Proton NMR Spectra and Conformations of *N*-Alkyl-*N*-benzyl- and *N*-Alkyl-*N*-(α-chlorobenzyl)carbamoyl Chlorides

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Rotational isomerization about the amide C–N bond of twelve *N*-alkyl-*N*-benzylcarbamoyl chlorides (C_6H_5-CHX-NR-COCl, **1**: X=H, **2**: X=Cl; R=CH_3, C_2H_5, *n*- and *i*-C_3H_7, *n*- and *t*-C_4H_9) was studied by proton NMR spectroscopy. The values of ΔG^* for the isomerization are 15.8—17.3 kcal/mol for compounds **1** and 13.3—15.9 kcal/mol for compounds **2**. Another kind of slow rotation was observed about the benzyl–nitrogen bond of **1**(R=*t*-C_4H_9) and the α-chlorobenzyl–nitrogen bond of **2**(R=CH_3) at low temperature. The chiral centers of compounds **2** produce large nonequivalences for the geminal protons of the 2-methylene group of **2**(R=*n*-C_3H_7) as well as **2**(R=*n*-C_4H_9) and for the geminal methyl protons of **2**(R=*i*-C_3H_7), reflecting some conformational preference of these compounds.

It is well established that the structure of amides can be represented by the hybrid structure I.

I

Extensive studies by NMR spectroscopy, which have been reviewed,[1,2] substantiate the assignment of a partial double bond character to the C–N bond of the amide group. This double bond character, as pointed out by Stewart and Siddall,[1] leads to the following consequences: A comparatively large barrier to the rotation about the C–N bond of the amide group, which can result in nonequivalent signals for the protons in R^1 and the corresponding ones in R^2 even if $R^1=R^2$; and subsidiary hindered rotations about other bonds as a consequence of a rigid, approximately planar framework of the amide group.

In the case of carbamoyl chlorides (I, R^3=Cl), kinetic studies of their amide C–N bond rotations have been reported, especially on dimethylcarbamoyl chloride[3–6] and also on some other derivatives.[7]

The present study examines the NMR spectra of a series of six *N*-alkyl-*N*-benzylcarbamoyl chlorides [**1**; $C_6H_5CH_2$–NR–COCl, R=CH_3 (**1-a**), C_2H_5 (**1-b**), *n*-C_3H_7 (**1-c**), *i*-C_3H_7 (**1-d**), *n*-C_4H_9 (**1-e**), *t*-C_4H_9 (**1-f**)] and of a series of six correspondingly *N*-alkylated (α-chlorobenzyl)carbamoyl chlorides (**2**; C_6H_5CHCl–NR–COCl). First, results of a kinetic study of the amide C–N bond rotations are presented. Secondly, evidence is presented that the restricted rotations about the amide C–N bond gives rise to another slow rotations about the benzyl–nitrogen bond of **1-f** and also the α-chlorobenzyl–nitrogen bond of **2-a** on NMR time scale as the temperature is lowered further. Thirdly, preference of rotational conformations about single bonds of compounds **2** is discussed in view of the nonequivalences of the 2-methylene geminal protons of **2-c** and the geminal methyl groups of **2-d**.

Experimental

The proton NMR spectra were recorded on a JEOL JNM-MH100 spectrometer operating at 100 MHz in the frequency-sweep and internal TMS-locked mode, using Iwasaki-Tsushin UC-80033 universal counter, for *ca.* 5% (w/v) degassed solution in $CDCl_3$ or in hexachloro-1,3-butadiene at various temperatures. Temperatures were calibrated with the hydroxyl shifts of methanol below room temperature and of 1,3-propanediol above room temperature.

The IR spectra were taken with a Japan Spectroscopic Co., Ltd. JASCO DS-403 grating infrared spectrometer.

N-Alkyl-N-benzylcarbamoyl Chlorides. To a stirred solution of 75 ml of a 12.5% solution of phosgene in benzene (0.15 mol of phosgene), maintained in an ice bath, was added, dropwise, a benzene solution (50 ml) of the appropriate *N*-alkylbenzylamine (0.07 mol). The reaction mixture was stirred at room temperature for an hour, and then filtered to remove amine hydrochloride. Benzene was removed from the solution by distillation to afford crude carbamoyl chloride.

*N-Methyl-N-benzylcarbamoyl Chloride (**1-a**)*:[8] Yield 57.5%; bp 81 °C (6×10^{-3} Torr);[9] mp 23 °C (recrystd from diethyl ether); IR (Nujol): $\nu_{C=O}$ 1751 cm^{-1}.

