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Lythraceous Alkaloids. XIV. Kinetic Equalization of Carbon-13 Nuclear Magnetic Resonance Chemical Shifts in *N,O*-Dimethyllythranidine, a Cyclophane Bearing Asymmetric Carbon Atoms[1)]

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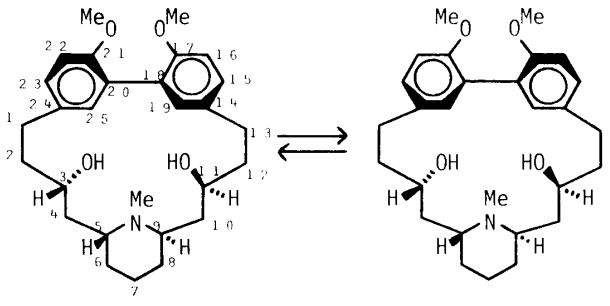
Temperature-dependent carbon-13 nuclear magnetic resonance (^{13}C-NMR) studies have disclosed that the mobile equilibrium in *N,O*-dimethyllythranidine (**1**) involves mainly two dynamic processes, which are rotation about the carbon–carbon bond between two phenyl rings and reversal of the piperidine ring. At ambient temperature, ^{13}C chemical shift differences due to rotational movement were averaged, while those due to ring flip of piperidine moiety were not. This provides another example of "selective kinetic equalization of chemical shifts."

Keywords——Lythrum alkaloid; *N,O*-dimethyllythranidine; biphenyl; cyclophane; ^{13}C-NMR; coalescence temperature; ring reversal; conformation

Lythraceous alkaloids of type A[2)] are regarded as heteraphanes[3)] possessing a *meta*, *meta*-biphenylene unit and a piperidine ring in the molecule. Detailed circular dichroism (CD) studies[4)] have disclosed that the chirality of the biphenyl moiety in these alkaloids and related compounds is not attributable to atropisomerism involving restricted rotation about the single bond between the two phenyl rings but is due to the difference in the population of rotamers (**1a** and **1b** in the case of *N,O*-dimethyllythranidine (**1**)). The degree of bias should be determined by the nature of the four asymmetric carbon atoms on the ansa-chain. The free energy difference between the two rotamers **1a** and **1b** of *N,O*-dimethyllythranidine has been estimated to be 0.8 kcal/mol.[4)] However, as temperature-dependent CD curves cannot afford kinetic parameters, we have studied the temperature-dependent carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra of **1** to obtain some data on this equilibrium process.



1a **1b**

Experimental

Material——*N,O*-Dimethyllythranidine was prepared from lythranidine according to the reported procedure.[5)]

Measurement of ^{13}C-NMR Spectra——A JEOL JNM-FX 100 or a Bruker HW-400 spectrometer was used. Temperature-dependent ^{13}C-NMR spectra were obtained with the former and recorded at 17 points between +20 °C and +80 °C.

A sample was prepared by dissolving 0.1 mmol of **1** in 0.5 ml of $CDCl_3$. Tetramethylsilane (TMS) was used as an internal standard.

Results and Discussion

The fast exchange spectrum (Fig. 1a) showed 16 peaks including that of $CDCl_3$. Except for peaks e and f, each peak in the aliphatic region was easily assigned by ^1H single frequency off-resonance decoupling (SFORD)[6,7] and selective proton irradiation[8] at 100 MHz at 27 °C. Assignment of the carbons in the aromatic part was achieved by application of the reported data[9] for symmetrically substituted biphenyls and SFORD. Shift values are listed in Table I.

The mobile equilibrium in *N,O*-dimethyllythranidine (**1**) involves three dynamic processes: i, rotational movement about the carbon–carbon bond between the two phenyl rings to cause an inversion of biphenyl chirality, ii, reversal of the piperidine ring; and iii, pyramidal inversion of the nitrogen atom. The last process can be excluded from consideration, because the free energy difference (ΔG°) (**2e**→**2a**) was determined to be 2.7 kcal/mol in cyclohexane[10,11] indicating that $\simeq 99\%$ of the molecules exist in the conformation with an equatorial *N*-methyl group. Conformational changes in **1** in terms of the processes i and ii are shown in Chart 1. Conformers **a** and **b** are super-imposable on **c** and **d**, respectively, as this molecule is symmetrically substituted. Therefore, when we discuss the conformational chirality[12] of the biphenyl moiety in **1**, only the pair **a** and **b** (or **c** and **d**) need be considered. The ^{13}C-NMR spectrum of **1** at 27 °C at 100 MHz afforded 28 peaks corresponding to all the carbon atoms in the molecule. This can be interpreted in either of two ways, *i.e.*, that the conformation of **1** is extremely biased to one side **a** or **b**, or the rate of biphenyl rotation is so rapid on the NMR time scale that each pair of signals corresponding to **a** and **b** is averaged. It can be concluded that the latter is the case, because the CD studies have shown that population of the favored conformer **a** at room temperature is *ca.* 80% ($\Delta G^\circ = 0.8$ kcal/mol).[4]

