SYNTHESIS AND PROPERTIES OF NORCARADIENE-CYCLOHEPTATRIENE SYSTEM FUSED WITH ISOXAZOLE RING

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Abstract —— Novel norcaradiene-cycloheptatriene systems fused with arylisoxazoles were synthesized and their temperature dependent ^{1}H nmr spectra were studied. While the fusion of isoxazole ring much shifted the norcaradiene-cycloheptatriene equilibrium to the side of norcaradiene form, the rapid isomerizations of the norcaradienes with their enantiomers were observed and their $\Delta G_c^{\ddagger}$ values were obtained.

The norcaradiene (NCD)-cycloheptatriene (CHT) valence tautomerism has been a long-standing subject which is still interest of organic chemists.[1]   Although theoretical[2] and experimental[3] investigations of this tautomerism have been continued, it is only recently that the parent norcaradiene itself has been directly observed and determination of the kinetics of the isomerization of NCD ⇌ CHT has appeared.[4]   While the CHT form is normally more stable, and the free energy difference has been revealed to be 4.0-4.5 kcal/mol,[3,4,5] structural modifications such as suitable bridging, substitution or fusion of aromatic ring can reverse the usual order of stability.   A few examples of NCD fused with
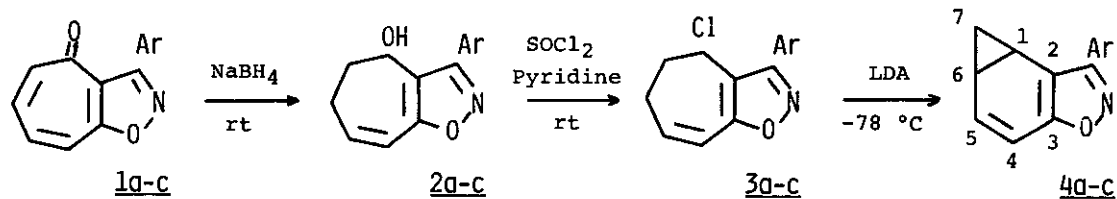
Scheme 1.   a: Ar = Ph; b: Ar = 4-ClC6H4; c: Ar = 4-MeOC6H4

heteroaromatic rings (pyrazole derivatives) have been reported, and the energy barrier of the equilibrium of the NCD with its enantiomer seems to be much dependent on the nature of the heteroaromatic rings.[6]   Thus, the annulation of heterocycles onto the NCD-CHT system may be helpful to estimate the aromatic character of heterocycles.   In connection with our previous studies concerning the stability of tropylium cation fused with isoxazole ring,[7] the synthesis and properties of the NCD-CHT system fused with arylisoxazole have been studied.   We report the preliminary results in this paper.

The reduction of 3-aryl-4H-cyclohept[d]isoxazol-4-ones (1a-c)[7,8] with sodium borohydride in ethanol gave alcohols 2a-c in good yields.   The compounds 2a-c were then converted to 3a-c[9] in 82, 92, and 90% yields, respectively, by the reaction with thionyl chloride in dichloromethane in the presence of pyridine at room temperature.[10]   The dehydrochlorination of 3a-c with lithium diisopropylamide (LDA) in tetrahydrofuran at -78 °C proceeded selectively, and the desired norcaradiene derivatives 4a-c were obtained in 61, 66, and 58% yields, respectively.[10,11]

