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Thermal Isomerization of Heterofulvenes. Dynamic Nuclear Magnetic Resonance Study

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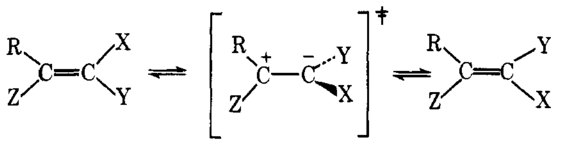
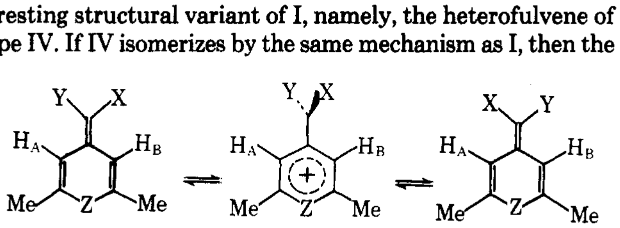
The dynamic behavior of heterofulvenes, derivatives of 2,6-dimethyl-γ-pyrone, -γ-thiopyrone, and *N*-butyl-2,6-dimethyl-γ-pyridone (IV), were investigated by variable temperature NMR technique. The observed process is the thermal isomerization about the exocyclic double bond of the above compounds. In each case the substituents on the exocyclic double bond are two different electron-withdrawing groups (NO_2, $COCH_3$, CO_2CH_3, $CONH_2$, CN) and H. The NMR line shape of the chemically nonequivalent H-3 and H-5 was studied. Complete line analysis was carried out on methyl 2,6-dimethyl-d_6-4*H*-pyran-4-ylidenenitroacetate (2) in HMPT-d_{18} and acetonitrile-d_3. A pronounced decrease in the enthalpy of activation ($\Delta\Delta H^{\ddagger}$ = 3.2 kcal/mol) was found in acetonitrile as compared to HMPT. The low entropies of activation (−21.7 and −27.4 eu) indicate extensive charge separation in the transition state for the isomerization process. The rate constants at the coalescence temperature for 22 additional compounds were determined, and the corresponding rate constants at 298 K were evaluated by applying the entropies found in the total line shape analysis experiments. This allows for the comparison of rate and activation data for the various compounds at a standard temperature. The isomerization was found to be moderately accelerated by polar solvents with a maximum rate enhancement factor of 80. The reaction rate is sensitive to the nature of the exocyclic substituents in three measurable series. The rates are enhanced in the order of the σ_R^- values of the substituents with a ρ value of ca. 8. The hetero ring atoms were found to accelerate the isomerization in the decreasing order of N > S > O which is at variance with previous results in similar, but acyclic, systems.

It has been demonstrated by us,[1] and also by others,[2,3] that some olefins may be thermally isomerized at rates which are on the NMR time scale. The double bond of such an olefin (I) is polarized by electron-withdrawing groups (X, Y), and an electron-releasing group (Z). The rates of the isomerization about the C=C double bond (I ⇌ III) were found to be extremely sensitive to structural factors.[1] Generally, this was taken as an indication that a charged transition state of type II is involved in the process. Approximate structure–reactivity relationships support the dipolar nature of the transition state (II).[1]



I II III

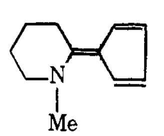
The present work concerns the dynamic behavior of an interesting structural variant of I, namely, the heterofulvene of type IV. If IV isomerizes by the same mechanism as I, then the thermal transition state V, analgous to II, may be invoked. Such a transition state is unique in that it creates an empty p orbital on C-4 which may now induce a cyclic delocalization of the 6π electrons of the heterocyclic ring. Since the corresponding charged heterocycles, pyrylium, pyridinium, and thiopyrylium cations exhibit extra stability, it would be of interest to find out whether the transition state (V) would respond to the potential stabilization of the 6π electrons, absent in the acyclic transition state II. Calculations (MINDO/2) by Dewar[4] of rotational barriers about the carbon–carbon double bond in methylenecyclopropene systems also bear on the above-mentioned point.



IV V VI

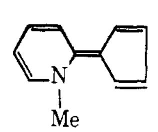
X, Y = CN, CO_2Me, COMe, $CONH_2$, NO_2, H
Z = S, O, N-Bu

Experimental results which shed light on this phenomenon can be found in the NMR work of Crabtree and Bartelli.[5] These authors have studied the systems IX and X where both termini of the double bond are incorporated into rings, which, in the transition state for isomerization about the C=C double bond, can be described as aromatic. Thus the difference in E_a for the thermal isomerization about the exocyclic double bond between IX and X reflects, in the author's opinion, the extra stability which is due to the formation of the pyridinium ring in the transition state. Although the difference (8.2 kcal/mol) is substantial, it amounts to only ca. ¼ of the resonance energy of pyridinium. This deficiency in stabilization was attributed to the extra energy required for charge separation in the transition state.



IX

E_a = 19.6 kcal/mol

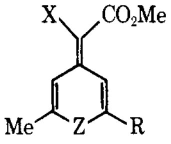


X

E_a = 11.4 kcal/mol

The work which is most closely related to the present one, although limited in scope, is that of Seitz et al.[6] and Jackman et al.[3] The results are summarized in Table I. For both XIb

Table I. Free Energy of Activation for Isomerization about the Exocyclic Double Bond in XI as Determined by NMR



XI

	X	R	Z	$\Delta G^{\ddagger}$, kcal/mol	Temp, K	Solvent	Ref
a	CN	Me	N-Bu	20.1	298	HMPT	3
				17.7	*a*	*a*	6
b	CN	Me	O	>27	*a*	HMPT	3
					>160[b]	Me_2SO	6
c	CN	Me	S	>27	*a*	HMPT	3
d	CN	Ph	N-Me	20.0	298	HMPT	3
e	CO_2Me	Ph	N-Bu	23.0	298	HMPT	3

[a] Temperature or solvent was not specified. [b] No coalescence of the NMR signals was attained at the above temperature.

and XIc, the rates are out of the NMR time scale. Inspection of the data for XIa and XId indicates that no substantial difference in $\Delta G^{\ddagger}_{298}$ is generated upon the substitution Me/Ph on the heterocyclic ring. It is also noted that in both reports[3,6] no other activation parameters are reported. Later we shall comment on the data of Table I.

