Hetera-*p*-carbophanes. III. Conformation of Amide Groups in and Internal Rotation of Diaza[*n*]paracyclophanes with Two Alkoxy Groups at the Benzene Ring[1]

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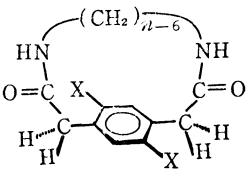
A series of diazadioxo[*n*]paracyclophane derivatives with two alkoxy groups at the benzene ring were prepared. The conformation of amide groups in these compounds were studied by infrared, PMR, and ^{13}C NMR spectra to draw a conclusion that both amide groups are *s-trans*. Thus the infrared absorptions at 3430 and 3405 cm^{-1} are attributed to N—H···π interacting and N—H···O bonded *trans* forms, respectively. NCH_2 protons, which are separated by 5 bonds from the asymmetric center, as well as benzylic protons, were found to be non-equivalent when the rotation of the aromatic ring was slow. PMR spectra of the compounds studied at various temperatures indicate that introducing alkoxy groups in place of methyls at the benzene ring increases the barrier to rotation of the aromatic ring to a great extent.

In a recent paper, preparation and internal rotation of diaza[*n*]paracyclophane derivatives ($\mathbf{1}_n$ and $\mathbf{2}_n$, n=12—16) were reported.[2] Two amide groups in these compounds were suggested to take single conformation. From the infrared N—H stretching (ν_{NH}) absorptions, there were two possibilities: *s-cis* or *s-trans* with N—H···π interaction. From the scale model of the molecule, single absorption due to N—H stretching at the lower region, and PMR results which showed a single signal for NCH_2 protons, *s-cis* conformation was considered favorable.



$\mathbf{1}_n$: X=H, n=12—16
$\mathbf{2}_n$: X=CH_3, n=11—16
$\mathbf{3}_n$: X=OCH_3, n=11—16 and 18
$\mathbf{4}_{18}$: X=OC_2H_5, n=18

Further evidence will be needed to confirm the conformation of the amide group, because formation of N—H···π bond will lower the ν_{NH} frequency to the region of ν_{NH} absorption due to *s-cis* conformation and PMR data themselves can not rule out the *s-trans* conformation. Furthermore, the scale model of a molecule may not be taken as decisive evidence. Introduction of methoxy groups to the benzene ring will increase electron density on the benzene ring to favor the N—H···π bond.[3] Thus investigation on diaza[*n*]paracyclophane with methoxy groups will lend help in interpretation of the conformation of the amide groups.

The purpose of this paper is four fold. The first is to report results of preparation and characterization of $\mathbf{3}_n$ and $\mathbf{4}_{18}$ which carry alkoxy groups at the benzene ring, the second is finding of N—H···π and N—H···O bondings in these compounds, the third is establishment of *s-trans* conformation of the amide group by various means, and the fourth is barriers to rotation of the dialkoxybenzene rings. A part of the results on the last item was reported briefly in a short communication.[1]

Experimental

The syntheses of $\mathbf{3}_n$ and $\mathbf{4}_{18}$ were accomplished by condensation of α,ω-diamines with 2,5-dialkoxy-1,4-phenylenediacetyl dichloride under high dilution conditions. The latter compounds were prepared from 1,4-dialkoxybenzene according to the previously reported scheme.[2]

2,5-Dimethoxy-1,4-bis(chloromethyl)benzene. A mixture of 46 g(0.33 mol) of 1,4-dimethoxybenzene, 70 g(0.87 mol) of 37% formalin, 350 ml of concd. hydrochloric acid, and 300 ml of glacial acetic acid was warmed at 50—60 °C for 7 hr with stirring and introducing dry hydrogen chloride. The resulting solid was collected by filtration and was washed with water. Recrystallization from chloroform gave 58 g (yield, 74%) of pure compound, mp 163—164 °C (lit,[4] mp 165 °C).

2,5-Diethoxy-1,4-bis(chloromethyl)benzene was obtained similarly in a 60% yield, mp 148—151 °C (from chloroform). IR: 1225 and 1055 (ν_{C-OEt}), 700(ν_{C-Cl}) cm^{-1}. NMR ($CDCl_3$,δ): 1.42(6H, t, J=8 Hz), 4.04(4H, q, J=8 Hz), 4.62(4H, s), 6.92(2H, s). This compound was directly used for the next reaction.

2,5-Dimethoxy-1,4-bis(cyanomethyl)benzene. A suspension of 35 g(0.15 mol) of the above dichloride in 400 ml of dimethyl sulfoxide was slowly added to a stirred solution of 26 g(0.53 mol) of sodium cyanide in 300 ml of dimethyl sulfoxide at room temperature during a period of 1.5 hr. After the addition, the reaction mixture was warmed at 50—60 °C for 2 hr with stirring. The reaction mixture was poured into ice-water (*ca.* 3 l) and the resulting solid was collected by filtration. Recrystallization from chloroform gave 28 g(85%) of pure compound, mp 191—192 °C. IR: 2250($\nu_{C\equiv N}$), 1225 and 1045(ν_{C-OMe}) cm^{-1}. NMR($CDCl_3$, δ): 3.70(4H, s), 3.85(6H, s), 6.93(2H, s).