Next, our attention was focused on the piperidine ring reversal. Though conformers **a** and **c** are identical, a dynamic equilibrium process should exist, where axial H-5 in **a** is

TABLE I. ^{13}C Chemical Shifts of **1**

Symbol	Assignment	Chemical shift, δ ppm	
		At 80 °C[a]	At 27 °C[b]
a	C-7	21.1	20.9
b	C-6, C-8	23.8	22.9, 24.4
c	C-1, C-13	30.2	29.9, 30.3
d	$-NCH_3$	35.1	34.9
e	C-2, C-12	38.3[c]	35.9, 39.5
f	C-4, C-10	38.7[c]	36.5, 40.3
g	$-OCH_3$	56.0	55.9, 56.0
h	C-5, C-9	57.8[d]	54.6, 62.0
i	C-3, C-11	71.5[d]	69.0, 74.7
j	C-16, C-22	111.4	110.6, 111.2
k	C-15, C-23	128.1	128.3, 128.8
l	C-18, C-20	128.8	128.5, 129.0
m	C-19, C-25	133.2	132.8, 133.7
n	C-14, C-24	134.5	133.8, 135.3
o	C-17, C-21	155.4	155.1, 155.4

a) At 25 MHz. *b*) At 100 MHz. *c*) Assignments might be reversed.
d) Broad signal.

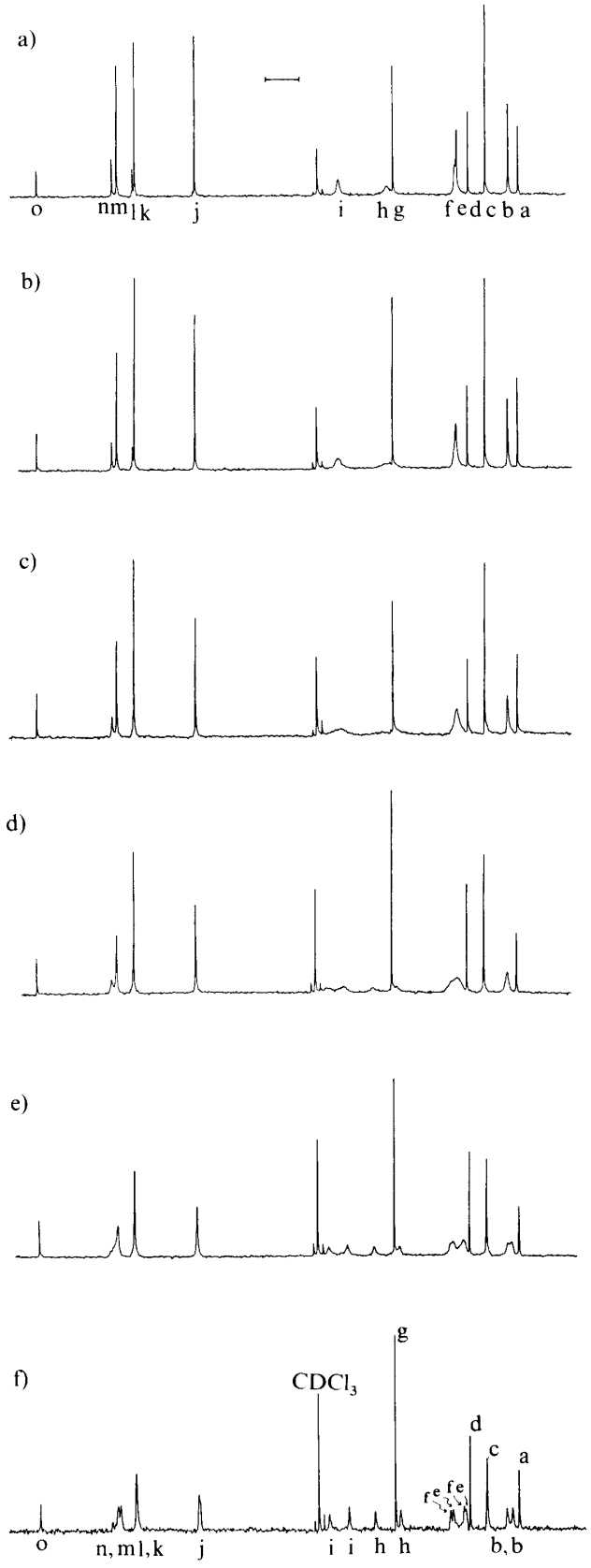


Fig. 1. ^{13}C-NMR Spectra of *N,O*-Dimethyllythranidine (**1**)

a) 80 °C, calibration bar represents 10 ppm; b) 70 °C; c) 60 °C; d) 50 °C; e) 40 °C; f) 30 °C.