The ^{1}H nmr spectra of the norcaradienes 4a-c in CS_2-CD_2Cl_2 (9:1) at various temperatures ranging from 19 °C to -100 °C show conclusively that the molecules are not rigid, and also provide informations on the barrier to tautomerizations of the NCD form.   The chemical shifts and coupling constants at 19 °C and -100 °C are summarized in Table 1.   The equivalence of the methylene protons (H_{7exo} and H_{7endo}) in the ^{1}H nmr spectra of 4a-c at 19 °C (Table 1) is consistent with rapidly oscillating pairs of norcaradienes 4a-c and their enantiomers 4A-C via cycloheptatrienes 5a-c (Scheme 2).   Observations of distinctly separate resonances for the methylene protons at -100 °C indicate that the valence isomerizations are frozen at this temperature in the nmr time scale, and provide unambiguous evidence in favor of the NCD forms.   The chemical shifts of H_1 and H_6 for 4a-c at 19 °C are almost the same as those in the spectra at -100 °C.   Therefore, it is suggested that compounds 4a-c (or 4A-C) almost exist in the NCD form, and population of the CHT 5a-c are very small even at 19 °C.   The spectral changes of H_1, H_6, H_{7exo}, and H_{7endo} of 4a are shown in Fig. 1.   At -50 °C, there is only a single very broaden peak of the methylene protons.   The spectral changes similar to 4a were also observed in the cases of 4b,c.   Thus, the coalescence temperatures and $\Delta G_C^{\ddagger}$ values for 4a-c were obtained to be -50 °C (9.9 kcal/mol), -40 °C (10.7 kcal/mol), and -50 °C (9.9 kcal/mol), respectively.[12]   No remarkable substituent effect of the aryl group

Table 1.   The ^{1}H nmr chemical shifts and coupling constants (J in Hz) at 19 °C
and –100 °C for <u>4a-c</u> (200 MHz, CS_2-CD_2Cl_2 9:1 in vol.)[a]

Compd.	Temp.	H_1	H_4	H_5	H_6	H_7
<u>4a</u>	19 °C	·2.52 $J_{1,6}$=7.3, $J_{1,7}$=6.9	6.46 $J_{4,5}$=10.0	6.55 $J_{5,6}$=5.5	2.09 $J_{6,7}$=7.2	0.84
	–100 °C	2.44 $J_{1,6}$=7.5, $J_{1,7exo}$=8.4, $J_{1,7endo}$=4.9	6.44 $J_{4,5}$=10.1	6.57 $J_{5,6}$=5.3	2.06 $J_{6,7exo}$=9.3 $J_{6,7endo}$=4.8	1.78 (exo) -0.14 (endo) J_{gem}=4.2
<u>4b</u>	19 °C	2.48 $J_{1,6}$=7.3, $J_{1,7}$=6.8	6.46 $J_{4,5}$=10.0	6.56 $J_{5,6}$=5.4	2.09 $J_{6,7}$=7.3	0.83
	–100 °C	2.42 $J_{1,6}$=7.6, $J_{1,7exo}$=8.1, $J_{1,7endo}$=4.9	6.43 $J_{4,5}$=10.1	6.57 $J_{5,6}$=5.1	2.06 $J_{6,7exo}$=9.0 $J_{6,7endo}$=4.7	1.78 (exo) -0.15 (endo) J_{gem}=4.5
<u>4c</u>	19 °C	2.50 $J_{1,6}$=7.2, $J_{1,7}$=6.8	6.43 $J_{4,5}$=10.0	6.52 $J_{5,6}$=5.4	2.08 $J_{6,7}$=7.1	0.82
	–100 °C	2.42 $J_{1,6}$=7.2, $J_{1,7exo}$=8.4, $J_{1,7endo}$=5.0	6.40 $J_{4,5}$=10.2	6.54 $J_{5,6}$=5.2	2.05 $J_{6,7exo}$=8.7 $J_{6,7endo}$=5.0	1.76 (exo) -0.16 (endo) J_{gem}=4.0

a The numbering of hydrogens in a way of norcaradiene system is employed as a
matter of convenience.
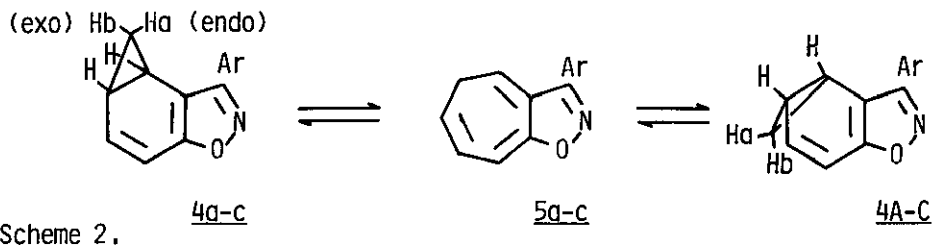
Scheme 2.

seems to be reflected in the valence isomerizations.

