

**Applications of  $^{13}\text{C}$  NMR Spectroscopy. 26.<sup>1</sup> Activation Parameters for the Degenerate Cope Rearrangement of Barbaralane and 3,7-Disubstituted Barbaralanes**

Harald Günther,\* Jan Runsink,<sup>†</sup> Hans Schmickler,<sup>†</sup> and Peter Schmitt

Fachbereich 8, OC II, University of Siegen, D-5900 Siegen, West Germany

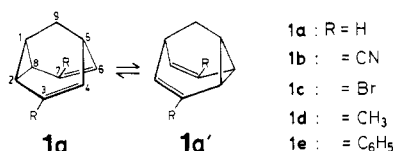
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The activation parameters for the degenerate Cope rearrangement of barbaralane and three 3,7-disubstituted barbaralanes ( $R = R' = \text{CN}, \text{Br}, \text{CH}_3$ ) have been determined by  $^{13}\text{C}$  NMR spectroscopy. For the parent system  $E_a = 7.71$  kcal/mol,  $\log A = 12.90$ ,  $\Delta H^\ddagger = 7.32$  kcal/mol, and  $\Delta S^\ddagger = -0.73$  eu. These are an average of two independent measurements at 20 and 100.6 MHz. The cyano group has no significant effect on  $\Delta H^\ddagger$ , while Br and  $\text{CH}_3$  increase  $\Delta H^\ddagger$  by 0.7 and 2.1 kcal/mol, respectively. The mechanistic implications of these results are discussed.

**Introduction**

The study of substituent effects on rate constants of fluxional systems has several interesting aspects. Firstly, theoretical models that predict substituent effects on energy barriers or enthalpy differences can be tested and, secondly, very subtle substituent effects on equilibrium constants can be measured if the system is nondegenerate and an equilibrium shift can be observed. Today, dynamic  $^{13}\text{C}$  FT-NMR spectroscopy provides a powerful tool for such investigations.<sup>2</sup>

Recent interest in the synthesis of substituted semibullvalenes<sup>3</sup> prompts us to report here results of a dynamic  $^{13}\text{C}$  NMR study of the degenerate Cope rearrangement of barbaralane ( $1a \rightleftharpoons 1a'$ ) and several 3,7-disubstituted barbaralanes ( $1b-d$ ).



The parent system  $1a$  belongs to the family of bridged homotropilidenes that has already found considerable attention by various dynamic NMR studies.<sup>4a-e</sup> Especially theoretical results indicating that suitably substituted derivatives—for example 2,4,6,8-tetracyanosemibullvalene—might show “negative activation energies” for their hypothetical valence tautomerism, i.e., homoaromatic

character,<sup>5,6</sup> have motivated synthetic chemists to verify this prediction experimentally. In this context the barrier-raising or lowering effect of substituents at various positions of the cisoid homotropilidene skeleton is of interest and the present work provides such data for  $1a$ .

**Results**

The fluxional system  $1a \rightleftharpoons 1a'$  so far has only been investigated by  $^1\text{H}$  NMR, taking  $^1\text{H}$ ,  $^1\text{H}$  spin-spin coupling into account by a first-order approach.<sup>4d</sup> Since complications through spin-spin coupling are absent in  $^1\text{H}$ -decoupled  $^{13}\text{C}$  spectra and a much larger temperature range can be studied due to the increased  $^{13}\text{C}$  chemical shift scale,  $1a$  was included in the present work. The reliability of our

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\* Present Address: Institut für Organische Chemie der Rheinisch-Westfälischen Technischen Hochschule Aachen.

<sup>†</sup> Present address: Institut für Organische Chemie, University of Cologne.