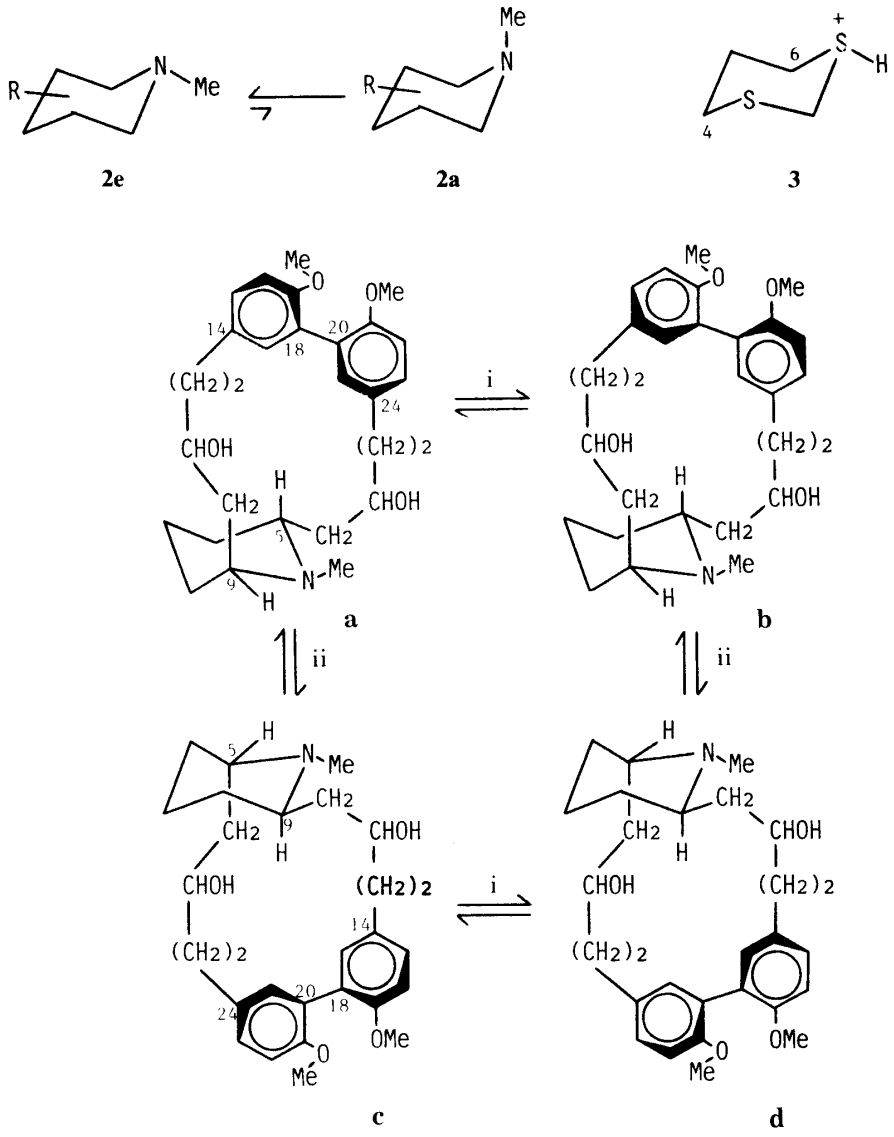


Chart 1. Mobile Equilibria in *N,O*-Dimethyllythranidine (**1**)

i, biphenyl rotation; ii, piperidine ring flip.

changed to equatorial by the piperidine ring flip. Temperature-dependent ^{13}C-NMR spectra of **1** showed that, as the temperature was raised, each pair of peaks b, e, f, h, i, j, and m became a single peak through distinct points of coalescence, as shown in Fig. 1. Free energies of activation ($\Delta G^{\neq}$) for the change in these resonances were calculated from the standard equation.[13] The value, $\Delta G^{\neq} \simeq 15.6$ at the pertinent temperature (Table II), is rather higher than normal values reported for piperidine ring reversal,[14] probably because of the cyclic nature of the molecule. The free energies of activation for aromatic peaks j and m are on the same level as that for aliphatic peaks indicating that piperidine ring reversal is directly transferred to the aromatic rings.

Lambert, Vulgaris, Featherman, and Majchrzak[15] have reported that in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of the protonated 1,3-dithiane **3** in fluorosulfonic acid at $+70\,^{\circ}$, proton exchange was rapid enough to average all geminal nonequivalencies but was still slow enough to retain separate identities at the 4 and 6 positions. This phenomenon was termed "selective kinetic equalization of chemical shifts." In the ^{13}C-NMR spectrum of **1** at around 20 °C, nonequivalencies of chemical shifts due to

TABLE II. Free Energies of Activation ($\Delta G^{\neq}$) for Pertinent Carbon Atoms

Carbon	Symbol	$\Delta G^{\neq}$ (kcal/mol)	Temp. (°C)
C-6, C-8	b	15.7±0.1	43
C-2, C-12	e	15.5±0.1	50
C-4, C-10	f	15.6±0.1	52
C-5, C-9	h	15.6±0.1	60
C-3, C-11	i	15.6±0.1	56
C-16, C-22	j	15.7±0.1	32
C-19, C-25	m	15.6±0.1	35

biphenyl rotation were averaged, but those due to piperidine ring flip were not. Therefore, the dynamic processes described here constitute another example of "selective kinetic equalization of chemical shifts" according to the above terminology.

References and Notes

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