*N-Ethyl-N-benzylcarbamoyl Chloride (**1-b**)*: Yield 32.7%; bp 84—85 °C (3×10^{-4} Torr); mp 21 °C (recrystd from diethyl ether); IR (Nujol): $\nu_{C=O}$ 1747 cm^{-1}. Found: C, 60.71; H, 5.84; Cl, 18.07; N, 6.98%. Calcd for $C_{10}H_{12}ClNO$: C, 60.76; H, 6.12; Cl, 17.94; N, 7.09%.

*N-Propyl-N-benzylcarbamoyl Chloride (**1-c**)*: Yield 35.7%; bp 83 °C (2×10^{-4} Torr); IR (Nujol): $\nu_{C=O}$ 1747 cm^{-1}. Found: C, 61.97; H, 6.48; Cl, 17.01; N, 6.68%. Calcd for $C_{11}H_{14}ClNO$: C, 62.41; H, 6.67; Cl, 16.75; N, 6.62%.

*N-Isopropyl-N-benzylcarbamoyl Chloride (**1-d**)*: Yield 38%; bp 92 °C (2×10^{-4} Torr); IR (Nujol): $\nu_{C=O}$ 1742 cm^{-1}. Found: C, 62.13; H, 6.55; Cl, 16.48; N, 6.61%. Calcd for $C_{11}H_{14}ClNO$: C, 62.41; H, 6.67; Cl, 16.75; N, 6.62%.

*N-Butyl-N-benzylcarbamoyl Chloride (**1-e**)*: Yield 40%; bp 100 °C (2×10^{-4} Torr); IR (Nujol); $\nu_{C=O}$ 1745 cm^{-1}. Found: C, 64.08; H, 7.16; Cl, 16.01; N, 6.42%. Calcd for $C_{12}H_{16}ClNO$: C, 63.85; H, 7.15; Cl, 15.71; N, 6.21%.

*N-t-Butyl-N-benzylcarbamoyl Chloride (**1-f**)*:[10] Yield 47.1%; mp 86—87 °C (recrystd from heptane); IR (Nujol): $\nu_{C=O}$ 1753 cm^{-1}.

N-Alkyl-N-(α-chlorobenzyl)carbamoyl Chlorides. By a procedure similar to that described for *N*-methyl-*N*-(α-chlorobenzyl)carbamoyl chloride (**2-a**),[11] the appropriate *N*-alkylbenzylideneamine was treated with phosgene to give the corresponding *N*-alkyl-*N*-(α-chlorobenzyl)carbamoyl chloride.

*N-Ethyl-N-(α-chlorobenzyl)carbamoyl Chloride (**2-b**)*: Yield 74.4%; bp 96—98 °C (3×10^{-3} Torr); IR (Nujol): $\nu_{C=O}$ 1749 cm^{-1}. Found: C, 51.77; H, 4.94; Cl, 30.51; N, 6.12%. Calcd for $C_{10}H_{11}Cl_2NO$: C, 51.75; H, 4.78; Cl, 30.55; N,

6.04%.

N-*Propyl*-N-*(α-chlorobenzyl)carbamoyl Chloride (**2-c**)*: Yield 56.9%; bp 99 °C (3×10^{-3} Torr); IR (Nujol): $\nu_{C=O}$ 1747 cm^{-1}. Found: C, 53.74; H, 5.50; Cl, 28.71; N, 5.66%. Calcd for $C_{11}H_{13}Cl_2NO$: C, 53.68; H, 5.32; Cl, 28.81; N, 5.69%.

N-*Isopropyl*-N-*(α-chlorobenzyl)carbamoyl Chloride (**2-d**)*: Yield 89%, mp 49—51 °C (recrystd from diethyl ether); IR (Nujol): $\nu_{C=O}$ 1758 cm^{-1}. Found: C, 53.47; H, 5.45; Cl, 28.60; N, 5.54%. Calcd for $C_{11}H_{13}Cl_2NO$: C, 53.68; H, 5.32; Cl, 28.81; N, 5.69%.