The systematic approach and the wider range of compounds which has been investigated in the present work allow for general quantitative correlations of structure and reactivity using the variable structural parameters X, Y, and Z (structure IV). Also the response of the rates to solvent polarity was studied.

Experimental Section

In all the variable temperature NMR studies the signals of H-3 and H-5 of the various heterocycles were analyzed. The complete line shape (CLS) analysis of **2** was simplified by exchanging the protons of the two ring methyls with deuterium,[7] thus eliminating the allylic spin coupling with H-3 and H-5.

All the NMR experiments were carried out on a JEOL C-60 HL high-resolution spectrometer equipped with variable temperature probe and controller. The temperature was calibrated with methanol (low temperature range) and ethylene glycol (high temperature range). All solvents were carefully dried. CLS analyses were carried out with solutions of methyl 2,6-dimethyl-d_6-4*H*-pyran-4-ylidenenitroacetate[7] (0.8 M) in acetonitrile-d_3 and hexamethylphosphoric triamide-d_{18}. The temperature was determined before and after each spectrum. The NMR spectrometer was operated in an internal lock mode using octamethyltetrasiloxane for locking. Care was taken to avoid saturation. The homogeneity was controlled by keeping the width at half-height of the internal CO_2Me signal at less than 0.5 Hz. The coordinate points of the experimental spectra and the computer-matched spectra (continuous line) are depicted in Figures 1 and 2. The rate constants at each temperature were calculated by a computer program REEP[8] (reduction of error in the estimation of parameters) which is designed to solve nonlinear estimation problems.[9] It fits by iterative method a theoretical NMR line to an experimentally observed line in the least-squares meaning by changing the following parameters: C, coefficient of intensity; τ, reciprocal of the rate constant; and $\Delta\nu$, the chemical shift difference between the two exchanging sites at slow exchange. Initial $\Delta\nu$ values were determined at low temperature as 4.50 (CD_3CN) and 20.7 Hz (HMPT-d_{18}). The spin coupling (J_{AB} = 2.10 and 2.05 Hz in acetonitrile and HMPT, respectively) is a constant parameter which was obtained directly from the spectrum. The relaxation time $T_2 = 1/W_{1/2}\pi$ ($W_{1/2}$ = width of the signal at half-height) was also taken as a constant. The calculated rate constant was found to be insensitive to variation in T_2. $W_{1/2}$ was measured at high temperature on the single line which resulted from the coalescence of the AB quartet. The standard error in τ was calculated at each temperature (0.5–4%). The rate constants so obtained were used to calculate the various activation parameters, using a weighted least-squares computer program ACTENG,[10] from the straight line of log $k = f(1/T)$ (Figure 3).

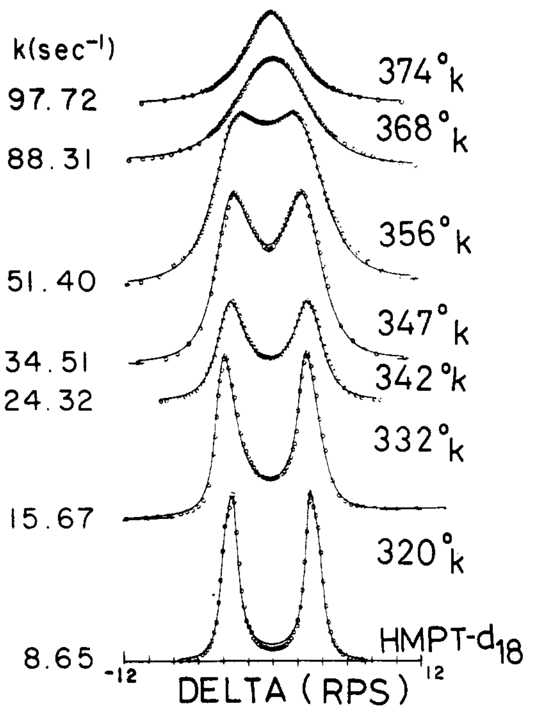


Figure 1. Rate constants and temperature-dependent NMR spectra of **2** in HMPT-d_{18}.

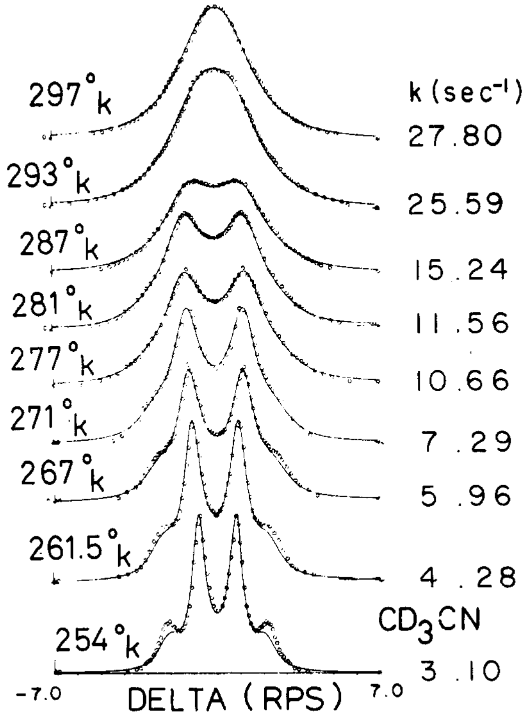


Figure 2. Rate constants and temperature-dependent NMR spectra of **2** in CD_3CN.

