl *cis*-4′-*tert*-butylcyclohexylmalonate (**3**), provide accurate models for these conformers, and constant temperature studies have demonstrated that their behaviors are also consistent with predominant fragmentation from their stable chair conformers.[3a,e] Malonates are

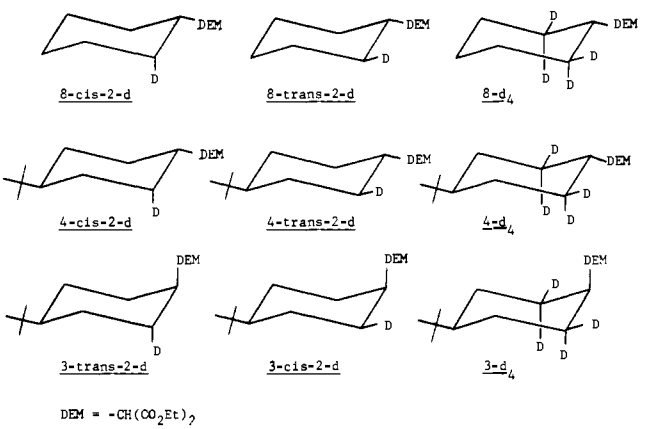


A B

additionally well suited to a temperature dependence study because, unlike the corresponding acetates, there is no evidence for the generation of the McLafferty ion by competing pathways proceeding through thermal artifacts.

Results and Discussion

The mass spectra of diethyl cyclohexylmalonate (**8**), diethyl *trans*-4′-*tert*-butylcyclohexylmalonate (**4**), and diethyl *cis*-4′-*tert*-butylcyclohexylmalonate (**3**) exhibit intense peaks at *m/e* 160 due to the loss of alkene from the molecular ion. The very weak metastable peaks observed for the McLafferty rearrangement, along with a more intense peak observed for the "McLafferty + 1" process, precluded stereochemical studies among these metastable reactions.



A series of mono- and tetradeuterated analogues of malonates **8** (**8**-*cis*-2-*d*, **8**-*trans*-2-*d*, **8**-d_4), **4** (**4**-*cis*-2-*d*, **4**-*trans*-2-*d*, **4**-d_4), and **3** (**3**-*trans*-2-*d*, **3**-*cis*-2-*d*, **3**-d_4) were synthesized to probe the stereochemistries of the hydrogen abstraction step at each ion source temperature. Ion source temperatures were selected at regular intervals of $1/T$ K. The relative intensities of the peaks of interest remained unchanged (within experimental error) as hot box and inlet temperatures were varied. These temperatures were kept constant (170–185 °C) during the ion intensity measurements described below.

The data and results of calculations obtained from the electron impact induced loss of alkene, at four ion source temperatures (348, 408, 458, and 508 K), from malonates **8**, **4**, and **3** and their monodeuterated analogues, are shown in Tables I, II, and III, respectively. Data from the mass spectra of the tetradeuterated analogues (**8**-d_4, **4**-d_4, and **3**-d_4) were not included in these tables, since these compounds showed that the elimination was greater than 98% specific at all temperatures.[3e] Hence no correction for

(4) See, for example: (a) Spiteller-Friedmann, M.; Eggers, S.; Spiteller, G. *Monatsh. Chem.* **1964**, *95*, 1740–1749. (b) Cassuto, A. "Mass Spectrometry"; Reed, R. I., Ed.; Academic Press: New York, 1965; p 283ff. (c) Spiteller-Friedmann, M.; Spiteller, G. *Chem. Ber.* **1967**, *100*, 79–92. (d) Meyerson, S. *Appl. Spectrosc.* **1968**, *22*, 30–33. (e) Jullien, J.; Pechine, J. M. *Org. Mass Spectrom.* **1970**, *4*, 325–341. (f) Levsen, L.; Beckey, H. D. *Int. J. Mass Spectrom. Ion Phys.* **1972**, *9*, 51–62. (g) Meisels, G. G.; Chen, C. T.; Giessner, B. G.; Emmel, R. H. *J. Chem. Phys.* **1972**, *56*, 793–800. (h) McLafferty, F. W.; Wachs, T.; Lifschitz, C.; Innorta, G.; Irving, P. *J. Am. Chem. Soc.* **1970**, *92*, 6867–6880. (i) Zamir, L.; Jensen, B. S.; Larsen, E. *Org. Mass Spectrom.* **1969**, *2*, 49–61. (j) Rennekamp, M. E.; Paukstelis, J. V.; Cooks, R. G. *Tetrahedron* **1971**, *27*, 4407–4415. (k) Pokrovsky, V. A.; Goldenfeld, I. V.; Korol, E. N. *Int. J. Mass Spectrom. Ion Phys.* **1973**, *11*, 1–8. (l) Solka, B. H.; Benyon, J. H.; Cooks, R. G. *J. Phys. Chem.* **1975**, *79*, 859–862. (m) Medved, M.; Cooks, R. G.; Beynon, J. H. *Int. J. Mass Spectrom. Ion Phys.* **1976**, *19*, 179–183. (n) Green, M. M.; Mangner, T. J.; Turner, S. P.; Brown, F. J. *J. Am. Chem. Soc.* **1976**, *98*, 7082–7083. (o) Green, M. M.; McCluskey, R. J.; Vogt, J. *Ibid.* **1982**, *104*, 2262–2269.