Found: C, 66.41; H, 5.36; N, 13.05%. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.39; N, 12.96%.

2,5-Diethoxy-1,4-bis(cyanomethyl)benzene was prepared similarly in a 90% yield, mp 177.5—178.5 °C (from hexane–ether). IR: 2250($\nu_{C\equiv N}$), 1230 and 1050(ν_{C-OEt}) cm^{-1}. NMR ($CDCl_3$, δ): 1.42(6H, t, J=8 Hz), 3.50(4H, s), 4.05(4H, q, J=8 Hz), 6.91(2H, s). This compound was directly used for the next reaction.

2,5-Dimethylphenylacetonitrile was obtained similarly from 2,5-dimethylbenzyl chloride[5] in an 86% yield, mp 29.5—31.0 °C (from hexane) (bp 126—128 °C/11—12 mmHg). IR (neat): 2250($\nu_{C\equiv N}$) cm^{-1}. NMR($CDCl_3$, δ): 2.28(3H, s), 2.32(3H, s), 3.60(2H, s), 7.07(2H, s), 7.16(1H, s).

Found: C, 82.88; H, 7.64; N, 9.65%. Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65%.

2,5-Dimethoxy-1,4-phenylenediacetic acid, mp 232—235 °C (decompn.), was prepared from the corresponding dicyanide by the previously reported method[2] in a 77% yield. IR: 1710($\nu_{C=O}$), 1230 and 1045(ν_{C-OMe}) cm^{-1},

Table 1. Diaza[*n*]paracyclophanes

Compound	Molecular formula	Mp (°C)	Analytical data C(%)	H(%)	N(%)	Mol wt (M^+)	Recrystallization solvent	Yield (%)	IR (KBr disk) (cm^{-1}) ν_{NH}	Amide I	Amide II	ν_{C-OR}
$\mathbf{2}_{11}$	$C_{17}H_{24}N_2O_2$	199.5—200.5	70.82	8.12	9.62[a]	288[a]	CH_2Cl_2—CCl_4	25	3340	1650	1545	
			70.80	8.39	9.71[a]	288.4[a]						
$\mathbf{3}_{11}$	$C_{17}H_{24}N_2O_4$	183.5—184.5	63.81	7.68	8.85	320	$CHCl_3$—CCl_4	11	3320	1665, 1640	1540	1220, 1045
			63.73	7.55	8.74	320.4						
$\mathbf{3}_{12}$	$C_{18}H_{26}N_2O_4$	183.5—184.0	64.36	7.86	8.23	334	$CHCl_3$—CCl_4	56	3320	1665	1520	1220, 1050
			64.65	7.84	8.38	334.4						
$\mathbf{3}_{13}$	$C_{19}H_{28}N_2O_4$	190.5—192.0	64.87	8.64	7.79	348	CH_3OH	46	3250	1640	1540	1215, 1040
			65.49	8.10	8.04	348.4						
$\mathbf{3}_{14}$	$C_{20}H_{30}N_2O_4$	156.5—157.5	66.02	8.63	7.54	362	CH_2Cl_2—CCl_4	71	3300	1650	1530	1215, 1040
			66.27	8.34	7.73	362.5						
$\mathbf{3}_{15}$	$C_{21}H_{32}N_2O_4$	180.0—181.5	66.77	8.79	7.37	376	$CHCl_3$	66	3280	1660, 1630	1545	1220, 1050
			66.99	8.57	7.44	376.5						
$\mathbf{3}_{16}$	$C_{22}H_{34}N_2O_4$	198.0—199.5	67.62	8.55	6.90	390	$CHCl_3$—CCl_4	18	3300	1645	1545	1220, 1050
			67.66	8.78	7.17	390.5						
$\mathbf{3}_{18}$	$C_{24}H_{38}N_2O_4$	234.0—235.0	68.70	9.11	6.88	418	$CHCl_3$—CCl_4	—	3300	1640	1545	1220, 1050
			68.87	9.15	6.69	418.6						
$\mathbf{4}_{18}$	$C_{26}H_{42}N_2O_4$	198.5—199.5	69.91	9.76	6.15	446	$CHCl_3$	—	3350, 3300	1645	1545	1200, 1060
			69.92	9.48	6.27	446.4						

a) The numerical data in the upper column are those found and those in the lower column are the calculated.

2,5-Diethoxy-1,4-phenylenediacetic acid, mp 218—221 °C (decompn.), was prepared similarly in a 70% yield. IR: 1710($\nu_{C=O}$), 1220 and 1045(ν_{C-OEt}) cm^{-1}.

2,5-Dimethylphenylacetic acid, mp 124.5—126.0 °C (from chloroform), was prepared similarly in a 74% yield. IR: 1700($\nu_{C=O}$) cm^{-1}.

Found: C, 73.07; H, 7.07%. Calcd for $C_{10}H_{12}O_2$: C, 73.20; H, 7.37%.

2,5-Dimethoxy-1,4-phenylenediacetyl dichloride was obtained by the action of thionyl chloride in absolute ether in an 81% yield, mp 141.0—143.0 °C (from ether). IR: 1800($\nu_{C=O}$), 1220 and 1040(ν_{C-OMe}) cm^{-1}. NMR($CDCl_3$, δ): 3.78(6H, s), 4.11(4H, s), 6.71(2H, s).