All the compounds which were used in this study were previously reported by us.[7]

Results and Discussion

The rates and activation parameters for the thermal isomerization about the exocyclic double bond in **2** in HMPT and acetonitrile, as obtained from Figure 3 are presented in Table II. The interesting feature of these results are the low $\Delta H^{\ddagger}$ values and the large negative $\Delta S^{\ddagger}$ values. Thus, although

Table II. Rates and Activation Parameters for Isomerization of 2

Solvent	k_{298}, s^{-1}	$\Delta H^\ddagger$, kcal/mol	$\Delta S^\ddagger$, eu	$\Delta G^\ddagger{}_{298}$, kcal/mol
HMPT-d_{18}	2.3 ± 0.2	10.5 ± 0.3	−21.7 ± 1	17.0 ± 0.3
CD_3CN	28.2 ± 2.7	7.3 ± 0.3	−27.4 ± 0.1	15.5 ± 0.3

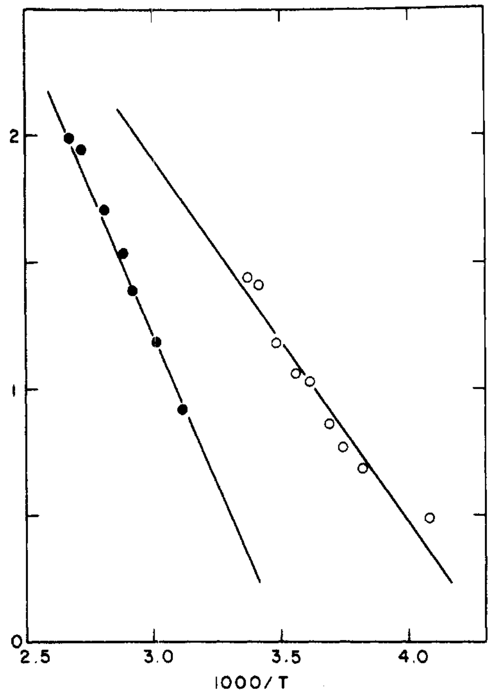


Figure 3. Plots of log k_{298} vs. 1000/T for 2 in HMPT-d_{18} (-●-●-●-) and CD_3CN (-○-○-○-).

the thermal barriers are small (7.3–10.5 kcal/mol), the rates of isomerization are apparently being retarded owing to the large negative entropy term. Considering a unimolecular reaction, the low entropy values are interpreted in terms of an extensively solvated transition state, which in turn indicates considerable charge separation in the above-mentioned state. Such a description is further corroborated by inspecting the activation data of 2 in the more polar acetonitrile, which indicates that the transition state is stabilized by $\Delta\Delta H^\ddagger = 3.2$ kcal/mol with respect to the less polar HMPT. However, the corresponding decrease in $\Delta G^\ddagger{}_{298}$ is only 1.5 kcal/mol, and must be due to the even more negative entropy in acetonitrile. Since the ground state of the molecule is also being affected by solvation, $\Delta\Delta H^\ddagger$ constitutes a minimum value of stabilization of the transition state of 2 in acetonitrile with respect to HMPT. The decrease in entropy in acetonitrile implies that, as a function of solvent polarity, $\Delta H^\ddagger$ and $\Delta S^\ddagger$ affect the rate of isomerization in opposite directions. It is noteworthy that should $\Delta S^\ddagger$ in acetonitrile be decreased by another 5 eu (constant $\Delta H^\ddagger$), the solvent effect on the rate would have been completely masked.

Complete line shape analysis is a time-consuming study, while the measurement of the reaction rate constant (k_c) at the coalescence temperature (T_c) is simple and straightforward. The rate constant is calculated from eq 1 and 2 for two singlets and an AB quartet, respectively.

$$k_c = \Delta\nu\pi/\sqrt{2} \qquad (1)$$

$$k_c = \pi\sqrt{(\Delta\nu)^2 + 6J^2}/\sqrt{2} \qquad (2)$$

The coalescence spectrum can be determined quite accurately, provided care is taken to optimize the homogenity of the NMR instrument (see Experimental Section). The error in k_c is determined by the probable error in $\Delta\nu$, which from our experiment never exceeds ±0.5 Hz. The error in T_c, which later enters in the calculation of $\Delta G_c^\ddagger$, is, from our experience, temperature dependent as follows: ±2 °C in the range of 0–100 °C; ±3 °C in the range of 100–150 °C; ±4–5 °C above 150 °C; and ca. ±3 °C in the range of −80 to 0 °C.

The coalescence temperatures of 23 compounds of type IV with variable X, Y, and Z groups were determined, some of them in sets of several solvents. The data T_C (°C) are arranged according to the type of the Z atom in Tables III–V. Some of the compounds in some of the solvents isomerize at rates which are either too low or too high for the NMR time scale. Accordingly low and high limits of the temperatures were recorded.

The free energy of activation values at $T_c(\Delta G_c^\ddagger)$ were calculated from the rearranged Eyring equation

$$\Delta G_c^\ddagger = 4.57T_c(10.32 + \log T_c/k_c) \qquad (3)$$

and are listed in Tables III–V, with the corresponding probable errors, taking the individual errors in T_c and $k_c = f(\Delta\nu)$, mentioned above.

In order to assess the response of the rates (or $\Delta G^\ddagger$ values) of the isomerization to the solvent polarity and to the various structural parameters, it is of course necessary to compare the rates or the activation data of the various compounds at a standard temperature (25 °C). The conversion of k_c and ΔG_c to k_{298} and $\Delta G^\ddagger{}_{298}$ requires knowledge of the entropy of activation for the process under consideration. Two such entropy values, from the CLS analyses of compound 2 in HMPT and MeCN, are available in the present work. We feel justified in applying these values to the rest of the compounds, in a manner to be described, on the following grounds. (a) The $\Delta S^\ddagger$ values of all the compounds are associated with an identical process, i.e., isomerization about the exocyclic double bond of IV. (b) The same type of compounds are considered throughout the whole series. (c) Similar negative $\Delta S^\ddagger$ values were encountered in the CLS analyses of the isomerization about the C=C bond in numerous compounds of type I, viz., −15 to −26 eu.[11] (d) The values of $\Delta G^\ddagger{}_{298}$ and k_{298} (**2**, Table III) from CLS analysis (values in brackets) are in good agreement with those calculated from the coalescence results. This of course only reflects on the accuracy of the coalescence technique itself, since the true $\Delta S^\ddagger$ values (from CLS analyses) were used in the calculations (to be described).