(5) Subsequently, photoelectron photoion coincidence spectrometry (PEPICO) data have been reported suggesting a non-Boltzmann distribution of ions undergoing McLafferty rearrangement, in this case, see ref 4o. A thermal equilibrium with the ion source walls has been previously established. See ref 4e.

(6) Bushweller, C. H., personal communication. See also ref 3e.

Table I. Temperature Dependence of the Electron Impact Induced Loss of Cyclohexene from Diethyl Cyclohexylmalonate and Deuterated Analogues

compd[a,b]	temp,[c] K	$(C_7H_{12}O_4)^{+\cdot}$[d]	$(C_7H_{11}DO_4)^{+\cdot}$[d] or $(C_7H_{13}O_4)^+$	$(C_7H_{12}DO_4)^{+\cdot}$[d]	$(C_7H_{11}DO_4)^{+\cdot}/(C_7H_{12}O_4)^{+\cdot}$[e]	$(C_7H_{11}DO_4)^{+\cdot}/\{(C_7H_{11}DO_4)^{+\cdot}+(C_7H_{12}O_4)^{+\cdot}\}$[e]
8	348	100	30	3		
	408	100	25	3		
	458	100	23	2		
	508	100	21	2		
8-*cis*-2-*d*	348	100	36	8	0.092 ± 0.003	0.08 ± 0.002
	408	100	35	7	0.118 ± 0.001	0.10 ± 0.001
	458	100	34	7	0.127 ± 0.003	0.11 ± 0.002
	508	100	33	6	0.141 ± 0.001	0.12 ± 0.001
8-*trans*-2-*d*	348	100	81	21	0.56 ± 0.01	0.36 ± 0.004
	408	100	75	17	0.53 ± 0.001	0.35 ± 0.001
	458	100	69	14	0.49 ± 0.002	0.33 ± 0.001
	508	100	66	13	0.48 ± 0.002	0.32 ± 0.001

[a] Data were obtained at 70 eV, using a heated all-glass inlet system at constant temperature (175 °C) and source temperatures as indicated. Peak intensities are the average of at least three determinations at each ion source temperature and are reproducible to ±0.5 intensity units. [b] Isotopic purity was determined from the mass spectrum of the trimethylsilyl ether derivatives of the appropriate precursor alcohol. [c] Only ion source temperature was varied. See footnote *a*. [d] Raw data, averaged over three distinct sets of measurements. [e] Ratios are corrected for interfering fragmentations (formation of $C_7H_{13}O_4^+$ and $C_7H_{12}DO_4^+$, see text) and isotopic impurities (^{13}C, ^{17}O, ^{18}O, and d_0). Error limits include extreme values observed in three distinct sets of measurements.

Table II. Temperature Dependence of the Electron Impact Induced Loss of 4-*tert*-Butylcyclohexene from Diethyl *trans*-4′-*tert*-Butylcyclohexylmalonate and Deuterated Analogues

compd[a,b]	temp,[c] K	$(C_7H_{12}O_4)^{+\cdot}$[d]	$(C_7H_{11}DO_4)^{+\cdot}$[d] or $(C_7H_{13}O_4)^+$	$(C_7H_{12}DO_4)^{+}$[d]	$(C_7H_{11}DO_4)^{+\cdot}/(C_7H_{12}O_4)^{+\cdot}$[e]	$(C_7H_{11}DO_4)^{+\cdot}/\{(C_7H_{11}DO_4)^{+\cdot}+(C_7H_{12}O_4)^{+\cdot}\}$[e]
4	348	100	51	5		
	408	100	44	4		
	458	100	39	4		
	508	100	35	4		
4-*cis*-2-*d*	348	100	47	17	0.056 ± 0.006	0.05 ± 0.005
	408	100	38	14	0.036 ± 0.005	0.04 ± 0.005
	458	100	36	12	0.052 ± 0.003	0.05 ± 0.003
	508	100	33	11	0.051 ± 0.009	0.05 ± 0.008
4-*trans*-2-*d*	348	88	100	39	0.83 ± 0.02	0.45 ± 0.002
	408	97	100	33	0.76 ± 0.02	0.43 ± 0.002
	458	100	100	30	0.77 ± 0.01	0.44 ± 0.003
	508	100	96	27	0.76 ± 0.01	0.43 ± 0.003