**Table I.**  $^{13}\text{C}$  Chemical Shifts (ppm) of Barbaralane (1a) and 3,7-Disubstituted Barbaralanes (1b-d) in the Fast (High Temperature) and Slow (Low Temperature) Exchange Region<sup>a</sup>

	R	T, °C	C-1	C-2,8	C-3,7	C-4,6	C-5	C-9	C(R)
1a	H	+32	24.7	73.9	121.3	73.9	24.7	18.2	
		-127	18.6	22.1	121.4	125.2	30.3	17.9	
1b	CN	+34	24.5	80.7	108.7	80.7	24.5	15.0	117.5
		-125	18.1	23.9	107.4	139.4	30.7	14.4	119.6
1c	Br	+34	27.6	77.7	113.4	77.7	27.6	17.0	
		-114	21.4	30.2	113.5	124.8	33.7	16.7	
1d	CH <sub>3</sub>	+34	23.6	72.4	128.2	72.4	23.6	19.4	23.9
		-101	17.6	24.4	128.3	120.1	29.7	19.1	24.0

<sup>a</sup> Internal reference, Me<sub>4</sub>Si.

conclusions for the substituted systems is thereby further improved, since any systematic errors that might arise are largely cancelled if all systems are measured under identical conditions.

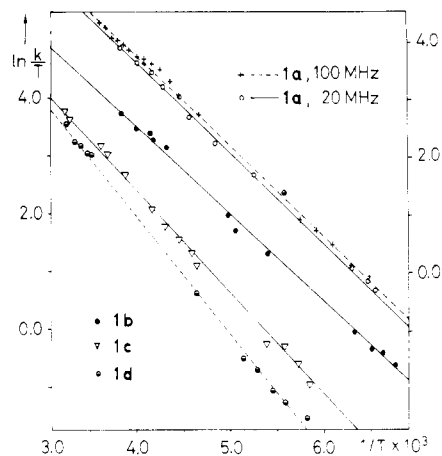
The  $^{13}\text{C}$  NMR spectra of 1a-d yield two simple equally populated two-site exchange systems (C-2,8/C-4,6, and C-1/C-5) with chemical shift differences of ca. 2000 and 200 Hz at 20 MHz, respectively. Spectra were run in the fast and slow exchange limit, omitting the coalescence region, where the lines are several hundred hertz wide, for sensitivity reasons. Rate constants  $k$  were calculated from the exchange-broadened linewidths at half-height,  $\Delta_{\text{ex}}$  (Hz), following eq 1 and 2 with  $\delta\nu$  (Hz) as the chemical shift difference between the two sites.

$$\text{slow exchange: } k = \pi\Delta_{\text{ex}} \quad (1)$$

$$\text{fast exchange: } k = \pi\delta\nu^2/2\Delta_{\text{ex}} \quad (2)$$

The natural linewidth  $\Delta$  (Hz) was obtained from the signals of C-3,7 and C-9 that are not affected by the chemical exchange process. Exchange broadening  $\Delta_{\text{ex}}$  was derived from the measured linewidths  $\Delta_{\text{exp}}$  by subtracting  $\Delta$ . The chemical shift difference  $\delta\nu$  was taken from the spectra at lowest temperature. Only in the case of 1b enough data points in the slow exchange limit were available to determine the temperature dependence of the  $^{13}\text{C}$  chemical shifts. The temperature effect on  $\delta$  ( $^{13}\text{C}$ ) is small (6.2 Hz or 0.3% between 148 and 158 K) and the kinetic parameters calculated with and without temperature dependent  $\delta\nu$  agreed within experimental error (see Experimental Section). Therefore, the use of uniform  $\delta\nu$  values for the other compounds, where less polar or even nonpolar substituents are present, does not introduce serious errors. This conclusion is further justified by the fact that the resonances measured in the fast exchange limit (32 °C) agree within experimental error with the mean values for the corresponding low-temperature (slow exchange limit) results (cf. data for C-1/C-5, and C-2,8/C-4,6 in Table I).<sup>8</sup> For 1d an independent analysis was performed by using a complete line shape calculation (see Experimental Section) that yielded the same results as obtained by the application of eq 1 and 2. Furthermore, in the case of 1a we took advantage of the possibility to repeat the measurements at 100.6 MHz in order to test the reproducibility of our results.

The  $^{13}\text{C}$  NMR data of 1a-d in the fast and slow exchange region at high and low temperature, respectively, are given in Table I. Table III (see supplementary material) shows the line widths measured at various temperatures as well as the chemical shift differences and the calculated rate constants. Eyring plots for the rate constants are given in Figure 1 and the kinetic parameters are

**Figure 1.** Eyring diagrams for the degenerate Cope rearrangement of 1a-d; right  $\ln(k/T)$  scale 1a, left scale 1b-d.

collected in Table II. Due to the simple form of eq 1 and 2, in addition to the statistical error analysis, a more rigorous error treatment that considers the error in  $k$  and  $T$  at the highest and lowest temperature used<sup>9</sup> was possible (see Experimental Section). These errors (in percent) are given in parenthesis in Table II which also contains results for 3,7-diphenylbarbaralane (1e)<sup>10</sup> that are relevant to the present study.

