STEREOCHEMISTRY IN LONG-CHAIN
BIRADICAL CYCLIZATION

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Abstract – The structures of 8-membered azalactone isomers produced from photocyclization of 2-(N,N-dibenzylamino)ethyl benzoylacetate were determined by the X-ray structure analysis to clarify the stereochemical behavior of a 1,8-biradical. The remarkable stereoselectivity in cyclization of the 1,8-biradical to form *cis*- and *trans*-isomers of the azalactone was not observed. The ring conformations were boat-chair like and dihedral angles between C_5- and C_6- phenyl groups were *ca* 45° in the both isomers. The 1,8-biradicals in the transition state for the cyclization would have nearly same boat-chair like conformation and twisted configuration with the dihedral angle of *ca* 45° as the corresponding isomer, and this is responsible for luck of stereoselectivity in long-chain biradical cyclization.

INTRODUCTION

Intramolecular hydrogen abstraction by excited carbonyl oxygen is one of the most well-known primary photochemical process in alkyl aryl ketones and intervention of biradical intermediates in the photoreactions *via* the abstraction is now well established.[2-8] The hydrogen abstraction from the γ-carbon is much faster than that from any other position because of stereoelectronic[5] or geometrical requirement.[6] Carbonyl compounds which lack suitably aligned γ-hydrogens by reason of conformation or substitution or in which a hydrogen on a carbon atom other than γ is activated by hetero atoms can still undergo hydrogen abstraction which may involve δ-[7] or ε-hydrogen atoms.[8,9] Hydrogen abstractions from more remote positions may be possible when the required transition state for the abstraction is achieved without severe distortion. Remote hydrogen abstraction through large-sized cyclic transition state has been observed.[10,11] Breslow has provided elegant examples of biomimetic remote hydrogen abstraction.[12] However, the hydrogen abstraction through medium-sized cyclic transition states has rarely been observed.[13-18] Behavior of long-chain molecules has been studied well to clarify conformational effect on intramolecular reactivity.[2,4,10,11] It is often assumed that if the corresponding bimolecular reaction is much slower than diffusion controlled, a preequiliblium will occur in the intramolecular reaction, and this reaction will be conformationally controlled.[11] We already reported that 2-(N,N-dibenzylamino)ethyl benzoylacetate **1** underwent photocyclization to give 8-membered azalactones **2-c** and **2-t** *via* remote hydrogen transfer from a charge-transfer state and suggested the charge-transfer interac-

tion was conformationally controlled.[13] Stereoselectivity in biradical cyclization, especially 1,4-biradical cyclization, is now well understood; a biradical generally gives a sterically more stable cyclic alcohol much predominantly over the unstable isomer in possible cyclization.[19] However, little is known about the nature of long-chain biradicals, especially on the factors which govern the product distribution in cyclization because of many possible ring conformations in transition states for cyclization. We report here stereochemistry in 1,8-biradical cyclization.

MATERIALS AND METHODS

Materials. Two azalactone isomers **2-c** and **2-t** were obtained from photoreaction of 2-(N,N-dibenzylamino)ethyl benzoylacetate.[13] Crystals of **2-c** and **2-t** were made by liquid diffusion recrystallization[20] from dichloromethane/n-hexane solution.

X-ray Structure Determination of 2-c and 2-t. A Rigaku AFC6S diffractometer with graphite monochromated Mo K_α radiation(0.71069 Å) was used. The unit-cell prarmeters were determined from 25 reflection with $25.02° \leq 2\theta \leq 26.95°$ for **2-c** and $25.13° \leq 2\theta \leq 28.14°$ for **2-t**. Intensity data with $2\theta \leq 55.1°$ for **2-c** and $2\theta \leq 55.2°$ for **2-t** were collected with the $\omega-2\theta$ scan technique(scan speed 4.0°/min[-1] for **2-c** and 8.0 for **2-t**) at 4456 reflections for **2-c** and 3930 for **2-t**. The intensities of three representative reflections which were measured after every 150 reflections remained constant throughout data collection indicating crystal and electronic stability. No decay correction was applied. The intensities were corrected for Lorentz and polarization factors, but not for absorption. The structure was solved using the direct methods program MITHRIL[21] and DIRDIF[22]. The full-matrix least-

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squares refinement for non-hydrogen atoms was carried out for $\Sigma w(|F_o|-|F_c|)^2$, where the weight $w = 4F_o^2/\sigma^2(F_o^2)$, for 1528 independent reflection with $F_o>3.00\sigma(F_o)$ for **2-c** and 1561 for **2-t**. The final discrepancy factors were R = 0.061 and R_w = 0.093 for **2-c** R = 0.095 and R_w = 0.049 for **2-t**. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.25 and −0.21 e/Å³, respectively, for **2-c** and 0.33 and −0.31, respectively, for **2-t**. Neutral atom scattering factors were taken from Cromer and Waber[23]. Anomalous dispersion effects were included in F_{calc}[24]; the values for $\Delta f'$ and $\Delta f''$ were those of Cromer[25]. All calculations were performed using the TEXSAN[26] crystallographic software package of Molecular Structure Corporation.