[a] Data were obtained at 70 eV, using a heated all-glass inlet system at constant temperature (175 °C) and source temperatures as indicated. Peak intensities are the average of at least three determinations at each ion source temperature and are reproducible to ±0.5 intensity units. [b] Isotopic purity was determined from the mass spectrum of the trimethylsilyl ether derivative of the appropriate precursor alcohol. [c] Only ion source temperature was varied. See footnote *a*. [d] Raw data, averaged over three distinct sets of measurements. [e] Ratios are corrected for interfering fragmentations (formation of $C_7H_{13}O_4^+$ and $C_7H_{12}DO_4^+$, see text) and isotopic impurities (^{13}C, ^{17}O, ^{18}O, and d_0). Error limits include extreme values observed in three distinct sets of measurements.

Table III. Temperature Dependence of the Electron Impact Induced Loss of 4-*tert*-Butylcyclohexene from Diethyl *cis*-4′-*tert*-Butylcyclohexylmalonate and Deuterated Analogues

compd[a,b]	temp,[c] K	$(C_7H_{12}O_4)^{+\cdot}$[d]	$(C_7H_{11}DO_4)^{+\cdot}$[d] or $(C_7H_{13}O_4)^+$	$(C_7H_{12}DO_4)^{+}$[d]	$(C_7H_{11}DO_4)^{+\cdot}/(C_7H_{12}O_4)^{+\cdot}$[e]	$(C_7H_{11}DO_4)^{+\cdot}/\{(C_7H_{11}DO_4)^{+\cdot}+(C_7H_{12}O_4)^{+\cdot}\}$[e]
3	348	100	51	5		
	408	100	42	4		
	458	100	36	4		
	508	100	32	3		
3-*trans*-2-*d*	348	100	42	10	0.00 ± 0.01	0.00 ± 0.01
	408	100	37	9	0.01 ± 0.01	0.01 ± 0.01
	458	100	35	8	0.03 ± 0.001	0.03 ± 0.001
	508	100	33	7	0.04 ± 0.001	0.04 ± 0.001
3-*cis*-2-*d*	348	100	96	35	0.81 ± 0.01	0.45 ± 0.003
	408	100	86	27	0.77 ± 0.01	0.44 ± 0.003
	458	100	80	23	0.76 ± 0.01	0.43 ± 0.003
	508	100	74	21	0.74 ± 0.01	0.43 ± 0.003

[a] Data were obtained at 70 eV, using a heated all-glass inlet system at constant temperature (175 °C) and source temperatures as indicated. Peak intensities are the average of at least three determinations at each ion source temperature and are reproducible to ±0.5 intensity units. [b] Isotopic purity was determined from the mass spectrum of the trimethylsilyl ether derivative of the appropriate precursor alcohol. [c] Only ion source temperature was varied. See footnote *a*. [d] Raw data, averaged over three distinct sets of measurements. [e] Ratios are corrected for interfering fragmentations (formation of $C_7H_{13}O_4^+$ and $C_7H_{12}DO_4^+$, see text) and isotopic impurities (^{13}C, ^{17}O, ^{18}O, and d_0). Error limits include extreme values observed in three distinct sets of measurements.

Table IV. Temperature Dependence of the Relative Rates of Hydrogen Abstraction in the Electron Impact Induced Loss of Alkene from Malonates

compd	temp, K	$I(K_h/K_d)$[a]	rel rates of abstraction[a,b] $K_t:K_c$
8	348	1.20 ± 0.02	1:0.248 ± 0.01
	408	1.16 ± 0.01	1:0.316 ± 0.003
	458	1.19 ± 0.01	1:0.356 ± 0.001
	508	1.17 ± 0.01	1:0.394 ± 0.003
4	348	0.97 ± 0.03	1:0.12 ± 0.02
	408	1.11 ± 0.03	1:0.09 ± 0.01
	458	1.06 ± 0.02	1:0.11 ± 0.01
	508	1.07 ± 0.04	1:0.11 ± 0.02
3	348	1.23 ± 0.02	0.00 ± 0.02:1
	408	1.24 ± 0.02	0.03 ± 0.005:1
	458	1.15 ± 0.01	0.07 ± 0.002:1
	508	1.14 ± 0.01	0.10 ± 0.002:1