In benzonorcaradiene[13] and pyrazolonorcaradiene[6] 7a, the methylene protons on the cyclopropane rings appear separately at room temperature. In fact, the coalescence temperatures for the valence isomerizations of benzonorcaradiene and 7a (Scheme 3) with their enantiomers via the corresponding CHT forms have been obtained to be 180 °C and 35 °C, respectively. The resonance energies of benzene and pyrazole are lost in the corresponding CHT forms in the valence isomerizations. The significant low 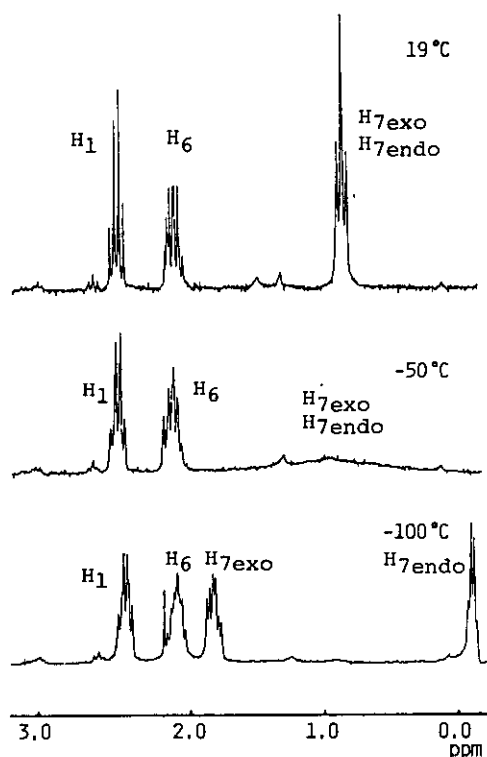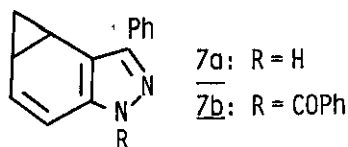coalescence temperature for 4a-c relative to those for benzonorcaradiene and 7a would be ascribed mainly to the low resonance energy of isoxazole as compared with those of benzene (36 kcal/mol) and pyrazole (25 ±6 kcal/mol).[14] Interesting is the coalescence temperature in the case of 7b, which has a benzoyl group on the nitrogen atom, has been obtained to be -35 °C. This value is close to that of 4a-c. The resonance energy of the benzoyl-substituted pyrazole in 7b would be reduced as compared with that in 7a.[15] The resonance energy of isoxazole has generally been accepted to be 6 ± 5 kcal/mol.[14] Thus, the low coalescence temperatures for 4a-c ⇌ 5a-c ⇌ 4A-C can also suggest that the lone pair electrons on the oxygen atom of the C=N-O group is not delocalized so much. This fact could also be correlated with our previous studies which demonstrated that tropylium ion annulated with isoxazole ring (pK_R+ < +1.0) is less stable than benzotropylium cation,[7] and 7-oxa-8-aza-tricyclo[$4.3.1.0^{1,6}$]deca-2,4,8- triene exists as norcaradiene form rather than a bridged oxazonine.[16]

The detailed analysis concerning the kinetics of the valence isomerization 4a-c

Fig. 1. ^{1}H NMR spectra of H_1, H_6, and H_7 protons of 4a at various temperatures.

7a: R = H
7b: R = COPh

Scheme 3.

⇌ 5a-c ⇌ 4A-C are now underway.

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9 For 2a: mp 99-100 °C.   For 2b: mp 82-84 °C.   For 2c: mp 94-96 °C (decomp).

10 Satisfactory elemental analyses or high resolution mass spectral data are obtained for all new compounds in this paper.

11 For 3a: bp 82 °C (10.6 Pa).   For 3b: mp 106-107 °C.   For 3c: mp 78-80 °C (decomp).

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