## Discussion

Because  $\Delta G^\ddagger$  is the most reliable parameter obtained from dynamic NMR studies, most discussions so far have focussed on free enthalpies. As will be shown below, however, the extraction of  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  values is essential if one wants to understand the subtle substituent effects operating in systems like  $1a \rightleftharpoons 1a'$ . In addition, the comparison with theoretically calculated energies must be based on enthalpy quantities.

Our results for 1a are in fair agreement with those of the earlier  $^1\text{H}$  work,<sup>4d</sup> where  $E_a = 8.6 \pm 0.2$  kcal/mol and  $\log A = 13.6 \pm 0.3$  was found and a 90% confidence limit of  $\pm 1$  kcal/mol was estimated for  $E_a$ . From the experimental data given there one calculates  $\Delta H^\ddagger = 8.24$  kcal/mol and  $\Delta S^\ddagger = 2.33$  eu. Both values are clearly higher than our results. Since the temperature range for our dynamic  $^{13}\text{C}$  NMR study is more than 5 times that used in the  $^1\text{H}$  work, we regard the  $^{13}\text{C}$  results to be the more reliable ones, especially since the two independent  $^{13}\text{C}$  measurements performed at two different field strengths are in perfect agreement.

A further point of interest concerns the sign of the activation entropy measured for the Cope rearrangement of bullvalene and 1a. Considering symmetry numbers<sup>11</sup> or the number of independent reaction pathways available,<sup>12</sup> a small positive  $\Delta S^\ddagger$  is expected for bullvalene. This is indeed found experimentally.<sup>4b</sup> For 1a, on the other hand, the ground state has  $C_s$  symmetry, the transition state  $C_{2v}$  symmetry, and only one reaction pathway is available. One therefore expects a negative  $\Delta S^\ddagger$  or  $\Delta S^\ddagger = 0$ . The small negative  $\Delta S^\ddagger$  values found for 1a-d are thus in agreement with these expectations that are based solely on statistical considerations.

Turning now to the substituent effects for 1a-d we first recall that three principle structures have to be considered

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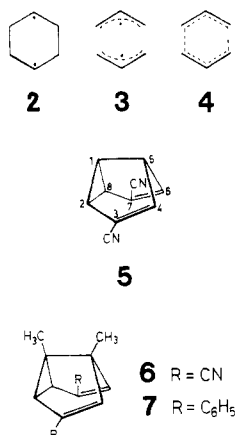
(8) An accidental compensation of the temperature gradients for the chemical shift of both sites cannot be excluded but is highly unlikely.

Table II. Activation Parameters<sup>a</sup> for the Degenerate Cope Rearrangement in Barbaralane (1a) and 3,7-Disubstituted Barbaralanes (1b-e) as Determined by <sup>13</sup>C NMR Spectroscopy at 20 MHz<sup>b</sup>

	1a	1b	1c	1d	1e
$E_a$	H 7.72 ± 0.05 7.70 ± 0.08 <sup>c</sup>	CN 7.45 ± 0.09	Br 8.49 ± 0.18	CH <sub>3</sub> 9.87 ± 0.12	C <sub>6</sub> H <sub>5</sub> <sup>e</sup>
log A	12.86 ± 0.06 12.94 ± 0.08	12.42 ± 0.12	12.26 ± 0.18	13.04 ± 0.12	
$\Delta H^\ddagger$	7.34 ± 0.05 (1.8) 7.30 ± 0.08 (1.6)	7.05 ± 0.09 (1.8)	8.06 ± 0.17 (1.5)	9.42 ± 0.12 (1.5)	6.8 ± 0.3
$\Delta S^\ddagger$	-0.87 ± 0.25 (99.7) -0.59 ± 0.37 (70.9)	-2.97 ± 0.56 (29.5)	-3.86 ± 0.79 (16.9)	-0.41 ± 0.53 (78.8)	-8.3 ± 1.2
$\Delta G^\ddagger_{298}$	7.60 (0.7)	7.90 (0.9)	9.21 (0.9)	9.54 (1.0)	9.3
$r^d$	0.999	0.998	0.997	0.999	