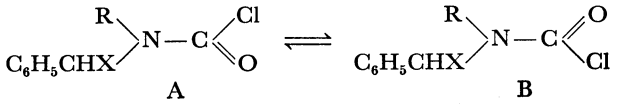
N-*Butyl*-N-*(α-chlorobenzyl)carbamoyl Chloride (**2-e**)*: Yield 51.9%; bp 118 °C (4×10^{-4} Torr); IR (Nujol): $\nu_{C=O}$ 1745 cm^{-1}. Found: C, 55.58; H, 5.92; Cl, 27.11; N, 5.44%. Calcd for $C_{12}H_{15}Cl_2NO$: C, 55.39; H, 5.81; Cl, 27.25; N, 5.38%.

N-t-*Butyl*-N-*(α-chlorobenzyl)carbamoyl Chloride (**2-f**)*: A sealed tube containing 22.5 g (0.14 mol) of freshly distd *N-t*-butylbenzylideneamine and 150 g of a 12.5% soultion of phosgene in benzene (0.3 mol of phosgene) was heated at about 50 °C for three days. The white precipitate produced (*N-t*-butylbenzylideneamine hydrochloride) was removed by filtration. Removal of benzene from the solution by distillation afforded 30.7 g (84.1% yield) of crude **2-f**; mp 44.5—46.5 °C (recrystd from heptane), dec above 100 °C;[12] IR (Nujol): $\nu_{C=O}$ 1760 cm^{-1}. Found: C, 55.37; H, 5.60; Cl, 27.10; N, 5.27%. Calcd for $C_{12}H_{15}Cl_2NO$: C, 55.39; H, 5.81; Cl, 27.25; N, 5.38%.

Results and Discussion

N-*Alkyl*-N-*benzylcarbamoyl Chlorides (Series **1**)*. Chemical shifts (δ, ppm) of the *N*-alkyl-*N*-benzylcarbamoyl chlorides (**1-a**, **1-b**, **1-c**, **1-d**, **1-e**, and **1-f**) at room temperature are listed in Table 1.

Rotational Isomerism about the Amide C–N Bond: The presence of a pair of singlet signals with unequal intensities for the benzyl α protons of **1-a**, **1-b**, **1-c**, and **1-e** and also a pair of singlet signals for the methyl protons of **1-a** can be interpreted in terms of rotational isomerism between conformers represented as A and B resulting from slow rotation about the amide C–N bond.[1,2]



X=H (Series **1**); X=Cl (Series **2**)

Isbrandt and Rogers[3c] showed, by the use of a europium shift reagent, that, of the two signals for dimethylcarbamoyl chloride, the lower-field resonance is assignable to the protons of the methyl group that is cis to the chlorine atom. By analogy, the benzyl α proton signals of the present carbamoyl chlorides at δ=4.6—4.9 ppm (the lower-field signals) can be assigned to those of conformer B, while those at δ=4.5—4.6 ppm (the higher-field signals) can be assigned to the benzylic protons of conformer A.

The fractional populations, P_A and P_B, for each pair of these conformers, together with their coalescence temperatures, are shown in Table 2. From these data, the free energies of activation for the rotational conversion from A to B (ΔG^*_A) and the reverse (ΔG^*_B) were calculated. The results are also included in Table 2.

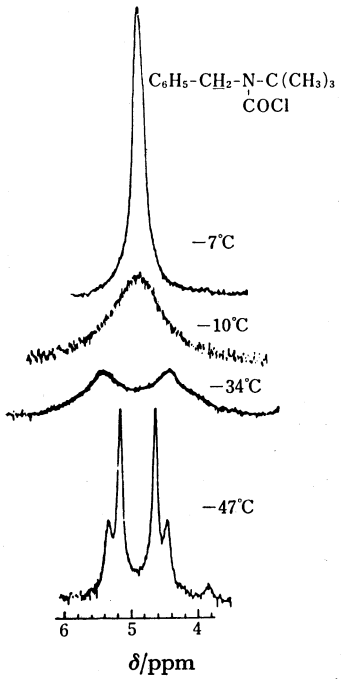


Fig. 1. The temperature dependence of the NMR spectrum of the benzyl protons of *N-t*-butyl-*N*-benzylcarbamoyl chloride, **1-f**, in $CDCl_3$.