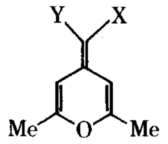
Most of the conclusions drawn from the data at the standard temperature could have also been reached by analyzing the data at T_c, since the coalescence temperatures of most of the compounds in Tables III–V do not appreciably deviate from the standard temperature. There is no doubt, however, that the entropy correction yields more accurate and meaningful results.

The values of $\Delta G^\ddagger{}_{298}$ were calculated from

$$\Delta G^\ddagger{}_{298} = \Delta G_c^\ddagger + \Delta S^\ddagger(T_c - 298) \qquad (4)$$

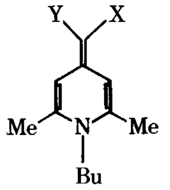
where both $\Delta G_c^\ddagger$ (eq 3) and T_c were experimentally determined. Since a variety of solvents was employed in the present study, the selection of a $\Delta S^\ddagger$ value for a particular solvent was made in the following way. Listed in Table VI are the solvents which were used in the present study with their corresponding Z values.[12] It should be recalled that the CLS analysis of compound 2 yielded entropy values of −21.7 and −27.4 eu in HMPT and acetonitrile, respectively. Thus, each of these

Table III. NMR Data, Rates, and Activation Parameters



Registry no.	Compd	X	Y	T_c, °C	$\Delta\nu$, Hz	Solvent	$\Delta G^‡_{T_c}$, kcal/mol	$-\Delta S^‡$, eu	$\Delta G^‡_{298}$, kcal/mol	k_{298}, s^{-1}
49810-74-4	1	CN	CO_2Me	>180	72	Me_2SO-d_6	>22.3	27	>18.1	<0.33
49810-68-6	2	NO_2	CO_2Me	93	21	HMPT-d_{18}	18.7 ± 0.1	22	(17.0) 17.2 ± 0.4	(2.29) 1.51 ± 0.26
				75	16	DMA	18.0 ± 0.2	27	16.6 ± 0.3	4.17 ± 0.36
				15	7.5	CD_3CN	15.2 ± 0.2	27	15.4 ± 0.2	(28.2) 31.6 ± 1.3
				−17	4.0	CD_3NO_2	13.5 ± 0.4	27	14.6 ± 0.4	122 ± 10
3280-35-1	3	CN	COMe	>180	95	Me_2SO-d_6	>22.1	27	>17.9	<0.46
49810-66-4	4	NO_2	COMe	8.0	29	$CDCl_3$	14.1 ± 0.1	22	14.5 ± 0.2	144 ± 6
				9.0	30	CH_2Cl_2	14.1 ± 0.1	22	14.5 ± 0.1	144 ± 6
				13.0	41	Acetone-d_6	14.3 ± 0.1	22	14.5 ± 0.1	144 ± 5
				−22.0	32	CD_3CN	12.5 ± 0.1	27	13.8 ± 0.3	470 ± 39
49810-69-7	5	NO_2	CN	>200	83	HCBD	>23.2	22	>19.3	<0.04
				126	79	Me_2SO-d_6	19.5 ± 0.2	27	16.8 ± 0.5	3.0 ± 0.5
49810-70-0	6	COMe	CO_2Me	60	28	Me_2SO-d_6	16.8 ± 0.1	27	15.8 ± 0.2	16.0 ± 1
49810-75-5	7	CN	$CONH_2$	>180	84	Me_2SO-d_6	>22.2	27	>18.0	<0.39
49810-67-5	8	H	NO_2	>180	78	Me_2SO-d_6	>22.2	27	>18.0	<0.39

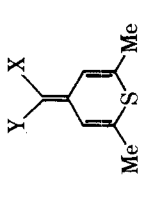
Table IV. NMR Data, Rates, and Activation Parameters



Registry no.	Compd	X	Y	Temp, °C	$\Delta\nu$, Hz	Solvent	$\Delta G^‡_{T_c}$, kcal/mol	$-\Delta S^‡$, eu	$\Delta G^‡_{298}$, kcal/mol	k_{298}, s^{-1}
49810-89-1	9	CN	CO_2Me	127	87	DMA	19.5 ± 0.2	27	16.7 ± 0.5	3.5 ± 0.6
				96	81	Me_2SO-d_6	17.9 ± 0.1	27	16.0 ± 0.4	11.5 ± 1.5
49775-29-3	10	NO_2	CO_2Me	<−90	70[a]	Acetone-d_6	<8.7	22	<11.2	>38 000
				<−90	70[a]	CH_2Cl_2	<8.7	22	<11.2	>38 000
49810-87-9	11	CN	COMe	80	114	$CDCl_3$	16.8 ± 0.1	22	15.6 ± 0.3	22.5 ± 2
				56	114	Acetone-d_6	15.7 ± 0.1	22	15.0 ± 0.2	62 ± 4
				48	117	CD_3CN	15.3 ± 0.1	27	14.7 ± 0.2	103 ± 6
				17	111	CD_3NO_2	13.8 ± 0.1	27	14.0 ± 0.1	336 ± 13
49810-84-6	12	NO_2	COMe	<−90	70[a]	Acetone-d_6	<8.7	22	<11.2	>38 000
49810-86-8	13	NO_2	CN	−30	96	CD_3CN	11.5 ± 0.1	27	13.0 ± 0.3	1820 ± 172
49810-90-4	14	CN	$CONH_2$	153	110	DMA	20.6 ± 0.2	27	17.1 ± 0.7	1.8 ± 0.4
				129	101	Me_2SO-d_6	19.4 ± 0.2	27	16.6 ± 0.6	4.2 ± 0.7
49810-88-0	15	H	CN	73	12.5	CD_3NO_2	18.9 ± 0.2	27	17.6 ± 0.3	0.77 ± 0.07
49810-85-7	16	H	NO_2	34	120	Me_2SO-d_6	14.6 ± 0.1	27	14.4 ± 0.1	171 ± 7
49810-93-7	17	H	COMe	40	114	Me_2SO-d_6	14.9 ± 0.1	27	14.7 ± 0.1	103 ± 5

[a] Estimated.