[a] Errors are statistically derived. [b] Relative rates of "1" are arbitrarily defined.

non-γ-hydrogen abstraction was necessary. The sixth column in these tables contains the calculated ratio of "deuterium loss" to "hydrogen loss" (i.e., $C_7H_{11}DO_4/C_7H_{12}O_4$) after deuterium (or hydrogen) abstraction from all possible abstraction sites in the deuterated isomer. These ratios were calculated from raw data, corrected for interfering fragmentations (formation of $C_7H_{13}O_4^+$ and $C_7H_{12}DO_4^+$) and isotopic impurities (^{13}C, ^{17}O, ^{18}O, and d_0). Since hydrogen–deuterium scrambling has been known to occur after electron impact ionization but before rearrangement in other systems,[7] the mass spectra of several deuterated analogues were obtained at near threshold ionization voltages (~13 eV) and the above ratios calculated for comparison. It was found that the values obtained agreed, within experimental error, with those calculated from 70-eV mass spectra data, at each corresponding ion source temperature. This result is consistent with little or no deuterium scrambling since these processes are known to predominate at low ionization voltages.[3e,7]

The $C_7H_{11}DO_4^{+\cdot}/C_7H_{12}O_4^{+\cdot}$ ratios in Tables I, II, and III can be used to calculate the relative rates of γ-hydrogen abstraction in malonates **8**, **4**, and **3**, respectively. Thus it can be written that

$$(C_7H_{11}DO_4^{+\cdot}/C_7H_{12}O_4^{+\cdot})^{348\ K}_{\mathbf{8}\text{-}cis\text{-}2\text{-}d} = \frac{K_c}{(2K_t + K_c + K_i)I} \quad (1)$$

where the fraction in parentheses is the "deuterium loss" to "hydrogen loss" ratio for malonate **8**-*cis*-*2*-*d* at an ion source temperature of 348 K, I is the average isotope effect (K_H/K_D), K_c is the average rate constant for cis γ-hydrogen abstraction, K_t is the average rate constant for trans γ-hydrogen abstraction, and K_i is the average rate constant for non-γ-hydrogen abstraction.[8] A similar equation can be formulated for the trans deuterated isomer, malonate **8**-*trans*-*2*-*d*. Thus

$$(C_7H_{11}DO_4^{+\cdot}/C_7H_{12}O_4^{+\cdot})^{348\ K}_{\mathbf{8}\text{-}trans\text{-}2\text{-}d} = \frac{K_t}{(2K_c + K_t + K_i)I} \quad (2)$$

These equations can be solved for the isotope effect (I = 1.20 ± 0.02) and the relative rates of hydrogen abstraction (K_t/K_c) at 348 K.[9] The isotope effects and relative rates of hydrogen abstraction at other ion source temperatures were separately calculated by the above method, as described earlier. The results of these calculations appear in Table IV.

Similarly, analogous equations can be derived and solved for the monodeuterated isomers of malonates **4** (**4**-*cis*-*2*-*d* and **4**-*trans*-*2*-*d*) and **3** (**3**-*trans*-*2*-*d* and **3**-*cis*-*2*-*d*) at each ion source temperature. The solution to these equations yields the isotope effects and relative rates shown in Table IV.

Table V. Percent of McLafferty Rearrangement of Diethyl Cyclohexylmalonate Proceeding through the Equatorial Conformation

compd	temp, K	% equatorial before ionization	% fragmentation through equatorial conformer: individual deriv[b]	% fragmentation through equatorial conformer: best value[c]
8-*cis*-*2*-*d*	348	95–92	92 ± 2	87 ± 3
8-*trans*-*2*-*d*			81 ± 2	
8-*cis*-*2*-*d*	408	93–89	87 ± 2	83 ± 3
8-*trans*-*2*-*d*			79 ± 2	
8-*cis*-*2*-*d*	458	91–87	85 ± 2	80 ± 3
8-*trans*-*2*-*d*			74 ± 2	
8-*cis*-*2*-*d*	508	89–84	82 ± 2	77 ± 3
8-*trans*-*2*-*d*			72 ± 2	

[a] Calculated composition before electron impact ionization, assuming ΔG = 1.7–2.1 kcal/mol and source temperature as indicated. See ref 6. [b] Calculated for each labeled compound using data and error limits in Tables I, II, and III and eq 3. [c] Value corresponds to least-squared error in combining each pair of data points.