<sup>a</sup> With statistical errors; calculated errors (in %, cf. Experimental Section) in parenthesis. <sup>b</sup>  $E_a$ ,  $\Delta H^\ddagger$ , and  $\Delta G^\ddagger_{298}$  in kcal/mol,  $\Delta S^\ddagger$  in eu. <sup>c</sup> Second entry 100.61 MHz analysis. <sup>d</sup> Correlation coefficient of Arrhenius and Eyring plot. <sup>e</sup> Reference 10.

for the transition state of the Cope rearrangement in bridged homotropilidenes: the diradical ("diyl") structure 2 with bond formation as the initial step, the diallyl structure 3 with bond breaking as the initial step, and 4 for a true pericyclic process.<sup>13-15</sup> 2-4 represent limiting cases and in practice the character of the transition state of a particular system is determined by geometry and by substituents.



With respect to these alternatives, simple MO arguments show that the strongest 3,7-substituent effects should result for 2, where essentially the radical stabilizing ability of the substituent is effective. For 3, on the other hand, no substituent effect is expected, since the central carbons of the allyl moieties bear the node in the highest occupied molecular orbital. An intermediate situation is met for 4, where symmetry allowed interactions between what is essentially a benzene  $E_{1g}$  orbital and the appropriate linear combination of the substituent LUMO's are possible. Their effectiveness, however, depends on the relative energy of the mixing orbitals in these subsystems.

Our results for 1b show that cyano groups in the 3,7-position have no pronounced effect on the rate of the barbaralane rearrangement, in contrast to 2,6-disubstitu-

tion.<sup>16</sup> In principle, relative to the parent system, this finding can be interpreted in three ways: (i) ground-state and transition-state free enthalpies are unchanged; (ii) both states are stabilized; (iii) both states are destabilized by the same amount. In this respect recent calculations for 3,7-dicyanosemibullvalene (5)<sup>17</sup> are of interest, because they allow us to decide between these alternatives. For 5, a ground-state stabilization of 8.2 kcal/mol was obtained, and a similar stabilization energy can be expected for 1b.<sup>18</sup> It then results that the transition state for 1b  $\rightleftharpoons$  1b' must be stabilized by the same amount and alternative ii is correct. In addition, the calculations show that the transition state for 5  $\rightleftharpoons$  5' is stabilized by 4.5 kcal/mol with respect to that of the rearrangement of the parent hydrocarbon, i.e., in the semibullvalene case, each cyano group only contributes ca. 2.0 kcal/mol transition-state stabilization. This is only half of the stabilization energy estimated for 1b and suggests that the transition state for 5  $\rightleftharpoons$  5' has more diallylic character than that for 1b  $\rightleftharpoons$  1b', in accord with Dewar's statement<sup>6</sup> that "evidently the transition state becomes increasingly like a pair of allyl radicals as the length of the bridge (i.e., the fragment between C-1 and C-5 of the homotropilidene partial structure) is decreased".

Experimental data for 1,5-dimethyl-3,7-dicyanosemibullvalene (6) have just become available,<sup>19</sup> which further support these arguments. The increase of  $\Delta H^\ddagger$  was indeed established ( $\Delta H^\ddagger = 0.8$  kcal/mol in comparison with the parent semibullvalene). It is smaller than that calculated, however, dimethyl substitution in positions 1 and 5 may lower the activation barrier, and both the calculated and the experimental data sets are subject to smaller errors. Comparing only the experimental results, there is definitely a barrier increase on 3,7-dicyano substitution for semibullvalene, which is absent for the barbaralane. Furthermore, this increase is practically due to an enthalpy change, while the activation entropy is not significantly affected, as one expects for a linear substituent like the cyano group.

As for the mechanistic alternative 2 discussed at the beginning, 2,5-dicyano substitution lowers the barrier of

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(15) Most recently, Quast and Christ [Quast, H.; Christ, J. *Angew. Chem.* 1984, 96, 606; *Angew. Chem., Int. Ed. Engl.* 1984, 23, 604] presented the first experimental evidence for an unsymmetrical transition state in a Cope rearrangement of a compound which could also rearrange via a symmetrical transition state: for 1,5-dimethyl-2,6-dicyanosemibullvalene structure 3 appears to be an intermediate; see also McIver [McIver, J. W., Jr. *Acc. Chem. Res.* 1973, 7, 72] for a discussion of unsymmetric transition states in pericyclic reactions.