2,5-Diethoxy-1,4-phenylenediacetyl dichloride, mp 110—112 °C (from ether), was prepared similarly in an 82% yield. IR: 1800($\nu_{C=O}$), 1225 and 1045(ν_{C-OEt}) cm^{-1}. NMR($CDCl_3$, δ): 1.39(6H, t, J=8 Hz), 4.00(4H, q, J=8 Hz), 4.10(4H, s), 6.73(2H, s).

2,5-Dimethylphenylacetyl chloride, yellowish oil, was prepared similarly in an almost quantitative yield. IR(neat): 1800 ($\nu_{C=O}$) cm^{-1}. NMR(CCl_4, δ): 2.26(3H, s), 2.31(3H, s), 4.02(2H, s), 7.00(3H, s).

Syntheses of Diaza[n]*paracyclophanes.*

Synthetic method will be described by taking the case of 13,16-dimethyl-3,9-diaza-2,10-dioxo[11]paracyclophane ($\mathbf{2}_{11}$) as an example.

A solution of 1.3 g(*ca.* 5 mmol) of 2,5-dimethyl-1,4-phenylenediacetyl dichloride in 100—150 ml of tetrahydrofuran was slowly added to a vigorously stirred and refluxing mixture of 2.0—3.0 g of potassium carbonate and 0.5 g (*ca.* 5 mmol) of pentamethylenediamine in 800 ml of tetrahydrofuran over a period of 26 hr, employing a high-dilution appratus. After filtration, the solvent was evaporated *in vacuo* to give a yellow solid. This solid was chromatographed on silica-gel (25 g). The fraction eluted with dichloromethane gave 370 mg(25%) of $\mathbf{2}_{11}$, mp 199.5—200 °C on recrystallization from carbon tetrachloride—dichloromethane. The melting points, the analytical data, and the solvent of recrystallization for each compound are summarized in Table 1.

N,N′-*Dipropyl-2,5-dimethoxy-1,4-phenylenediacetamide*(**5**) was prepared by the previously reported method[2] in an 86% yield, mp 197.0—197.5 °C (from carbon tetrachloride—chloroform). IR: 3290(ν_{NH}), 1645(amide I), 1550(amide II), 1220 and 1050(ν_{C-OMe}) cm^{-1}. NMR($CDCl_3$, δ): 0.85 (6H, m), 1.45(4H, m), 3.15(4H, q), 3.51(4H, s), 3.81(6H, s), 5.95(2H, b), 6.82(2H s).

Found: C, 64.30; H, 8.37; N, 8.16%. Calcd for $C_{18}H_{28}N_2O_4$: C, 64.62; H, 8.39; N, 8.33%.

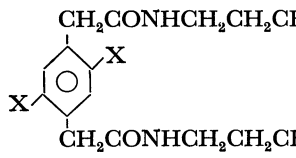
N,N′-*Hexamethylenebis(2,5-dimethylphenylacetamide)*. A stirred mixture of 0.5 g(43 mmol) of hexamethylenediamine, 1.5 g(0.83 mmol) of the 2,5-dimethylphenylacetyl chloride, 3 g of potassium carbonate, and 100 ml of tetrahydrofuran was refluxed for 2 hr. The resulting solid was collected by filtration and washed with water. After recrystallization from carbon tetrachloride—chloroform, it was obtained in an almost quantitative yield, mp 176.5—177.0 °C. IR: 3300(ν_{NH}), 1640(amide I), 1540(amide II) cm^{-1}. NMR ($CDCl_3$, δ): 1.0—1.6(8H, b), 2.22(6H, s), 2.30(6H, s), 3.13 (4H, q), 3.51(4H, s), 5.15—5.60(2H, b), 6.9—7.1(6H, m).

Found: C, 76.26; H, 9.06; N, 6.62%. Calcd for $C_{26}H_{36}N_2O_2$: C, 76.43; H, 8.88; N, 6.86%.

Measurement of the Spectra. The infrared spectra were recorded on either a Hitachi EPI-G2 grating infra-red spectrometer (4000—400 cm^{-1}) with KBr disk or a Perkin-Elmer 112G single beam grating spectrophotometer (3500—3000 cm^{-1}) with dilute chloroform solution. The PMR spectra were measured on a Hitachi R-20B spectrometer operating at 60 MHz at 34 °C. Samples were dissolved in deuteriochloroform, using TMS as an internal reference. Chemical shifts are recorded as ppm down field from TMS. Lanthanide induced shift measurements were performed by the stepwise addition of lanthanide shift reagents (either $Eu(fod)_3$-d_{27} or $Eu(dpm)_3$) to the deuteriochloroform solution of substrate. The molar ratios of the shift reagent to the substrate were from 0 through 0.6. ^{13}C FT NMR spectra were taken with a JEOL PFT-100 spectrometer in the deuteriochloroform-locked mode at 15.358808 MHz. Samples were dissolved in deuteriochloroform and TMS was used an internal reference. The mass spectra were observed on a Hitachi RMU-6L spectrometer.

Results and Discussion

Infrared Spectra. The ν_{NH} absorptions of these compounds are summarized in Table 2 together with those of compounds $\mathbf{1}_n$, $\mathbf{2}_n$, and open-chain models of **5**, **6**, and **7**.