The data shown in Tables I, II, and III can also be used to calculate the fraction of total rearrangement occurring from the equatorial conformation of malonate **8** (⟨Eq⟩) at each temperature. This calculation can be carried out with data obtained from the trans deuterated isomer of malonate **8** (**8**-*trans*-*2*-*d*) and its corresponding analogues in malonates **4** and **3** (**4**-*trans*-*2*-*d* and **3**-*trans*-*2*-*d*, respectively) or independently, with the data obtained from the cis deuterated isomer of malonate **8** (**8**-*cis*-*2*-*d*) and its corresponding analogues in malonates **4** and **3** (**4**-*cis*-*2*-*d* and **3**-*cis*-*2*-*d*, respectively). Thus, for example

$$\langle Eq \rangle = (F_r - F_{ax})/(R_{eq} - F_{ax}) \quad (3)$$

where F_r, F_{ax}, and F_{eq} are the fractions of McLafferty peak intensities corresponding to deuterium abstraction in malonates **8**-*trans*-*2*-*d*, **3**-*trans*-*2*-*d*, and **4**-*trans*-*2*-*d*, respectively, at a given ion source temperature (i.e., $C_7H_{11}DO_4^{+\cdot}/(C_7H_{11}DO_4^{+\cdot} + C_7H_{12}O_4^{+\cdot})$, at each temperature). These fractions are obtained by simple arithmetic from the $C_7H_{11}DO_4^{+\cdot}/C_7H_{12}O_4^{+\cdot}$ ratios in Tables I, II, and III and appear on these same tables. The results obtained from eq 3 at each temperature, and from both independent groups of malonates (vide supra), appear in Table V. The derivation of eq 3 has been discussed earlier.[3e]

Diethyl *trans*-4′-*tert*-Butylcyclohexylmalonate (4) and Diethyl *cis*-4′-*tert*-Butylcyclohexylmalonate (3). The relative rates of hydrogen abstraction for malonates **4** and **3**, at four ion source temperatures, are shown in Table IV.

The stereochemistry of hydrogen abstraction in diethyl *trans*-4′-*tert*-butylcyclohexylmalonate (**4**) shows a strong preference for trans equatorial hydrogen abstraction at all ion source temperatures, consistent with results reported earlier.[3e] In addition, no trend was observed in the overall stereochemistry of hydrogen abstraction as the temperature was increased from 348 to 508 K. These results are consistent with little or no change in the essential structural features of malonate **4** within the above thermal range. Hence, the rearrangement is occurring from the diequatorial chair conformer of malonate **4**, as would be predicted from solution chemistry data.

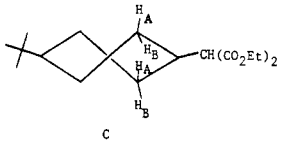
The sterochemistry of hydrogen abstraction in diethyl *cis*-4′-*tert*-butylcyclohexylmalonate (**3**) shows a very strong preference for cis equatorial hydrogen abstraction at all ion source temperatures, consistent with results reported earlier.[3e] However, unlike malonate **4**, malonate **3** shows a modest trend toward increasing trans axial hydrogen abstraction as the ion source temperature rises. Since the trans axial hydrogen cannot be approached by the carbonyl oxygen, within the requisite 1.8 Å for hydrogen abstraction,[10] this trend must reflect an increasing

(7) See, for example: (a) Carpenter, W.; Duffield, A. M.; Djerassi, C. *J. Am. Chem. Soc.* **1968**, *90*, 160–164. (b) Yeo, A. N. H.; Cooks, R. G.; Williams, D. H. *Chem. Commun.* **1968**, 1269–1270. (c) Yeo, A. N. H.; Williams, D. H. *J. Am. Chem. Soc.* **1969**, *91*, 3582–3589.

(8) Since rearrangement of malonates **8**, **4**, and **3** was found to be >98% γ-hydrogen specific, this term can be excluded (K_i = 0).

(9) See ref 3e and 3g for a detailed description.

fraction of total rearrangement occurring from a conformation different from that at 348 K, where essentially no trans axial hydrogen abstraction occurs ($K_t/K_c = 0.00 \pm 0.02$, see Table IV). A twist conformer of malonate **3**, such as C, where the ester substituent is placed within the requisite interatomic range[10] for abstraction of the originally trans axial hydrogen (H_B), may be responsible for the observed trend. Although the twist conformer



C

of cyclohexane is known to be about 5 kcal/mol less stable than the chair conformation,[11] the plurality of twist conformers available to malonate **3** and the strain introduced by a bulky axial diethylmalonate group (1.7–2.1 kcal/mol)[6] may lead to their involvement in the fragmentation process at higher temperatures. This argument is consistent with the fact that malonate **4** shows no trend, since the malonate group is in the unstrained equatorial orientation in the stable chair conformer.