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(18) A referee has pointed out that the stabilization energy for the cyano group is probably smaller than the value calculated. While this is true for isolated double bonds, the situation for a more complicated molecule like 5, where through-bond and through-space interactions are possible, might well be different. Furthermore, our argument in favor of alternative ii does not depend on the absolute value of the stabilization energy.

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1,5-hexadiene rearrangements by 10.8 kcal/mol.<sup>13</sup> Taking into account a ground-state stabilization by 8.2 kcal/mol, as above, one finds a stabilization effect of 9.5 kcal/mol per cyano group, which is even higher than the average radical stabilization effect of  $6.4 \pm 2$  kcal/mol<sup>13</sup> extracted from different sources and more than twice the value estimated for the barbaralane or the semibullvalene system. This supports the opinion that the transition state for the Cope rearrangement of 1,5-hexadiene is closer to the diyl limiting case than that for the bridged homotropilidene or bullvalene type rearrangements.

Considering now the activation enthalpy of the phenyl-substituted system  $1e \rightleftharpoons 1e'$ , a similar compensating effect for ground-state and transition-state stabilization must be present. Since no data for the ground state are available, a discussion of the quantitative aspect as given above for the cyano group is not possible. However, the data of Müllen and Sauer,<sup>19</sup> who found a  $\Delta H^\ddagger$  of +1.3 kcal/mol for 1,5-dimethyl-3,7-diphenylsemibullvalene (7), again show that a strongly conjugating substituent in position 3,7 of semibullvalene stabilizes the transition state less than the ground state, while for 1b and 1e the stabilization for both states is the same. This supports anew the higher diallyl character of the Cope rearrangement in semibullvalene.

The results for  $1e \rightleftharpoons 1e'$  also show that different  $\Delta G^\ddagger$  values for 1a and 1e result from entropy changes. While experimental  $\Delta G^\ddagger$  values are often preferred because of their higher accuracy, the discussion of substituent effects based on  $\Delta G^\ddagger$  values alone may thus be misleading.

A barrier increase is found for 1c (+0.7 kcal/mol) and is more pronounced for 1d (+2.1 kcal/mole) if  $\Delta H^\ddagger$  values are considered. Both bromine and methyl are electron-rich substituents, the latter even electron releasing, a property which should destabilize the transition state according to the calculations.<sup>5,6</sup> For the methyl group, the effect found here is smaller than that observed in the case of 2,6-dimethylhomotropilidene, where  $\Delta H^\ddagger$  is +5.9 kcal/mol.<sup>10</sup> This trend can be understood on the basis of the change in local electron density,  $\Delta q$ , induced by passing from the reactant to the transition state. For position 3  $\Delta q$  increases<sup>6</sup> (that means position 3 becomes more negative) in the order semibullvalene ( $\Delta q_3 = 66 \times 10^{-4}$ ), 1a ( $\Delta q_3 = 322 \times 10^{-4}$ ), and bullvalene ( $\Delta q_3 = 772 \times 10^{-4}$ ). Thus, stronger electron repulsion with an electron-releasing substituent should destabilize the transition state in the same order. Since it can be assumed that the cisoid transition state of the homotropilidene rearrangement<sup>4a</sup> is closer in geometry and thus electronic structure to the transition state of the bullvalene rearrangement than to that of the other systems, a similar or even larger  $\Delta q_3$  term can be expected, thus leading to a stronger destabilization effect by the methyl group.

### Conclusion

Substitution of barbaralane at the 3,7-position leads to moderate changes for the activation parameters of its valence tautomerism, in accord with earlier estimates obtained for substituents like Cl and OCH<sub>3</sub> by Hoffmann.<sup>20</sup> Only electron-releasing groups like CH<sub>3</sub> have a significant effect on  $\Delta H^\ddagger$ , which increases upon substitution. Electron-withdrawing substituents like CN and phenyl stabilize ground and transition state by the same amount and variations in  $\Delta G^\ddagger$  result from entropy changes. The ex-

perimental observations are in agreement with theoretical predictions<sup>5,6,17</sup> and lend support to the statement<sup>6</sup> that the transition state of the Cope rearrangement in semibullvalene has more diallyl character than that in barbaralane or bullvalene.