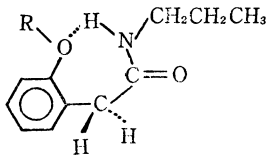
5: X=OCH_3
6: X=H
7: X=CH_3

Table 2. Absorption maxima due to N—H stretching vibration of diaza[n]paracyclophanes and related compounds in $CHCl_3$ (cm^{-1})[a]

	s-trans	*s-cis* or N—H···π interacting	*s-trans*	*s-cis* or N—H···π interacting	*s-cis* or N—H···π interacting	N—H···O interacting
		$\mathbf{1}_n$		$\mathbf{2}_n$		$\mathbf{3}_n$
n=11				3428(272)	3432(200)	3408(70)
12		3436(277)		3433(423)	3433(176)	3404(91)
13		3436(171)		3431(259)	3431(130)	3407(108)
14		3437(251)		3433(244)	3436(141)	3404(105)
15		3440(267)		3432(188)	3434(117)	3406(75)
16		3439(181)		3431(161)	3435(107)	3403(71)
						$\mathbf{4}_{18}$
					3432(148)	3390(80)
		6		**7**		**5**
	3453(133)	3437(223)	3449(64)	3427(192)	3433(185)	3400(78)

a) The numerical data in parentheses are ε_{max}.

As are seen from Table 2, hetera-*p*-carbophanes which carry alkoxy groups at the benzene ring show two ν_{NH} absorptions in contrast to the presence of only one ν_{NH} absorption in $\mathbf{1}_n$ and $\mathbf{2}_n$. These absorptions occur at *ca.* 3430—3440 cm^{-1} region for compounds $\mathbf{1}_n$ and $\mathbf{2}_n$, whereas $\mathbf{3}_n$ and $\mathbf{4}_{18}$ show absorption at *ca.* 3405 cm^{-1} in addition to an absorption corresponding to those of $\mathbf{1}_n$ and $\mathbf{2}_n$. As a clue to solve the assignment problem, the model compounds (**5**, **6**, and **7**) may be examined. The amide groups in these open-chain compounds may be assumed to take *s-trans* conformation.[2] Interestingly, those which do not possess alkoxy group showed only one absorption due to N—H stretching, whereas **5** showed two ν_{NH} absorptions which correspond to those of $\mathbf{3}_n$ and $\mathbf{4}_{18}$. The absorption at the higher frequency which is common for both types of compounds may be assigned to the *s-trans* amide which is interacting with the π-electrons of the benzene ring.[3] Since the extra band existing in the alkoxy compounds is located at lower frequency than that of N—H···π interacting form, it can not be attributed to a free form. The most probable candidate for the absorption is the N—H···O hydrogen bonded form (**8**), because it is improbable to assume that *s-cis* conformation is possible for compound **5** and the N—H···O bond will lower ν_{NH} frequency to a considerable extent.[6]



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The same discussion will apply to the assignment of the N—H stretching absorption of $\mathbf{3}_n$ and $\mathbf{4}_{18}$. Thus the ν_{NH} absorption at *ca.* 3405 cm^{-1} is attributed to intramolecular N—H···O bond. However the origin of the absorption at higher frequency is not yet established because none of the possibilities of *s-cis* conformation and N—H···π interaction has yet been ruled out. Thus evidence from other sources is needed for assignment of the IR absorption.

PMR Spectra. PMR spectral data of $\mathbf{3}_n$ and $\mathbf{4}_{18}$ are summarized in Table 3 as well as those of $\mathbf{2}_{11}$ and open-chain compound for comparison. Change in signal shapes of the bridge methylene protons, except the NCH_2 in $\mathbf{3}_n$, according to the bridge length resembles the case of $\mathbf{2}_n$ and reflects rigidity and mobility of the molecules. However the chemical shifts of the bridge methylenes of $\mathbf{3}_n$ with small ring size are located at the higher field, relative to the corresponding methylenes of $\mathbf{2}_n$, by *ca.* 0.1 ppm, suggesting the larger anisotropy effect of the dimethoxybenzene ring. Benzylic protons of $\mathbf{2}_{11}$ and $\mathbf{3}_{11}$—$\mathbf{3}_{16}$ gave signals of the AB type, whereas those of $\mathbf{3}_{18}$, $\mathbf{4}_{18}$, and the open-chain amide (**5**) gave singlet signals. These changes must be interpreted by assuming the fast internal rotation of the benzene ring for the compounds showing the A_2 type signals and the slow rotation for the compounds showing the AB type, because these compounds are expected to give rise to nonequivalent benzylic protons when the internal rotation is frozen on the NMR time scale.

