SYNTHESIS OF METHYL 2-CYANO-(1,2-DIMETHYLCYCLOHEPTA[*b*]-PYRROL-6-YLIDENE)ACETATE. A STERIC EFFECT TO ACCELERATE THE GEOMETRICAL ISOMERISM OF THE EXOCYCLIC C=C BOND OF HETEROCYCLE-FUSED HEPTAFULVENES

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Abstract———The rotational barriers of the exocyclic C=C bonds of heptafulvenes condensed with furan, pyrrole, and thiophene rings were largely dependent on the steric repulsion around the exocyclic C=C bonds; newly synthesized methyl 2-cyano-(1,2-dimethylcyclohepta[*b*]pyrrol-6-ylidene)acetate and its furanylidene analogue revealed higher energy barriers than the corresponding methyl 2-cyano-(1,2-dimethylcyclohepta[*b*]pyrrol-8-ylidene)acetate and the furan derivative.

Recently, we reported the rotation around the exocyclic C=C bonds of heptafulvenes carrying electron-withdrawing groups, *e.g.*, methyl 2-cyano-(1,2-dimethylcyclohepta[*b*]pyrrol-8-ylidene)acetate (**1**), methyl 2-cyano-(2-methylcyclohepta[*b*]thiophen-8-ylidene)acetate (**2**), and methyl 2-cyano-(2-methylcyclohepta[*b*]furan-8-ylidene)acetate (**3**) in CD_3CN.[1] Among them, the most sterically hindered pyrrolo derivative (**1**) showed the smallest $\Delta G^{\ddagger}$ value, whereas the rate of furan derivative (**3**) was unmeasurable on the nmr time scale.

The large negative activation entropies ($\Delta S^{\ddagger}$) for **1** and **2** indicated that both have an extensively polarized transition state and the rates of rotation depend on the $\Delta S^{\ddagger}$ values. The lowest activation energy of rotation was observed with pyrrole derivative (**1**), and it is explained in terms of electronic and/or steric factors.[1] Herein, we report the convincing evidence for the steric acceleration of the rotation of the exocyclic C=C of heptafulvenes

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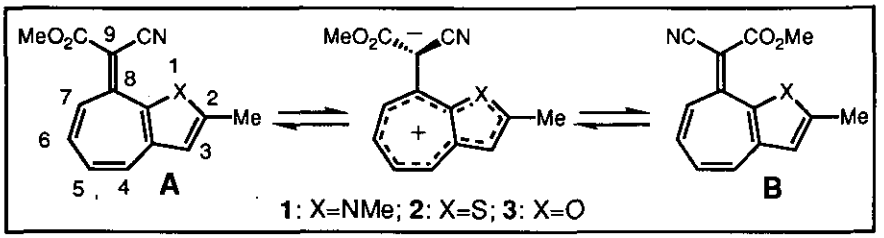

on the basis of reluctant rotation observed in methyl 2-cyano-(1,2-dimethylcyclohepta[*b*]pyrrol-6-ylidene)acetate (**4**), a sterically unhindered isomer of **1**, together with the barriers of heptafulvenes (**1**-**3**) in DMF-d_7.[2] Desired compound (**4**) and methyl 2-cyano-(2-methylcyclohepta[*b*]furan-6-ylidene)acetate (**5**) were prepared *via* Claisen rearrangement of 4-(2-chloropropenyloxy)tropone (**6**), obtained from 4-hydroxytropone (**7**) and 1,2-dichloro-2-propene, to 2-methylcyclohepta[*b*]furan-6-one (**8**),[3] the $MeNH_2$-treatment of **8** to 2-methylcyclohepta[*b*]pyrrol-6-one (**9**), and Ac_2O-mediated condensation of **8** and **9**, respectively, with methyl cyanoacetate.

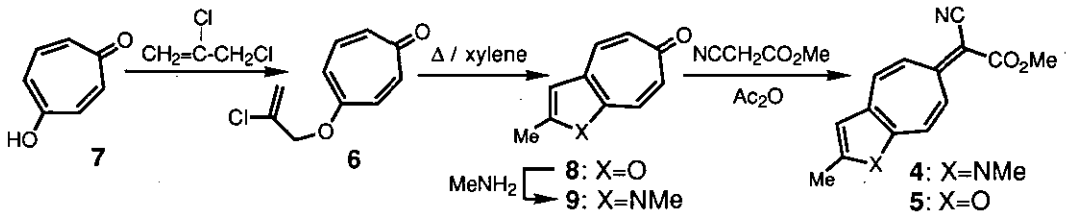

Table 1. Activation parameters for the change from **A** to **B** in DMF-d_7 and in CD_3CN