Table V. NMR Data, Rates, and Activation Parameters



Registry no.	Compd	X	Y	Temp, °C	Δν, Hz	Solvent	$-\Delta S^‡$, eu	$\Delta G^‡_{Tc}$, kcal/mol	$\Delta G^‡_{298}$ kcal/mol	k_{298}, s^{-1}
49810-83-5	18	CN	CO_2Me	>180	80	Me_2SO-d_6	27	>22.2	>18.0	<0.39
49810-79-9	19	NO_2	CO_2Me	32	30	$CDCl_3$	22	15.3 ± 0.1	15.1 ± 0.1	52.5 ± 2
				40	40	Acetone-d_6	22	14.9 ± 0.1	14.6 ± 0.1	122 ± 5
49810-82-4	20	CN	COMe	135	102	Me_2SO-d_6	27	19.7 ± 0.2	16.7 ± 0.6	3.5 ± 0.6
49810-78-8	21	NO_2	COMe	−80	51	Acetone-d_6	22	9.3 ± 0.2	11.6 ± 0.6	19 300 ± 3400
49810-80-2	22	CN	NO_2	36	96	Me_2SO-d_6	27	14.8 ± 0.1	14.5 ± 0.1	144 ± 6
49775-28-2	23	H	NO_2	>160	90	Me_2SO-d_6	27	>21.1	>17.4	<1.08

Table VI

Solvent	Z value,[12]	kcal/mol
Nitromethane	71.5	$\Delta S^‡ = -27$ eu (measured in acetonitrile)
Acetonitrile	71.3	
Dimethyl sulfoxide	71.1	
Dimethylacetamide	66.9	
Acetone	65.7	$\Delta S^‡ = -22$ eu (measured in HMPT)
Methylene chloride	64.2	
Chloroform	62.8	
Hexamethylphosphorictriamide	62.8	

values was assigned to a *group* of solvents with *similar Z* values according to Table VI.

The approach outlined above deserves some comments. Firstly, we consider the different $\Delta S^‡$ values in HMPT and acetonitrile as being significant. A single intermediate value of $\Delta S^‡$ could have been selected and applied to all the compounds. This would have seriously affected neither the final values of $\Delta G^‡_{298}$ nor their relative order. Secondly, we assume that the entropy values in each group of solvents of similar polarities do not vary significantly from the assigned values. This assumption is reasonable since the experimental range of $\Delta S^‡$, which was determined by CLS analysis, applies to two solvents of extreme polarities, and thus $\Delta S^‡$ values for the other solvents are expected to fall within this range. Furthermore, a probable error of ±5 eu was taken for the error calculation in $\Delta G^‡_{298}$ (eq 4). Thirdly, the enthalpy of activation is considered to be constant over the experimental temperature range. This is an inherent assumption in every dynamic NMR study, since different compounds exhibit the spectral changes at different temperature ranges. It is doubtful, however, if such an assumption would introduce an error which is greater than the experimental one. It is also true that the greater the difference $T_c - 298$, the larger would be the error in $\Delta G^‡_{298}$. Nevertheless, in the absence of CLS analysis data for each compound, this is probably the best way to correlate a large body of kinetic data without overlooking the entropy effect on the rate on one hand, and recalling all the assumptions and errors thus introduced on the other hand.

The activation data in Tables III–V contain a considerable amount of information regarding the behavior of the system as a function of the solvent, the X and Y substituents, and the heteroatom Z. Each of these topics will be analyzed separately and finally we shall return to the problem of rate assistance due to potential aromaticity in the transition state.

Solvent Effect on the Rates. Tables III–V contain rate and activation data for a wide variety of solvents from the most polar nitromethane ($Z = 71.5$) to the least polar HMPT ($Z = 62.8$). It should be emphasized that in some of the cases the choice of solvent was dictated by the specific spectral and solubility behavior of a given compound and the boiling point of the solvent. It has already been noted from the CLS study of **2** that the isomerization process is accelerated in more polar medium. This is further supported by the results of Tables III–V. Thus, the order of the rate constants of compound **2** (Table III) in the four solvents follows the order of the *Z* values of the solvents. The rate and $\Delta G^‡_{298}$ values of compound **2** (in brackets) in HMPT and acetonitrile (Table III) are those which were calculated from the CLS analyses. Although a discrepancy does exist, its magnitude is negligible and does not offset the observed trend and the general conclusions. The solvent effect on the rate is moderate; factors of 80 and 15 in the rates between the solvents of extreme polarities were recorded for **2** and **11**, respectively. As stated previously, the reason for this rather poor sensitivity is attributed to the large