The spectral feature of $\mathbf{3}_{11}$—$\mathbf{3}_{16}$ is that they show two signals at *ca.* 2.8 and *ca.* 3.5 ppm due to NCH_2 protons. In sharp contrast, $\mathbf{2}_n$ was reported to show only one signal for the NCH_2 groups. $\mathbf{3}_{18}$, $\mathbf{4}_{18}$, and **5** also show one signal for the NCH_2. The internal

TABLE 3. NMR DATA OF DIAZA[*n*]PARACYCLOPHANES AND RELATED COMPOUND IN $CDCl_3$ AT 34 °C (δ from internal TMS)[a]

Compound	Ar-H	NH	OCH_3	CH_2CO	NCH_2	NCH_2'	β-CH_2[b]	γ—δ-CH_2[b]
$\mathbf{2}_{11}$	7.08	4.85	2.32[c]	3.56 (q, J=15.0,	3.15		1.25	0.3—0.9
	(s, 2H)	(b, 2H)	(s, 6H)	$\Delta\delta$=17.3 Hz, 4H)	(m, 4H)		(m, 4H)	(m, 2H)
$\mathbf{3}_{11}$	6.88	5.32	3.84	3.56 (q, J=14.7,	3.40	2.85	1.15	0.2—0.8
	(s, 2H)	(b, 2H)	(s, 6H)	$\Delta\delta$=49.3 Hz, 4H)	(m, 4H)		(b, 4H)	(m, 2H)
$\mathbf{3}_{12}$	6.87	5.57	3.85	3.56 (q, J=14.7,	3.40	2.85	1.23	0.80
	(s, 2H)	(b, 2H)	(s, 6H)	$\Delta\delta$=46.5 Hz, 4H)	(m, 4H)		(b, 4H)	(b, 4H)
$\mathbf{3}_{13}$	6.91	5.82	3.84	3.57 (q, J=13.8,	3.55	2.80	1.25	0.88
	(s, 2H)	(b, 2H)	(s, 6H)	$\Delta\delta$=47.1 Hz, 4H)	(m, 4H)		(b, 4H)	(b, 6H)
$\mathbf{3}_{14}$	6.88	5.85	3.84	3.57 (q, J=14.6,	3.50	2.80		1.60—0.60
	(s, 2H)	(b, 2H)	(s, 6H)	$\Delta\delta$=44.3 Hz, 4H)	(m, 4H)			(b, 12H)
$\mathbf{3}_{15}$	6.87	5.88	3.84	3.52 (q, J=14.7,	3.50	2.85		1.60—0.85
	(s, 2H)	(b, 2H)	(s, 6H)	$\Delta\delta$=43.0 Hz, 4H)	(m, 4H)			(b, 14H)
$\mathbf{3}_{16}$	6.87	5.95	3.83	3.50 (q, J=14.4,	3.50	2.85		1.60—0.85
	(s, 2H)	(b, 2H)	(s, 6H)	$\Delta\delta$=39.8 Hz, 4H)	(m, 4H)			(b, 16H)
$\mathbf{3}_{18}$	6.82	5.85	3.81	3.52	3.22			1.70—1.00
	(s, 2H)	(b, 2H)	(s, 6H)	(s, 4H)	(q, 4H)			(b, 20H)
$\mathbf{4}_{18}$	6.83	5.93		3.52	3.21			1.70—1.05
	(s, 2H)	(b, 2H)		(s, 4H)	(q, 4H)			(b, 20H)
5	6.82	5.95	3.81	3.51	3.15		1.45	0.85[d]
	(s, 2H)	(b, 2H)	(s, 6H)	(s, 4H)	(q, 4H)		(m, 4H)	(m, 6H)

a) s=singlet, q=quartet, m=multiplet, b=broad signal b) relative to N-atom c) aromatic methyl
d) propyl methyl

rotation in compounds $\mathbf{3}_{11}$—$\mathbf{3}_{16}$ is slow, as will be discussed later, whereas that in $\mathbf{3}_{18}$ and $\mathbf{4}_{18}$ is fast. Bifurcation of the NCH_2 signals of $\mathbf{3}_{11}$—$\mathbf{3}_{16}$ may arise from such a steric environment. Namely, because of severe steric conditions in these compounds, one of the amide groups may take *s-cis* conformation, while the other takes *s-trans* conformation. Even in $\mathbf{3}_{18}$ and $\mathbf{4}_{18}$, the amide groups may be *s-cis* and *s-trans*, although they may exchange rapidly at the temperature in question. There is another possibility, however, for the apparent two signals for the NCH_2 group. That is although both amide groups take *s-trans* conformations, the NCH_2 protons are stereoheterotopic due to the slow internal rotation in $\mathbf{3}_{11}$—$\mathbf{3}_{16}$, whereas they become homotopic due to the fast rotation in $\mathbf{3}_{18}$ and $\mathbf{4}_{18}$. In the former case, the NCH_2 protons become nonequivalent and give different chemical shifts, though they both belong to the *s-trans* conformation of amides.

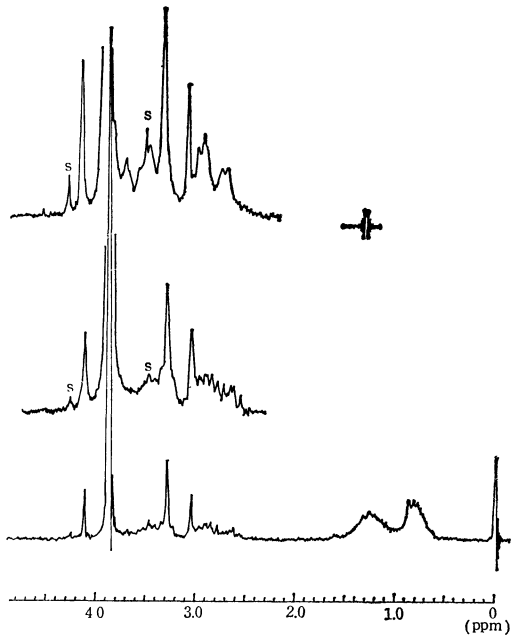


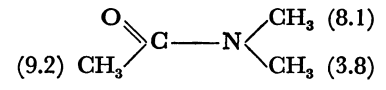
Fig. 1. Normal and decoupled (irradiated at *ca.* 1.3 ppm) PMR spectra of $\mathbf{3}_{12}$.
s: side band of OCH_3 at 3.85 ppm.