	A/B (temp/°C)	$\Delta H^{\ddagger}$/k J mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}	$\Delta G^{\ddagger}$/k J mol^{-1} (at 298 K)	r (Solvents)	ref.
1	34/66 (-49.6)	38.0±1.1	-57.7±4.1	55.2±2.4	0.9993 (DMF-d_7)	
	30/70 (-39.9)	39.5±1.0	-47.7±3.7	53.8±2.1	0.9995 (CD_3CN)	1.
2	90/10 (-49.8)	35.4±1.1	-94.1±4.3	63.5±2.4	0.9988 (DMF-d_7)	
	91/9 (-39.8)	39.7±2.2	-77.9±8.0	62.9±4.6	0.9970 (CD_3CN)	1.
3	91/9 (19.9)	60.5±1.7	-65.1±5.1	79.9±3.3	0.9991 (DMF-d_7)	
	92/8 (27.0)	-	-	-	(CD_3CN)	1.
4	48/52 (40.0)	57.6±2.4	-67.0±7.2	77.6±4.6	0.9986 (DMF-d_7)	
5	47/53 (50.1)	-	-	-	(DMF-d_7)	

The rotational barrier of **4** in DMF-d_7 was determined by the 500 MHz-variable temperature (29.9 to 99.6 °C) ^{1}H nmr spectroscopy through the complete line shape analysis.[4] On the other hand, the furan analogue (**5**) showed no nmr change even in DMF-d_7. At the same time, the activation parameters of **1**, **2**, and **3** were determined (270 MHz-^{1}H nmr) in the same solvent, DMF-d_7 (-50 to 120 °C), for comparison, and are included in Table 1; previously, those of **1**-**3** were measured in CD_3CN. The thermodynamic parameters of **1** and **2** from the both solvents were very similar, and mutually consistent. They have a large negative $\Delta S^{\ddagger}$ value and the rates of the rotation decrease in the order, N>S>O. Among them, **3** has the largest value of the activation enthalpy ($\Delta H^{\ddagger}$) and **2** has the largest $\Delta S^{\ddagger}$ value. Previously, Shvo *et al.* have reported the dynamic behavior of heterofulvenes of 2,6-dimethyl-γ-pyrone, -γ-thiopyrone, and *N*-butyl-2,6-dimethyl-γ-pyridone, in which the hetero ring atoms accelerated the isomerization in the decreasing order of N>S>O.[5] The result is similar to the present study. They proposed an ionic transition state to explain the result from the order of the delocalization of p electron of the hetero atoms.

We previously speculated that the chemical shift differences ($\Delta\delta$(**3**)=158.5-81.7=76.8, $\Delta\delta$(**2**)=156.6-89.0=67.6, and $\Delta\delta$ (**1**)=151.7-85.5=66.2), of the exocyclic C=C bonds reflect the contribution of the charge-separation of the exocyclic C=C bonds.[1,6] The chemical shift of C-9 of **3** is highest, while that of C-8 of **3** is lowest. It would be suggested that the charge-separation of the exocyclic C=C bond of **3** is largest among them to most stabilize the ground state energy by the tight solvation. Thus, it was explained that the $\Delta H^{\ddagger}$ value of **3** was larger than the others.

The activation barrier of **4** is quite high compared from that of **1**. Similarly, **5** has a higher activation barrier than **3**, as compound (**5**) revealed insufficient spectral changes even at 120 °C in DMF-d_7. The activation parameters of **4** are in agreement with those of the furan derivative (**3**) within the experimental error. The lack of the steric hindrance in **4** increases the rotational barrier. This indicated that the steric factor is clearly playing the more decisive role than the electronic one for the rotation. The importance of the steric factor on the rotation was further supported by that the $\Delta\delta$ of the exocyclic carbons of the two cycloheptafurans (**3** and **5**) are not different so much ($\Delta\delta$(**3**)-$\Delta\delta$(**5**)=+4.7), while the $\Delta\delta$ of the two cycloheptapyrroles (**1** and **4**) are quite different ($\Delta\delta$(**1**)-$\Delta\delta$(**4**)=-10.8).

In the respect of ^{13}C nmr chemical shift differences of the exocyclic C=C bond ($\Delta\delta$(**4**)=77.0, $\Delta\delta$ (**5**)=72.1), the greater electron-donating pyrrole derivative showed a tendency of rotation, but the smaller electron-donating furan derivative did not. The $\Delta G^{\ddagger}$ value difference (22.4 kcal/mol) between **1** and **4** is attributed to the steric acceleration for the bulky methylamino group in **1**.

In DMF-d_7, the ratio of **4A**:**4B** was 48:52, and there is no reason to deviate from 1:1. However, this should not be the cases in **1-3**. The major isomer of **1** in DMF-d_7 is **1B**, the sterically more crowded isomer. In toluene-d_8, the ratio of **1A**:**1B** was 55:45 at 0 °C. The less crowded isomer is major. Thus, the ratio of **1A**:**1B** is dependent on the solvent polarity. It is explained that the more crowded **1B** was stabilized in a polar DMF than **1A** since MNDO-PM3 calculations indicate that **1B** (4.227 D) has the larger dipole moment than **1A** (2.796 D).[7]

In conclusion, the result obtained from **4** clearly indicates that the rotational rate of the exocyclic C=C bond of **1-3** is accelerated by the steric factor.[8] The low $\Delta G^{\ddagger}$ value of **1** is interpreted in terms of the destabilization of the ground state due to the steric repulsion that is relieved in going to the transition state by the rotation of the exocyclic C=C bond.

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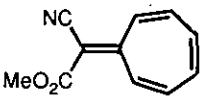

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7. Detailed results for the calculations will be published in a full paper.

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