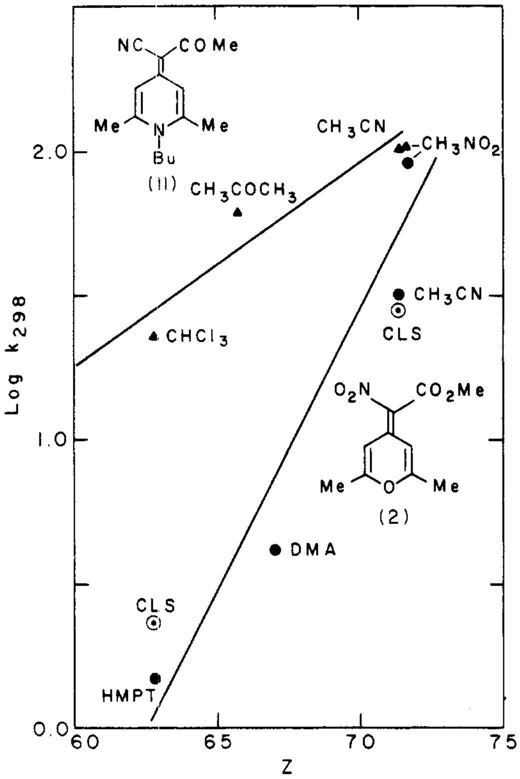


Figure 4. Plots of log k_{298} vs. the Z values of the solvents for **2** and **11** based on data from Tables III and IV, respectively. CLS points correspond to rate constants from NMR total line shape analyses in HMPT and acetonitrile (not used in plotting).

negative $\Delta S^{\ddagger}$ values of this process which masks part of the rate acceleration, anticipated from the decrease in $\Delta H^{\ddagger}$ in more polar solvents.

Compound **5** (Table III) constitutes a case where the solvent polarity is clearly responsible for the observation of the isomerization process on the NMR time scale. No coalescence of the H-3 and H-5 signals of **5** could be observed in hexachlorobutadiene at 200 °C, while in the more polar Me_2SO, coalescence takes place at 126 °C, and the rate constant could be evaluated.

In Figure 4 we present least-squares plots of log k_{298} vs. the Z values of the various solvents for **2** and **11**. The rate constants obtained from CLS analyses were not used in constructing the plots, but they are presented on the graph of **2** and marked CLS; their deviation from the line is not serious. The reasonably good straight lines indicate that no change in mechanism occurs in the range of solvent polarities which was studied. Compound **2**, which isomerizes slower than **11**, is more sensitive to changes in the polarity of the solvent than **11**, as anticipated from simple considerations.

In conclusion, while the spectral phenomena yield a wide range of $\Delta G^{\ddagger}$ values at T_c, detail analysis reveals that this is due to a temperature effect associated with large negative entropies of activation. The isomerization is accelerated only moderately in polar solvents. The data accumulated allows for the selection of the proper solvent in order to bring the spectral phenomena into the NMR time scale. The available rate data correlate well with the Z values of the solvents, and the positive slope indicates that the rates are enhanced in polar solvents. The implication is that charge is being developed in the transition state of the isomerization process as depicted by V.

Finally our results for compounds **1** and **18** (Tables III and V) agree with those reported for XIb[3] and XIc[3] (Table I), respectively. Furthermore, compound XIa,[3] which corresponds to **9** (Table IV), appropriately exhibits the highest $\Delta G^{\ddagger}_{298}$ value, being measured in the least polar HMPT ($\Delta G^{\ddagger}_{298}$ = 20.1 kcal/mol).

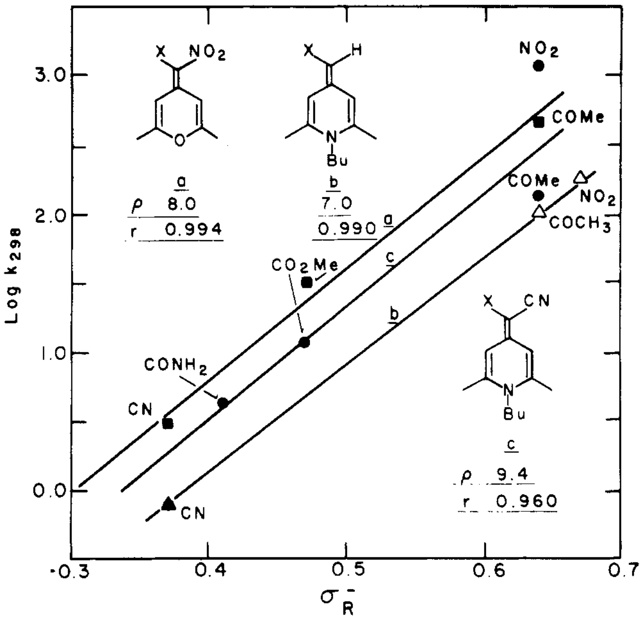


Figure 5. Plots of log k_{298} vs. σ_R^- values of the variable X substituents based on data from Tables III and IV. ρ = slope; r = correlation coefficient.

Substituents' Effect on the Rate. The evaluation of the effect of the substituents on the exocyclic double bond (X, Y) on the rate (k_{298}) of the isomerization should be made within a series having the same Z atom and either in the same solvent or in solvents of very close Z values. Inspection of the relevant data in Tables III–V reveals that in all cases the rates are proportional to the σ_R^- values[13a] of the substituents, which follow the order $NO_2 > COCH_3 > CO_2CH_3 > CONH_2 > CN > H$. This behavior lends further support to the charged transition state model V which requires rate enhancement by X and Y groups capable of effectively delocalizing a negative charge. Thus the combinations of a nitro and acetyl group in the three heteroatom series (compounds **4**, **12**, and **21**) produce the largest rate constants. In fact compound **12** (Table III) in the nitrogen series isomerizes too fast to be measured by NMR and a lower limit of 3.8×10^4 s^{-1} was calculated for the rate constant. On the other hand, the combination of $CONH_2$ and CN, the two weakest electron-withdrawing groups, gives rise to low rates (**7** and **14**). We have tried to place the results on a more quantitative basis by plotting log k_{298} vs. σ_R^- values. This can be done by keeping one substituent constant, varying the other, and observing its effect on the rate constants. Three such series can be constructed from Tables III and IV by selecting the rate constants either in the same solvents or in solvents of very similar Z values. The rate constants of compounds **2**, **4**, and **5** (Table III), which have a nitro group in common, were plotted against the σ_R^- values of the other substituents (Figure 5, curve a). Although the data are limited, the correlation is satisfactory (0.994) and the calculated slope is 8.0. Such a large ρ value, which reflects the large sensitivity of the rate to the substituent, must be due to the proximity of the substituent to the reaction site. Extrapolation of this line to $\sigma_R^- = 0$ for X = H (compound **8**, Table III) yields a rate constant of 3.8×10^{-3} s^{-1}. This value places the isomerization rate of **8** out of the NMR scale, which was indeed confirmed experimentally by the upper limit (3.9×10^{-1} s^{-1}) calculated for this compound (Table III). This correlation (curve a, Figure 5) also predicts that for X = $CONH_2$, k_{298} = 7.4 s^{-1}, while for X = NO_2, a compound which for symmetry reasons cannot be measured by NMR, k_{298} = 912 s^{-1}, still on the NMR time scale.