Crystal Data of **2-c**. $C_{25}H_{25}O_3N$, M = 387.48. Monoclinic, a = 13.250 Å, b = 9.694 Å, c = 15.924 Å, β = 94.592°, V = 2039 Å³. Space group $P2_1/c$, Z = 4, D_x = 1.262 g/cm³. Colorless prism. Crystal dimensions: 0.600 × 0.400 × 0.200 mm³, $\mu(MoK_\alpha)$ = 0.77 cm⁻¹. F(000) = 824. T = 292 K.

Crystal Data of **2-t**. $C_{25}H_{25}O_3N$, M = 387.48. Monoclinic, a = 9.114 Å, b = 11.142 Å, c = 19.81 Å, β = 102.25°, V = 1966 Å³. Space group $P2_1/c$, Z = 4, D_x = 1.309 g/cm³. Colorless prism. Crystal dimensions: 0.400 × 0.500 × 0.200 mm³, $\mu(MoK_\alpha)$ = 0.80 cm⁻¹. F(000) = 824. T = 292 K.

RESULTS AND DISCUSSION

The benzoylacetate **1** underwent photocyclization to give 8-membered azalactones **2-c** and **2-t** in 21 and 31% yield, respectively, *via* remote hydrogen transfer from a charge-transfer state.[13] Charge-transfer interaction occurs in aminoalkyl ketones and the rate of the interaction is generally much higher than that of the intramolecular hydrogen abstraction when the connecting link is short. Proton transfer to carbonyl oxygen occurring in
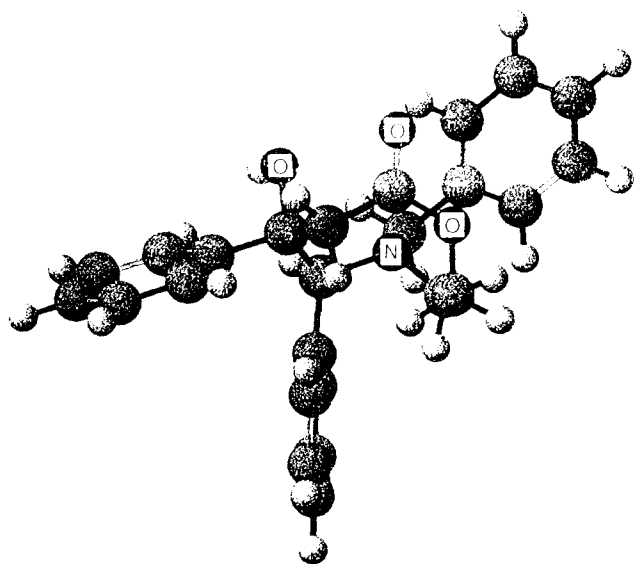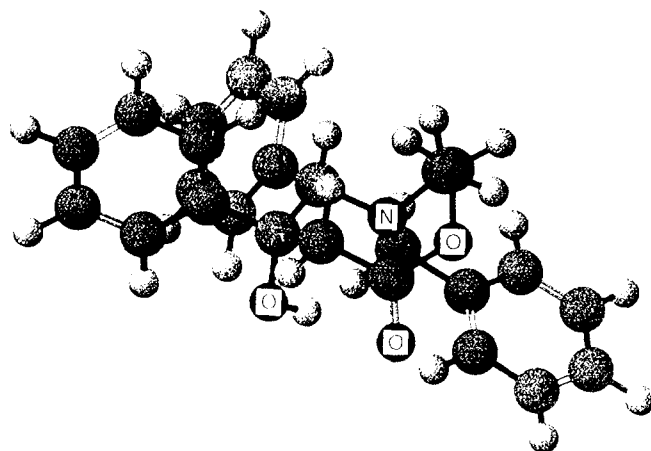

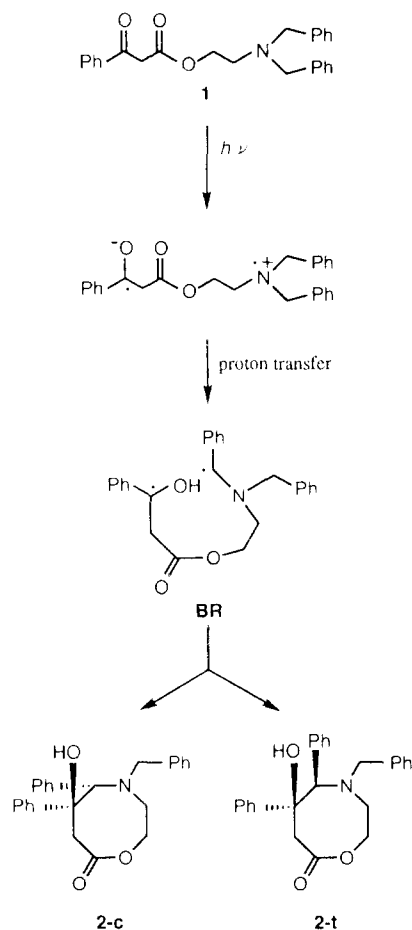Figure 2. Structure of **2-t**. Dihedral angle of C_5- and C_6-phenyl groups is 45.0°.