For those compounds in which the *N*-alkyl substituent, R, is primary (**1-a**, **1-b**, **1-c**, and **1-e**), conformer A is more stable than conformer B. In those cases in which R is secondary (**1-d**) or tertiary (**1-f**), the reverse occurs. The order of relative populations of conformer A (P_A) is **1-a**≈**1-b**>**1-c**≈**1-e**>**1-d**≫**1-f**. That is, the sterically larger alkyl groups exibit a preference for sites which are further from the chlorine atom (cis to the oxygen atom). For the *N*-methyl derivative (**1-a**), the free energies of activation, ΔG^*_A and ΔG^*_B, are 17.3 and 17.1 kcal/mol, respectively, which are comparable with the value (17 kcal/mol) reported for dimethylcarbamoyl chloride.[3a,3b,4,5,6] With increasing bulkiness of the *N*-alkyl group, the free energy of activation for such rotations decreases. This trend is the same as observed with *N,N*-dialkylamides.[14]

*Nonequivalence of the Benzyl α Protons of **1-f***: The geminal protons at the benzyl α position of **1-f**, which exists in conformation B exclusively (*cf.* Table 2), resonate nonequivalently at temperatures below −34 °C (AB quartet, ν_{AB}=72.3 Hz, J_{AB}=19.0 Hz), as shown in Fig. 1. Although the benzyl α protons of some *N*-alkyl-*N-t*-butylbenzylamines are nonequivalent because of slow rates of nitrogen inversion,[15] such explanation is unlikely in the present case. The rationale for this conclusion is based on a comparison of the infrared spectrum of **1-f** with that of its α-chlorobenzyl analogue (**2-f**). The carbonyl absorptions are indicative of as much double bond character of the amide C–N bond of **1-f** ($\nu_{C=O}$=1753 cm^{-1}) as that of **2-f** ($\nu_{C=O}$=1760 cm^{-1}). Such double bond character of the amide C–N bond in **2-f** is established by NMR data, which indicates that **2-f** exists in two conformations as a results of restricted rotation about this bond (see the following section). Therefore, the hybridization state of the nitrogen atom of **1-f** is probably sp^2 or nearly so.

Table 1. Proton NMR chemical shifts of *N*-alkyl-*N*-benzylcarbamoyl chlorides at room temperature

Compound[a]		δ/ppm for protons[b]						
		$C_6H_5CH_2$-		H^1		H^2	H^3	H^4
	R	A	B	A	B			
1-a	CH_3	4.553	4.702	3.050	2.985			
1-b	C_2H_5	4.555	4.671	3.410		1.148		
1-c	*n*-C_3H_7	4.561	4.680	3.314		1.561	0.871	
1-d	*i*-C_3H_7	4.639		4.204		1.172		
1-e	*n*-C_4H_9	4.570	4.688	3.350		1.591	1.331	0.890
1-f	*t*-C_4H_9		4.865			1.430		

a) $C_6H_5CH_2$-NR-COCl. b) Numbering of alkyl protons: *n*-C_3H_7=-CH^1_2-CH^2_2-CH^3_3, *i*-C_3H_7=-CH^1-$(CH^2_3)_2$, *t*-C_4H_9=-$C(CH^2_3)_3$.

Table 2. Chemical shift, population, coalescence temperature and free energy of activation for interconversion of conformers A and B of *N*-alkyl-*N*-benzylcarbamoyl chlorides

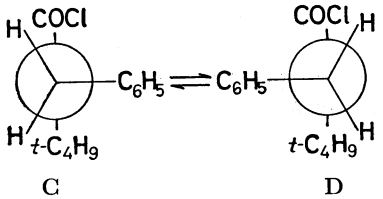
Compound[a]		Proton[b]					T_c	ΔG^*_A	ΔG^{*c}_B
	R	observed	δ_A	δ_B	P_A	P_B	°C	kcal/mol	
1-a	CH_3	$\underline{CH_3}$	3.080	3.015	0.567	0.433	47.0	17.3	17.1
		$C_6H_5\underline{CH_2}$	4.596	4.730	0.570	0.430	54.5	17.3	17.1
1-b	C_2H_5	$C_6H_5\underline{CH_2}$	4.568	4.704	0.532	0.468	45.0	16.6	16.5
1-c	*n*-C_3H_7	$C_6H_5\underline{CH_2}$	4.573	4.704	0.524	0.476	47.5	16.8	16.7
1-d	*i*-C_3H_7	$C_6H_5\underline{CH_2}$	4.545	4.661	0.312	0.688	30.5	15.8	16.5
1-e	*n*-C_4H_9	$C_6H_5\underline{CH_2}$	4.580	4.711	0.524	0.476	47.5	16.8	16.7
1-f	*t*-C_4H_9	$C_6H_5\underline{CH_2}$		4.874	0	1			