Table VII. Rates and Free Energy of Activation Data

Compd	X	Y	Z	$\Delta G^{\ddagger}_{298}$, kcal/mol	k_{298}, s^{-1}	Solvent
4	NO_2	$COCH_3$	O	14.5 ± 0.1	144	Acetone
21	NO_2	$COCH_3$	S	11.6 ± 0.6	19 300	Acetone
12	NO_2	$COCH_3$	N-Bu	<11.2	>37 900	Acetone
5	NO_2	CN	O	16.8 ± 0.5	2.97	Me_2SO
22	NO_2	CN	S	14.5 ± 0.1	144	Me_2SO
13	NO_2	CN	N-Bu	13.0 ± 0.3	1820	CD_3CN
3	$COCH_3$	CN	O	>17.9	<0.46	Me_2SO
20	$COCH_3$	CN	S	16.7 ± 0.6	3.52	Me_2SO
11	$COCH_3$	CN	N-Bu	14.7 ± 0.2	103	CD_3CN

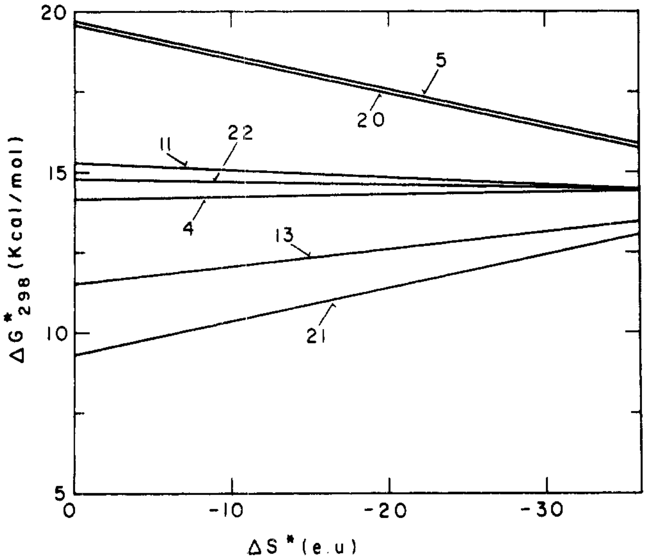


Figure 6. Plots of $\Delta G^{\ddagger}_{298}$ vs. $\Delta S^{\ddagger}$. The numbers on the plots correspond to the compounds in Tables III–V.

In the nitrogen series, compounds **10** and **12** (Table IV) are substituted with the strongest electron-withdrawing groups and were found to isomerize at rates (>3.79 × 10^4 s^{-1}) which are out of the NMR time scale. Again a combination of the two weakest electron-withdrawing groups, CN and H (**15**), produces the smallest rate constants in this series.

In the nitrogen series (Table IV) the plot of log k_{298} vs. σ_R^- for compounds **9, 11, 13, 14,** and **15** in Me_2SO (Z = 71.1) and acetonitrile (Z = 71.3) is presented (curve c) in Figure 5. The constant substituent of the exocyclic double bond is CN. This line has a poor correlation coefficient (0.96) and a slope of 8.6, similar to the previous plot. For **15** (X = H), the σ_R^- value of the CN was used since it actually represents the capacity of the double bond substituents to delocalize the negative charge. A third plot (curve b) was constructed in the nitrogen series by keeping H constant and varying X (compounds **15, 16,** and **17**, Table IV). It should be noted that curves b and c have a common point, i.e., **15** (X = CN; Y = H).

All three curves have similar, positive, and relatively large slopes. The high positive ρ values are indicative of a negative charge formation in close proximity to the variable X group, which indeed is the case; namely, the carbon of the exocyclic double bond. The fact that all three plots have reasonably good correlation coefficients supports our experimental and computational approach.

The inherent assumption in plotting log k_{298} vs. σ_R^- in the above systems, which are cross conjugated, is that the constant functional group is electronically perturbed to the same extent by the variable X group within a series. This is most probably true in series b and c (Figure 5) where the constant groups H and CN have relatively small σ_R^- values. It should be added that plots of log k_{298} vs. the combined σ_R^- values of the *two* substituents failed to give linear behavior. The above plots are also useful in estimating the rate constants of other compounds which were not examined here.

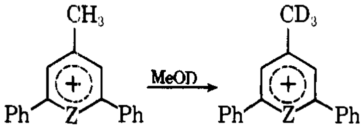
No sufficient quantitative data in the S-heterocyclic compounds (Table V) are available for Hammett plots. Qualitatively, the order of the rates correlate with the σ_R^- values of the double bond substituents, when the appropriate pairs are compared, viz., **18** and **19, 20** and **21, 22** and **23**.