Double resonance technique would lend help in determining which of the two is the real reason for the bifurcation. Thus β-methylene protons to the nitrogen were irradiated and signals due to α-methylenes were observed. As are seen in Fig. 1, which shows the spectrum of $\mathbf{3}_{12}$ as a typical example, the α-methylenes seem to give a broad AB type signal which is coupled with a proton on nitrogen, although the signals at the lower field are obscured by other strong signals. The broadness of the signals owes to the presence of nitrogen. Thus double resonance experiment is in favor of the postulation that the bifurcation is caused because of the heterotopic nature of the NCH_2 protons. If the bifurcation were to be attributed to the presence of *s-cis* and *s-trans* conformations, the methylene signals would have appeared as a pair of doublets at two magnetic fields. The fact that the mean chemical shift of two signals due to NCH_2's of $\mathbf{3}_{11}$—$\mathbf{3}_{16}$ is very close to the chemical shift of those of diaza[18]paracyclophanes ($\mathbf{3}_{18}$ and $\mathbf{4}_{18}$) in which the dialkoxybenzene ring is rotating rapidly, may be taken as another piece of supporting evidence for the sole presence of *s-trans* conformation.

If the change from heterotopic to homotopic protons *vice versa* could be detected by the temperature dependence study of the PMR spectra, it would be almost a decisive support for the cause that the bifurcation is due to the heterotopy. Thus PMR spectra of $\mathbf{3}_{16}$ in tetrachloroethane were observed at elevated temperatures. The temperature-raise caused coalescence of the two signals in question at 2.9 and 3.5 ppm and a new signal was observed at 3.2 ppm which is very close to the chemical shift of NCH_2's of $\mathbf{3}_{18}$. On the contrary, lowering the temperature of $\mathbf{4}_{18}$ in deuteriochloroform caused the separation of NCH_2 signal at 3.2 ppm into two, at 2.9 and 3.5 ppm. These results suggest that the cause of bifurcation of the NCH_2 signal in these compounds is really the heterotopic nature of the protons of the *s-trans* conformation.

^{13}C NMR Spectra. It was recently reported that the conformation of *N*-monosubstituted amides had a significant effect upon the chemical shifts of carbonyl carbons and those of carbons adjacent to the nitrogen. The difference in chemical shifts due to *s-cis* and *s-trans* conformations amounts to 3.4 ppm in *N*-methylformamide and differences between the two methylene (or methyl) carbons attached to nitrogen in *N,N'*-dimethylformamide, *N,N'*-dibutylformamide, and *N,N'*-dibutylacetamide are found to be 5.1, 5.2, and 3.3 ppm, respectively.[7] Therefore, it is expected that, if the amide groups in diaza[*n*]paracyclophanes in question took *s-cis* and *s-trans* conformation, ^{13}C NMR spectra of these compounds would show a pair of carbonyl carbon signals and pairs of other carbons which are α, β, *etc.* to the nitrogens. Contrary to the expectation, however, ^1H-noise-decoupled ^{13}C FT NMR spectra of $\mathbf{3}_{12}$ and $\mathbf{3}_{13}$ in deuteriochloroform gave rise to nine and ten signals, respectively, as are listed in Table 4 which includes data of $\mathbf{2}_{12}$ and **5** also. The signals are tentatively assigned by use of the single frequency off-resonance ^1H-decoupling technique, known chemical shift rules for various kinds of carbons,[8] and signal intensities. The number of different carbon signals of diaza[*n*]paracyclophanes points out that these should exist as a single conformer which has C_2 symmetry element.

Lanthanide Induced Shift. Lanthanide shift reagent would provide further information about the conformations of amides. In the absence of the steric hindrance, protons in a methyl group *cis* to the carbonyl oxygen in amide moiety are known to experience a larger shift than their counterparts at *trans* position.[9] Thus in *N,N'*-dimethylacetamide, the following data are known.[10]



Since lanthanide shift reagents are known to cause appearence of unexpected peaks and this effect depends

Table 4. ^{13}C NMR data of diaza[n]paracyclophanes ($\mathbf{2}_{12}$, $\mathbf{3}_{12}$, and $\mathbf{3}_{13}$) and related compound (**5**) in $CDCl_3$[a)]

Compound	$\mathbf{2}_{12}$ (50 °C)	$\mathbf{3}_{12}$ (28 °C)	$\mathbf{3}_{13}$ (28 °C)	**5** (50 °C)
C=O	170.4	171.5 (s)	171.6	170.9
Aromatic C—OMe	135.6 (C-Me)	150.9 (s)	150.7	151.3
Aromatic C—CH_2	134.1	124.8 (s)	124.6	123.9
Aromatic C—H	132.8	113.8 (d)	113.7	114.3
O—CH_3	18.8 (C-Me)	56.4 (q)	56.3	56.2
Ar-CH_2—CO	41.7	39.3 (t)	38.4	41.3
$NHCH_2$	39.3	38.3 (t)	38.1	38.8
β-CH_2	28.5	29.6 (t)	27.6	22.9
γ-CH_2	27.7	27.8 (t)	26.3	11.2 (CH_3)
δ-CH_2			26.5	

a) Chemical shifts are written as ppm down field from internal TMS on the δ scale.