Since the stereochemistries of hydrogen abstraction in malonates **4** and **3** exhibit only small changes as the ion source temperature rises, these compounds will be adequate models for the equatorial and axial conformers of malonate **8**, respectively. Moreover, these results will considerably simplify the interpretation of data obtained from the conformationally mobile malonate **8**.

Diethyl Cyclohexylmalonate (8). The relative rates of hydrogen abstraction in malonate **8**, at four ion source temperatures, are shown in Table IV.

Malonate **8** shows an overall preference for trans hydrogen abstraction at all ion source temperatures, consistent with results reported earlier.[3e] This result is also in accord with rearrangement occurring predominantly from the equatorial conformer of malonate **8A**. However, the overall stereochemistry of hydrogen abstraction exhibits a lower preference for trans hydrogen abstraction than that of malonate **4** at all ion source temperatures. In addition, unlike malonate **4**, malonate **8** shows a trend toward increasing cis hydrogen abstraction as the ion source temperature rises (see Table IV).[12] This trend is consistent with an increase in the fraction of total rearrangement occurring through the axial conformer of malonate **8B** as the ion source temperature rises, since malonate **3** rearranges with very predominant cis hydrogen abstraction at all ion source temperatures.

If the stereochemical trend observed for malonate **8** is due to a conformational change caused by an increase in ion source temperature and if the resulting conformer distribution among precursor neutrals (from which rearranging ions are formed) is preserved throughout the ionization process and up to the moment of rearrangement,[13] then the relative rates of hydrogen abstraction must exhibit an Arrhenius dependence[4n] with ion source temperature. Thus, an Arrhenius plot ($\ln K_t/K_c$ vs. $1/T$ K) was constructed with the data shown in Table IV (see Figure 1). The resulting graph confirms that in fact an Arrhenius dependency

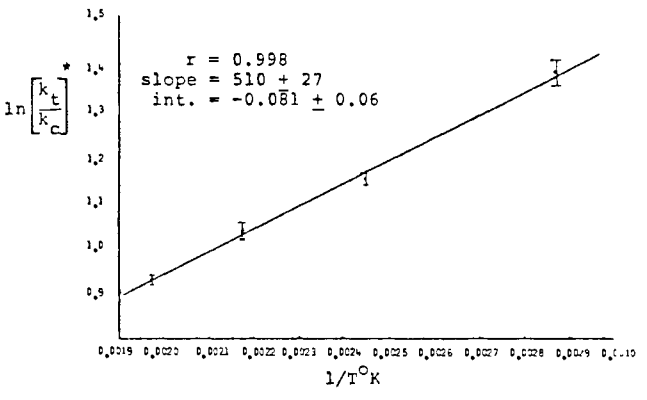


Figure 1. Temperature dependence of the relative rates of hydrogen abstraction in the electron impact induced loss of alkene from diethyl cyclohexylmalonate (**8**). The asterisk indicates a value calculated with data obtained from Table IV.

exists ($R = 0.998$) and that the above assumptions are correct. It should be pointed out, however, that the Arrhenius dependence observed here does not require a Boltzmann distribution of internal energies among rearranging ions.[14]

The data reported in Figure 1 for malonate **8** are strictly analogous to those reported by Green[4n] for rearrangement through numerous low energy conformers, and since rigid models of those conformers are not available to define the stereochemistry of elimination, Green could not attempt to correlate the trend with temperature to a specific change in the conformation of the rearranging ions. In the present study, such limitations do not exist.

The data in Tables I, II, and III can be used to calculate the fraction of total rearrangement occurring through the equatorial conformer of malonate **8A**,[3e] by using eq 3. The results of these calculations are shown in Table V.

The data in Table V show a trend toward an increasing percentage of total rearrangement occurring through the axial conformer of malonate **8B** with increasing temperature. It is also evident that the percentage of total rearrangement through the equatorial conformation correlates well with the conformational composition of malonate **8** before ionization (based on solution chemistry data).[6] This result is very important, since it establishes a relation between the temperature of the precursor neutral and the conformation through which ions rearrange.