Scheme

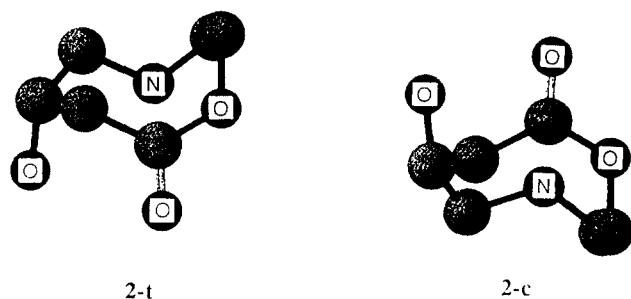

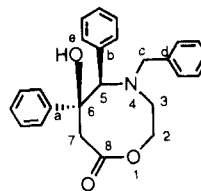Figure 1. Structure of **2-c**. Dihedral angle of C_5- and C_6-phenyl groups is 46.3°.

the charge-transfer state results in formation of the same biradical intermediate as that produced from possible direct hydrogen abstraction.[27,28] Therefore, the stereoselectivity in a long-chain biradical cyclization would be clarified by stereochemical analysis of the behavior of the 1,8-biradical produced from **1**.

2-t   2-c

Figure 3. Ring conformation of 2-t and 2-c.

Table 1. Distances between Atoms in 2-c and 2-t.

Atom	Atom	Distance/ Å	
		2-c	2-t
C(2)	C(7)	2.874	2.914
C(3)	C(6)	3.454	3.499
C(5)	C(8)	3.152	3.057
C(8)	N(4)	2.699	2.595
C(a)	C(b)	3.037	3.008
C(a)	C(c)	4.773	4.750
C(a)	C(d)	5.986	6.008
C(b)	O(e)	3.789	3.088
N(4)	O(1)	2.776	2.674

The conformation of the 1,8-biradical **BR** governing stereochemistry of the cyclization products should closely resemble those of the products. The structures of the 8-membered cyclic products **2-c** and **2-t** were determined by the X-ray structure analysis (Figs. 1 and 2). It should be noted that the 8-membered ring in both **2-c** and **2-t** existed in boat-chair like conformation (Fig. 3). Since the boat-chair conformation has been reported to be the energetically most stable in cyclooctane from molecular mechanics calculations,[29] the 8-membered ring in the azalactones **2-c** and **2-t** takes the boat-chair like conformation. The conformation of the 1,8-biradical **BR** just in cyclization should be boat-chair like form.

The distance between nitrogen and carbonyl carbon in **2-c** is shorter than that in **2-t** (Table 1), so that the transannular interaction between the nitrogen and the carbon[30] in **2-t** should be stronger than that in **2-c**. Indeed, the characteristic C=O stretching absorptions in the IR spectrum of **2-t** appeared at rather lower wavenumber than **2-c** (**2-t**, 1690; **2-c**, 1710 cm⁻¹). We previously reported that the C_5- and C_6- phenyl groups were *cis* to each other in **2-c** and *trans* in **2-t** by the inspection of Dreiding molecular model on consideration of the transannular interaction.[13] The x-ray structure analysis gave the same results. It should be note that the dihedral angle between the C_5- and C_6- phenyl groups in **2-c** is 46.3° and that in **2-t** is 45.0°. This twisted configuration with the dihedral angle of *ca* 45° might be characteristic in medium-sized cyclic compounds and be allowed by comparably flexible ring conformation in **2-c** and **2-t**. The long-chain 1,8-biradicals just in cyclization should have nearly the same configuration as the medium-sized cyclic compounds **2-c** and **2-t**, and also have the boat-chair like conformation. This would be responsible for the high *cis* to *trans* ratio(68%) in photoproducts from 1. The ratio in cyclobutanol formation in the Type II reaction of alkyl phenyl ketones which have no methyl groups on α-carbon is generally less than 30%.[19]

In conclusion, twisted configuration between substituents on the radical centers and boat-chair like ring conformation of the 1,8-biradical in the transition state for cyclization gives comparable possibility to form *cis*- and *trans*-isomers in long-chain biradical cyclization.

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