Table 5. Relative slopes of LIS *vs.* [L]/[S][a)]

Compound $\mathbf{3}_n$	$n=11$	12	13	14	15	16	18
CH_2CO	1	1	1 (1)	1	1	1	1
NCH_2[b)]	1.06	0.93	1.05 (1.07)	0.97	0.95	1.02	0.81
NCH_2'[c)]	0.67	0.73	0.62 (0.62)	0.69	0.72	0.81	
OCH_3	0.22	0.19	0.21 (0.18)	0.20	0.20	0.20	0.18
Ar-H	0.66	0.54	0.61 (0.65)	0.54	0.53	0.52	0.47
$\frac{R_{CH_2N} + R_{CH_2N'}}{2}$	0.87	0.83	0.84 (0.84)	0.83	0.84	0.87	(0.81)[d)]

Compound	**4**	**5**	$\mathbf{2}_{12}$	$\mathbf{2}_{13}$	$C_{26}H_{36}N_2O_2$[e)]
CH_2CO	1	1 (1)	1 (1)	1	1 (1)
NCH_2	0.85	0.77 (0.80)	0.96 (0.98)	0.90	0.91 (1.00)
OCH_3 or OCH_2	0.18	0.19 (0.12)			
Ar-CH_3			0.41 (0.40)	0.42	0.30 (0.36)
Ar-H	0.47	0.45 (0.47)	0.45 (0.44)	0.47	0.30 (0.36) 0.10 (0.08)

a) The numerical data in parentheses are obtained by using $Eu(dpm)_3$ and the others by using $Eu(fod)_3$-d_{27}. b) NCH_2 signal at the lower magnetic field. c) NCH_2 signal at the higher magnetic field. d) This signal appeared as a quartet. e) *N,N'*-Hexamethylenebis(2,5-dimethylphenylacetamide).

on the nature of the shift reagents used,[11)] careful examination of the spectra will be necessary. However, under the conditions examined, none of the anomalous peaks appeared, the lanthanide shift reagent causing no trouble in obtaining the relative lanthanide induced shift (LIS).

LIS was plotted against [L]/[S] where [L] and [S] are the molar concentrations of a lanthanide shift reagent and a substrate, respectively. These plots yielded good linear relationships and relative slopes of various protons, taking the slope of CH_2CO as a reference, were calculated. The results are listed in Table 5. $Eu(fod)_3$-d_{27} was mainly used but $Eu(dpm)_3$ gave very close values.

The results may be interpreted that the predominant interaction between amides under investigation and the lanthanide reagent is of pseudo-contact nature.[12)] The lower field multiplets for NCH_2' proton suffered a larger induced shift than the NCH_2 proton at a higher magnetic field. The first look of these data would lead to an assignment of the higher and the lower signals to *s-cis* and *s-trans* conformations, respectively, because the signal of NCH_2 protons *trans* to carbonyl is known to appear at the higher magnetic field than that of the *cis*.[13)] Looking carefully at the relative ratios, however, a rather large relative slope for the signals at the lower magnetic field is noticed. The relative slope for the methyl which is *cis* to the acetyl methyl group in *N,N'*-dimethylacetamide is 0.41 (*loc. cit.*) and NCH_2 protons of *N*-methyl-γ-butyrolactam gives the relative slope of 0.41.[14)] Our results on ε-caprolactam indicate that the relative slope for NCH_2 is 0.4, using $Eu(fod)_3$-d_{27}. Although the complexing site of europium may vary from compound to compound to some extent, the relative slope seems to be fairly small in these compounds. On the other hand, the relative ratios of the signals at the lower magnetic field are 0.6—0.8. In addition, average slopes of the two NCH_2 signals are close to the relative slope of NCH_2 in $\mathbf{3}_{18}$ and to those of open-chain amides examined. These results favor that the both amide groups take *s-trans* conformation.

All the above discussions support that the amide groups in $\mathbf{3}_n$ are the *s-trans* form. This necessarily leads to a conclusion that the ν_{NH} absorption of $\mathbf{3}_n$ at *ca.* 3430 cm^{-1} is due to the N—H···π interacting *s-trans* form.

Amide Conformations as Reinvestigated with the Aid of Lathanide Shift Reagent. Since all the evidence presented above indicate that the amide groups in

$\mathbf{3}_n$ take *s-trans* conformation, reinvestigation of the conformations of amides in $\mathbf{1}_n$ and $\mathbf{2}_n$ becomes necessary. Thus $\mathbf{2}_{12}$ and $\mathbf{2}_{13}$ were submitted to the study with the aid of lanthanide shift reagent. The results are shown in Table 5. The PMR spectral data suggest that these compounds take also *s-trans* form only, because the ratios of the chemical shifts of NCH_2 protons referred to that of CH_2CO protons are characteristic of the *s-trans* form. Thus we wish to correct our earlier suggestion that $\mathbf{1}_n$ and $\mathbf{2}_n$ take *s-cis* conformations as regard the amide groups. The ring strain associated with the formation of this kind of cyclophanes does not seem to be large enough to cause preference of the *s-cis* form over the *s-trans*. Thus the ν_{NH} absorption at *ca.* 3430 cm^{-1} of $\mathbf{1}_n$ and $\mathbf{2}_n$ should now be attributed to the N—H$\cdots\pi$ interacting form rather than the *s-cis* conformation.