Inspection of Table V demonstrates that, at each temperature, fragmentation through the equatorial conformer is more predominant for the cis-labeled derivative than for the trans-labeled derivative. This discrepancy is consistent with an isotope effect induced slowing of the rate of McLafferty ion formation. For example, the predominant mechanism of McLafferty ion formation from the equatorial conformer involves abstraction of a trans hydrogen or deuterium; if a trans deuterium is present, that conformer's McLafferty reaction will be slowed, allowing competing processes to intervene and leading to an underestimate of the extent of McLafferty rearrangement from the equatorial conformer of the unlabeled derivative. Similarly the predominant mechanism of McLafferty ion formation from the axial conformer involves abstraction of a cis hydrogen or deuterium—if a cis deuterium is present, that conformer's McLafferty reaction will be slowed, allowing competing processes to intervene and thus leading to an underestimate of the extent of the McLafferty rearrangement from the axial conformer of the unlabeled derivative. In this context, competing processes might constitute either fragmentations or chair–chair interconversions at rates comparable to those of the McLafferty rearrangement. The "true" extent of McLafferty fragmentation from the equatorial conformer of unlabeled **8** will be intermediate between the values calculated for the cis- and trans-labeled analogues. For purposes of this study,

(10) (a) Beard, C.; Wilson, J. N.; Budzikiewicz, H.; Djerassi, C. *J. Am. Chem. Soc.* **1964**, *86*, 269–284. (b) Djerassi, C.; von Mutzenbecher, G.; Fajkos, J.; Williams, D. H.; Budzikiewicz, H. *Ibid.* **1965**, *87*, 817–826. (c) Williams, D. H.; Wilson, J. N.; Budzikiewicz, H.; Djerassi, C. *Ibid.* **1963**, *85*, 2091–2105.

(11) (a) Hazebroek, P.; Oosterhoff, L. J. *Discuss. Faraday Soc.* **1951**, *10*, 87–93. (b) Allinger, N. L. *J. Am. Chem. Soc.* **1959**, *81*, 5727–5733. (c) Hendrickson, J. B. *Ibid.* **1961**, *83*, 4537–4547.

(12) A referee pointed out that "the trend observed for malonate **8** in Table IV may be due to participation of a twist conformer of **8** (as in the case of **3**) where the diethyl malonate substituent is placed in nearly the same distance from the originally 2-*cis* and *trans* hydrogens". However, the trend observed for malonate **8** is opposite to that of malonate **3**. While overall cis elimination increases with ion source temperature in **8**, decreasing cis elimination is observed in **3**. Meanwhile, no trend is observed in malonate **4**. Hence, although the magnitude of the trend in **8** may be attenuated by the intervention of a twist conformer, the basic qualitative conclusions of this experiment are still valid.

(13) In other words, if the rate of chair–chair interconversion after ionization is lower than the rate of rearrangement.

(14) The internal energy of rearranging ions is determined by the original internal energy of the precursor neutral (Boltzmann distribution) plus the energy deposited in excess of the ionization energy (of unknown magnitude and distribution).

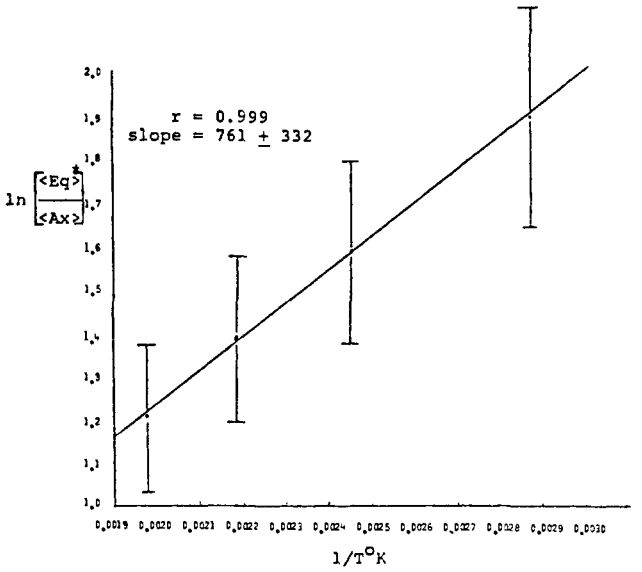


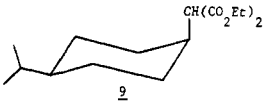
Figure 2. Temperature dependence of the relative extent of rearrangement occurring through the axial and equatorial conformers of malonate **8**. The asterisk indicates a value calculated with data obtained from Table V.

this value has been approximated by combining the data points generated from the two labeled analogues using a least-squared error minimization procedure.