### Experimental Section

The compounds were gifts from Prof. Dr. W. R. Roth and Dr. J. Hedding, University of Bochum, and their purity was checked by <sup>13</sup>C and <sup>1</sup>H NMR.

For the rate measurements, the following solvents and concentrations were used: 1a THF/CS<sub>2</sub> (1:5), 0.62 M; 1b CHCl<sub>3</sub>/CD<sub>2</sub>CDCl<sub>3</sub> (5:1:1), 0.30 M; 1c THF/CS<sub>2</sub> (1:5), 0.24 M; 1d THF/CS<sub>2</sub> (1:5), 0.50 M. <sup>13</sup>C NMR spectra were obtained under conditions of <sup>1</sup>H broad band decoupling with a Varian CFT 20 spectrometer operating at 20 MHz, using 8-mm od sample tubes and a <sup>2</sup>H lock with THF-*d*<sub>8</sub>. A sweep width of 4 kHz was used and 3000 transients with 4 K data points were accumulated. The temperature was recorded before and after each measurement under <sup>1</sup>H-decoupling conditions within a nonspinning sample tube filled with acetone using a calibrated gold/silver thermocouple. During data acquisition a second thermocouple situated in the N<sub>2</sub> cooling gas stream immediately beneath the sample tube was used to monitor temperature constancy. For the measurement at 100.61 MHz a Bruker WH 400 spectrometer equipped with the temperature control unit BVT-1000 was used. The latter was calibrated with a PT 100 thermoresistor in a nonspinning sample tube.

For the calculation with eq 1 and 2 the frequency parameters given in Table III were used. For 1a at 100.61 MHz the signals of C-1,5 could only be analyzed in the slow exchange limit because of line overlap at higher temperatures. The complete lineshape analysis performed for 1d was based on the Gutowsky-Holm equation<sup>21</sup> employing a standard program.<sup>22</sup> The results ( $E_a = 9.86 \pm 0.10$  kcal/mol,  $\log A = 13.02 \pm 0.10$ ,  $\Delta H^\ddagger = 9.41 \pm 0.10$  kcal/mol,  $\Delta S^\ddagger = -0.48 \pm 0.43$  eu) are virtually identical with those obtained by the use of eq 1 and 2 (cf. Table II). For 1b the following chemical shift differences  $\delta\nu$  (2,4) were measured in the slow exchange limit: 148 K 2309.8 Hz; 251 K 2307.6 Hz; 255 K 2305.4 Hz; 258 K 2303.6 Hz. On this basis the  $\delta\nu$  (2,4) values at the higher temperatures were extrapolated assuming linear behavior and the following activation parameters were calculated:  $E_a = 7.41 \pm 0.09$  kcal/mol;  $\log A = 12.37 \pm 0.12$ ;  $\Delta H^\ddagger = 7.03 \pm 0.09$ ;  $\Delta S^\ddagger = -3.07 \pm 0.55$  eu. The natural line width was determined in all measurements at 20 MHz from the C-3 signal (cf. Table III) and agreed within 20% with the Me<sub>4</sub>Si line width. For 1a a 0.6-Hz difference was observed for the line widths of C-3 on the one hand and C-1,5 and C-2,4 on the other at 262 K where  $\Delta_{ex} = 0$ . This was ascribed to nonuniform decoupler power and the C-3 line widths measured were corrected for this difference. At 100.61 MHz and below 244 K nonuniform decoupler power again resulted in different natural line widths in the high- and low-field region of the spectrum as determined from the signals of C-9 and C-3,7, respectively. In the fast exchange limit the arithmetic mean of these linewidths was used because the signal of C-2,4 appears in the central part of the spectrum.

The errors given in Table II are statistical errors that result from the regression analysis of the Arrhenius and Eyring plots, respectively. In addition, the error treatment for kinetic parameters given by Benson<sup>9</sup> was used for the Eyring parameters. It is based on the errors in  $k$  and  $T$  at the highest and lowest temperature employed for the measurements.<sup>23</sup> The error in  $k$  was 10% at 20 MHz and 5% at 100.6 MHz owing to the error in line width. The error in  $T$  was estimated to be  $\pm 1$  K. The percental errors determined in this way are given in parenthesis in Table II.