Internal Rotation of the Dialkoxybenzene Ring. Temperature dependence of the PMR spectra was studied to obtain the free energies of activation for the internal rotation of the aromatic ring. Those of which ansa chain members are 15 or less do not show any temperature dependency on raising the temperature. The barrier to rotation seems very high for these compounds. The AB quartet of $\mathbf{3}_{16}$ in tetrachloroethane gradually broadened on raising the temperature but coalescence was not observed up to 174 °C, though the NCH_2 signals coalesced into a broad singlet at about 160 °C. On changing the solvent to hexadeuteriodimethyl sulfoxide, however, the signals coalesced at 141 °C. On the other hand, the signal of benzylic protons of $\mathbf{4}_{18}$ in deuteriochloroform broadened considerably at low temperatures: the coalescence temperature was found to be −30 °C. Attempts at observing exact chemical shifts and coupling constant of the AB type protons of $\mathbf{4}_{18}$ were unsuccessful because of broadening of signals, and poor solubility in solvents at low temperatures.

The free energies of activation were obtained by putting the NMR parameters into the following equation:[15]

$$\Delta G_c^{\ddagger} = 4.57\, T_c\{9.97+\log_{10}(T_c/\sqrt{\Delta\delta_{AB}^2+6J_{AB}^2})\}$$

The parameters of $\mathbf{3}_{16}$ obtained at 34 °C were used. On the other hand it was not possible to obtain $\Delta\delta_{AB}$ and J_{AB} for $\mathbf{3}_{18}$ and $\mathbf{4}_{18}$. Thus those parameters for compound $\mathbf{3}_{16}$ were used to obtain approximate barriers to rotation of $\mathbf{3}_{18}$ and $\mathbf{4}_{18}$. It will not be too unreasonable to use these parameters because the structures of these compounds are alike. The results are shown in Table 6.

$\mathbf{3}_{16}$ which has two methoxy groups at the aromatic ring shows higher free energy of activation for rotation of the aromatic ring than that of $\mathbf{2}_{16}$ with two methyl groups by about 10 kcal/mol. This large difference in activation energies must be caused by replacement of the methyl groups by the methoxy because the other part of the molecules is the same. Since much difference in energies of the ground states of these molecules is not expected, the results may be attributed to the difference in energies at the transition states. Then the methoxy group must give more steric hindrance at the transition state than the methyl group.

The apparent bulkiness of the methoxy and the methyl groups in these compounds is just the opposite of the generally accepted. Methyl group is known to retard racemization of biphenyls more effectively than methoxy group,[16] even though the latter group contains more atoms than the former. This apparent reversal in giving the steric effect is understood by assuming that, by taking a conformation in which methoxy methyl is far from the site of interaction, oxygen only becomes the part giving steric hindrance. This deduction was supported by essentially the same ultraviolet absorption spectra of 2-*n*-alkylbiphenyls.[17]

In the process of internal rotation of $\mathbf{3}_{16}$, however, the methoxy group must pass through the space provided by the ansa chain. Namely, the methoxy group gives steric effect to the transition state not by the oxygen only but by the group as a whole. The apparent bulkiness of the methoxy group may be reduced by torsion from the coplanarity with the aromatic ring. But this torsion occurs only at the expense of resonance energy.[18] Therefore, the barrier to rotation of the benzene ring is high irrespective to the steric situation of the methoxy group. This, we believe, is the first example that the methoxy group is proven to be bulkier than the methyl.[19]

The ethoxy group seems to be even bulkier than the methoxy group along the lines expected from the above discussion, because it was impossible to observe coalescence temperature for $\mathbf{3}_{18}$ under the similar conditions. Although the ethoxy group may be folded at the transition state to minimize the free energy of activation for rotation, it is still bulkier than the methoxy group. It is expected that other alkoxy groups will affect the barrier to rotation of the aromatic ring in a similar fashion.

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Table 6. Free energies of activation for internal rotation of the aromatic ring[a]

Compound	$\Delta\delta_{AB}$ (Hz)	J_{AB} (Hz)	T_c (°C)	$\Delta G_c^{\ddagger}$ (kcal/mol)	Solvent
$\mathbf{2}_{16}$[2]	(14.1)	(15.9)	< − 50	<10.8	$CDCl_3$
$\mathbf{3}_{16}$	36.8	14.4	> 174	>22.2	$CHCl_2CHCl_2$
	32.9	13.8	141	20.6	DMSO-d_6
$\mathbf{3}_{18}$	(39.8)[b]	(14.4)	< − 50	<10.9	$CDCl_3$
$\mathbf{4}_{18}$	(39.8)[b]	(14.4)	− 30	11.9	$CDCl_3$

a) The figures in parentheses are the assumed values. b) Chemical shift difference of AB protons of $\mathbf{3}_{16}$ in $CDCl_3$.

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