The data shown in Table V can be used to calculate the enthalpy difference for chair-to-chair interconversion in malonate **8**. Thus, by using the well-known van't Hoff equation (eq 4), a plot of ln

$$\ln (\langle Eq \rangle / \langle Ax \rangle) = (-\Delta H/RT) + C \qquad (4)$$

$\langle Eq \rangle / \langle Ax \rangle$ vs. $1/T$ K was constructed (Figure 2), and the graphically determined enthalpy difference was found to be −1.51 ± 0.66 kcal/mol. Although this parameter has not been previously determined for malonate **8** in solution, the "A" value of the diethyl malonate group has been estimated from the NMR spectrum of *cis*-4′-isopropylcyclohexylmalonate (**9**) to be −1.7 to −2.1 kcal/



9

mol.[6] If it is assumed that the entropy difference for chair-to-chair interconversion of isopropylcyclohexane (2.3 eu)[15] is similar to that of malonate **8**, then the enthalpy difference for malonate **8** would be estimated to be −1.0 to −1.4 kcal/mol, in reasonable agreement with the value calculated from mass spectral data. This result further supports the notion that the observed temperature dependent fragmentation behavior of malonate **8** is directly related to the conformation through which it rearranges and that the conformations involved are mostly the axial and equatorial chair forms, with little or no rearrangement through other high-energy conformations.

Finally it should be pointed out that these results suggest that temperature-dependence studies are useful in the qualitative description of the electron impact induced behavior of mobile systems, but they do not support the use of mass spectrometry as a tool for obtaining gas-phase thermodynamic data. This fact becomes evident in the determination of the enthalpy difference of chair interconversion for malonate **8**, which yields an uncertainty of ±45% within 95% confidence limits (2σ), −1.51 ± 0.66. However, the high uncertainty is due primarily to the inherently small changes in the conformational composition of malonate **8** during rearrangement (see Table IV), within the thermal range used.

Conclusions

These experiments have led to an important empirical observation. The conformational distribution from which hydrogen abstraction occurs in the McLafferty rearrangement of these compounds is closely correlated with that predicted from solution chemistry data and ion source temperature. This result, if shown to be general, will facilitate interpretation of the temperature dependence of the mass spectra of conformationally mobile systems and the prediction of the influence of stereochemistry on the course of electron impact induced fragmentations. In addition these experiments have demonstrated a viable technique for detecting and quantitating relatively small changes in the conformer population among fragmenting ions. This will permit further studies of the influence of additional instrumental parameters and other ionization techniques on conformer population, with the long-range goal of defining conditions most conducive to discriminating among stereoisomers, based on their mass spectral behavior.

Experimental Section

All deuterated and nondeuterated malonates were prepared as previously described.[3a,c] Mass spectra were obtained from an AEI-MS902 mass spectrometer, using a heated all-glass inlet system; hot box and inlet temperatures were maintained at a constant 170–175 °C, while the ion source temperature was set at the temperatures indicated in Tables I, II, and III.

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Registry No. **3**, 66821-91-8; **3** (radical cation), 90026-13-4; **3**-*trans*-*2-d*, 57340-69-9; **3**-*trans*-*2-d* (radical cation), 90026-09-8; **3**-*cis*-*2-d*, 57340-68-8; **3**-*cis*-*2-d* (radical cation), 90026-10-1; **3**-d_4, 89959-89-7; **3**-d_4 (radical cation), 90026-11-2; **4**, 66821-87-2; **4** (radical cation), 90026-12-3; **4**-*cis*-*2-d*, 57340-66-6; **4**-*cis*-*2-d* (radical cation), 90026-06-5; **4**-*trans*-*2-d*, 57340-67-7; **4**-*trans*-*2-d* (radical cation), 90026-07-6; **4**-d_4, 89959-88-6; **4**-d_4 (radical cation), 90026-08-7; **8**, 2163-44-2; **8** (radical cation), 89959-91-1; **8**-*cis*-*2-d*, 70473-24-4; **8**-*cis*-*2-d* (radical cation), 90026-04-3; **8**-*trans*-*2-d*, 70473-25-5; **8**-*trans*-*2-d* (radical cation), 90026-05-4; **8**-d_4, 89959-87-5; **8**-d_4 (radical cation), 89959-90-0; deuterium, 7782-39-0; hydrogen, 1333-74-0.

(15) (a) Booth, H.; Everett, J. R. *J. Chem. Soc., Perkin Trans. 2* **1980**, 255–259. (b) Allinger, N. L.; Hirsch, J. A.; Miller, M. A.; Tyminski, I. J.; Van Catledge, F. A. *J. Am. Chem. Soc.* **1968**, *90*, 1199–1210.