Finally we would like to comment on the relative order of $\Delta G^{\ddagger}_{298}$ of XId and XIe (Table I). Using the line of reasoning presented here, the above results imply that in the transition state the CN group stabilizes the negative charge better than CO_2CH_3 ($\Delta\Delta G^{\ddagger}$ = 3 kcal/mol). This is at variance with the known order of σ_R^- and our experimental findings. From the plot (Figure 5, curve a) and from the data in Table III, it is clearly evident that compound **2** (in $CDCl_3$ and even in DMA) isomerizes faster than **5** in Me_2SO. Furthermore, also from the data for the nitrogen series (Table IV) it is clear that **10** in acetone and CH_2Cl_2, isomerizes substantially faster than **13** even in the more polar CD_3CN. Unless the reason for the observed order in XId and XIe is due to the fact that the N atom carries different alkyl groups, it is difficult to rationalize the contradictory results. There is no doubt that one or both CO_2Me groups in XIe are twisted out of the double bond plane.[7,14] This implies on one hand steric acceleration of the process under consideration, while on the other hand the increase of the double bond order in the ground state may retard the rate of isomerization.

The Effect of the Z Atom on the Rates. In analyzing the effect of the Z atom on the rates, X and Y must be kept identical. For convenience, the relevant data are collected in Table VII. Three series are presented and the data clearly point out that the three heteroatoms accelerate the isomerization in the decreasing order of N > S > O.

It is important to ascertain that the particular selection of $\Delta S^{\ddagger}$ values which were employed in our calculations of $\Delta G^{\ddagger}_{298}$ is actually not responsible for the observed order of $\Delta G^{\ddagger}_{298}$ values which are being analyzed as a function of the Z atom (Table VII). To this end we have plotted $\Delta G^{\ddagger}_{298}$ as a function of $\Delta S^{\ddagger}$ (Figure 6) using eq 4. The results should be analyzed within a series for which X and Y are constants. Thus, checking the plots of **5** and **22** (Figure 6) reveals that no common $\Delta G^{\ddagger}$ value exists for these two compounds between 0 and −36 eu, which means that regardless of the choice of $\Delta S^{\ddagger}$ the relationship between $\Delta G^{\ddagger}_{298}$ for these two compounds cannot be inverted. The same is true for the pair **22** and **13** and thus the whole order of $\Delta G^{\ddagger}_{298}$ values for **5, 22,** and **13** (Table VII) is indeed meaningful. The same conclusions are reached from analysis of the plots for the two pairs **4, 21** and **20, 11**. Only at *unreasonable* values of $\Delta S^{\ddagger}$ (<−40 eu) the above results do not hold true.

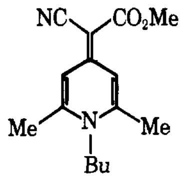
The above experimental order of the rates of isomerization for the three types of heterocyclic systems corresponds neither to the electronegativity nor to the σ_p or the σ_p^+ orders of the three elements (when carrying methyl groups).[13b] It should be noted that from our previous work concerning the isomerization of compounds of type I it turns out that when X = Y = CO_2Me and R = Me the rate of isomerization about the C=C double bond was accelerated according to the decreasing order of Z = N > O > S.[1a–c] This is satisfactorily accounted for by the $\sigma_p{}^+$ relationship of Me_2N, MeO, and MeS.[13b] But, with respect to the present findings, the relative position of the O and S atoms was interchanged. If V correctly describes the nature of the transition state of the isomerization process, then, all other parameters being equal, it must draw its stability from the charge delocalization in the heterocyclic ring. Electronically, the heterocyclic rings of the transition state resemble the *stable* charged heterocycles and we are therefore led to the conclusion that the thiopyrylium cation is more stable than the pyrylium cation. Experimental data which bear on this point are the recent findings[15] that the rate of deuterium exchange in the following charged heterocycles as a function of the Z atom follows the decreasing order O > S > N, implying that the acidity of the hydrogens of the methyl group also follows the above order. The kinetic acidity of these hydrogens can be regarded as being inversely proportional to the magnitude of the positive charge on the Z atom, or alternatively to the capacity of the Z atom to participate in p–π conjugation. Therefore, the conclusion drawn from the exchange experiment is that the order in which the Z atoms can delocalize their p electrons in the above charged heterocycles is N > S > O. Recent calculations (SCF–MO)[16] show that while the O atom in pyrylium carries 1.284 π electrons the S atom in thiopyrylium carries only 1.146 π electrons, which is in agreement with the above experimentally established order.



Z = N, O, S

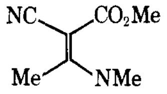
Since the above two findings are in agreement with the order found by us, we are justified in assigning structure V to the transition state of our process inasmuch as the heterocyclic ring resembles the corresponding stable heterocyclic cations. Admittedly, the above relative order is still at variance with our results in the acyclic series I as well as with the relative order of the $\sigma_p{}^+$ values of the three atoms. The simple conclusion is that when incorporated into a cyclic π system, a sulfur atom is more effective in p–π conjugation than in an acyclic π system.

Finally we come to the question of the importance of the aromatic nature of the heterocyclic ring in the transition state V. The quantitative answer to this question is hampered by the unavailability of proper models for comparison. Thus if one compares the activation data of **9** and **24**,[1c] no significant difference is apparent. Comparison of XIe and **25**[1c] clearly reveals that the latter isomerizes faster than the former. Such a comparison suffers from the difference in the position of the N atom with respect to the reactive double bond. The closer models for quantitative evaluation of the aromaticity effect in **9** and other heterocycles is the dihydro derivative of **9** and of similar heterocycles, which are not yet available for evaluation.



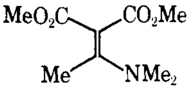
9

$\Delta G^{\ddagger}{}_{298}(\mathrm{DMA}) = 16.7$ kcal/mol



24

$\Delta G^{\ddagger}{}_{312}(\mathrm{CH_2Cl_2}) = 15.1$ kcal/mol



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$\Delta G^{\ddagger}{}_{182}(\mathrm{CH_2Cl_2}) = <9.1$ kcal/mol

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