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Registry No. 1a, 14693-11-9; 1b, 93783-08-5; 1c, 82093-56-9;

1d, 60643-98-3; 1e, 60643-97-2.

**Supplementary Material Available:** Table III;  $^{13}\text{C}$  chemical shift differences  $\delta\nu$  (Hz), temperature-dependent line widths (Hz), and calculated rate constants  $k$  ( $\text{s}^{-1}$ ) of 1a-d (2 pages). Ordering information is given on any current masthead page.

## Studies on the Reaction of Mitomycin C with Potassium Thiobenzoate under Reductive Conditions

Mary Bean<sup>1a</sup> and Harold Kohn<sup>\*1b</sup>

Department of Chemistry, University of Houston—University Park, Houston, Texas 77004

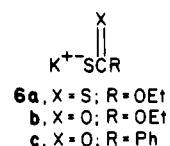
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Treatment of mitomycin C (1) with the ambident nucleophile potassium thiobenzoate (6c) under reductive conditions (sodium dithionite) at approximately neutral pH led to the formation of predominantly *trans*-aziridine ring-opened mitosene adducts. The ratio of *trans* to *cis* derivatives was greater than 9:1. The principal site of reaction in reduced 1 was determined to be carbon-1. The ratio of carbon-1 monosubstituted adducts vs. carbons-1,10 disubstituted adducts was greater than 10:1. The structural identity of each product was confirmed by high-field  $^1\text{H}$  NMR studies as well as by additional spectral analyses. In all cases, substitution at carbons-1 and -10 occurred with attack at the sulfur terminus. The implications of these reactions in relation to the mode of action of mitomycin C (1) are discussed. Moreover, various NMR relationships have been established which provide useful information concerning the conformation of these mitosene adducts.

Mitomycin C (1) is a member of a class of antibiotics that exhibit potent, specific antitumor activity.<sup>2</sup> The cytotoxic effects of the mitomycins have been attributed to the bioreductive alkylation of DNA.<sup>3</sup> In the most widely accepted mechanism (Scheme I), attachment of the drug to the genetic material is conjectured to occur at carbons-1 and -10 of 1.<sup>4</sup> Special emphasis has been placed on the potential ability of mitomycin C (1) to cross-link complementary strands of DNA.<sup>2,3</sup>

Studies of the reactions of various nucleophiles<sup>5-13</sup> with 1 under reductive conditions have generally supported this mechanism (Scheme I). Initial covalent linkage to 3 is

believed to proceed by an  $\text{S}_{\text{N}}1$ -type reaction at carbon-1. This pathway suggests the formation of equal amounts of carbon-1 *cis*- and *trans*-substituted products. However, a variety of *cis/trans* product ratios have been observed. Treatment of reduced 1 with either potassium ethyl xanthate<sup>6,7</sup> (6a) or potassium ethyl monothiocarbonate<sup>8</sup>



(6b) gave the *cis*- and *trans*-1,2-disubstituted mitosenes in the expected 1:1 ratio. On the other hand, reaction of reduced mitomycin C (1) with 5'-guanylic acid led to the isolation of solely the *cis* adduct,<sup>12</sup> while treatment with d(GpC) gave only the *trans* derivative after enzymatic degradation.<sup>11</sup>

In this paper, we investigate the role of the nucleophile in determining the eventual stereochemistry at carbon-1 in ring-opened mitosenes. We describe the reaction of mitomycin C (1) with the ambident reagent potassium thiobenzoate<sup>14</sup> (6c), a nucleophile similar to that used in previous studies<sup>6-8</sup> but of reduced activity. Under reductive conditions at approximately neutral pH, 1,2-*trans*-substituted adducts were the predominant products. This surprising result has aided our interpretation of the varying product ratios obtained in related investigations. Moreover, detailed analysis of the high-field  $^1\text{H}$  NMR data for these and comparable compounds has suggested that a preferred pyrrolidine ring conformation exists in both *cis*- and *trans*-disubstituted mitosene derivatives.

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