a) $C_6H_5CH_2$-NR-COCl. b) The protons whose resonances are observed are indicated by underlines. c) Free energy of activation at the coalescence temperature. Throughout this paper 1 cal_{th}=4.184 J. The equations used to calculate the free energies of activation are as follows. $1/\tau=1/\tau_A+1/\tau_B$, when τ_A and τ_B are the lifetimes of species A and B, respectively. Case 1) $P_A=P_B$, $1/2\tau=(\pi/\sqrt{2})\cdot\Delta\nu$, $\Delta G^*=RT_c\ln(2\tau kT_c/h)$. Case 2)[13] $P_A\neq P_B$, $X=2\pi\Delta\nu\tau$, $P_A-P_B=\Delta P=\{(X^2-2)/3\}^{3/2}\cdot 1/X$, $\Delta G^*_A=RT_c\ln\{2\tau kT_c/h(1-\Delta P)\}$, $\Delta G^*_B=RT_c\ln\{2\tau kT_c/h(1+\Delta P)\}$.

Table 3. Proton NMR chemical shifts of *N*-alkyl-*N*-(α-chlorobenzyl)carbamoyl chlorides at room temperature

Compound[a]		δ/ppm for protons[b]				
	R	H^1	H^2	$H^{(2)}$	H^3	H^4
2-a	CH_3	2.940				
2-b	C_2H_5	3.376	0.970			
2-c	*n*-C_3H_7	3.231	1.591 1.165		0.684	
2-d	*i*-C_3H_7	3.663	1.465	1.006		
2-e	*n*-C_4H_9	3.255	1.58 1.06		1.059	0.741
2-f	*t*-C_4H_9		1.515			

a) C_6H_5CHCl-NR-COCl. b) Numbering of alkyl protons: *n*-C_3H_7=-CH^1_2-CH^2_2-CH^3_3, *i*-C_3H_7=-$CH^1(CH^2_3)CH^{(2)}_3$, *t*-C_4H_9=-$C(CH^2_3)_3$.



C D

Fig. 2. The Newman projection formulas for staggered conformations of *N*-*t*-butyl-*N*-benzylcarbamoyl chloride, **1-f**, with respect to the rotation about the benzyl–nitrogen bond.

The nonequivalence of the benzyl α protons of **1-f** at temperatures below −34 °C can be explained in terms of the molecular asymmetry produced by slow rotation about the benzyl–nitrogen bond, the rotational barriers of which result from the rigidity of the amide plane and the bulkiness of the *t*-butyl group. The most stable conformations are probably staggered conformations C and D in Fig. 2. When the interconversion is slow, the asymmetric field will be brought about on the benzyl α geminal protons. The mean barrier height between C and D was calculated to be 11.4

Table 4. Chemical shift, population, coalescence temperature and free energy of activation for interconversion of conformers A and B of *N*-alkyl-*N*-(α-chlorobenzyl)carbamoyl chlorides

Compound[a]	R[b]	δ_A	δ_B	P_A	P_B	T_c °C	ΔG^*_A kcal/mol	ΔG^*_B[d] kcal/mol
2-a	$\underline{CH_3}$	2.931	2.831	0.645	0.355	24.5	15.9	15.6
2-b	$\underline{CH_2}CH_3$	3.426	3.325	0.539	0.461	16.0	15.2	15.2
2-c	$\underline{CH_2}C_2H_5$	3.270	3.190	0.5	0.5	6—7	14.7	14.7
2-d	$\underline{CH}(CH_3)_2$	3.654				7—9[c]		
2-e	$\underline{CH_2}C_3H_7$	3.329	3.248	0.5	0.5	14.3	15.2	15.2
2-f	$C(\underline{CH_3})_3$	1.670	1.400	0.386	0.614	9.0	13.3	13.5

a) C_6H_5CHCl-NR-COCl. b) The protons whose resonances are observed are indicated by underlines. c) The multiplet blurred in the temperature range, and it could not be analyzed at lower temperature. d) Free energies of activation at the coalescence temperature, calculated by the use of the equations in Table 2. note c).

kcal/mol from the values of T_c, $\Delta\nu_{AB}$, and J_{AB}.[16]

Kiefer[17] reported that the geminal protons of the chloromethyl group of *N*-*t*-butyl-*N*-(chloromethyl)carbamoyl chloride are nonequivalent. This can be interpreted in terms of slow rotation about the chloromethyl–nitrogen bond, in view of the present conclusion on the case of **1-f**.

N-Alkyl-N-(α-chlorobenzyl)carbamoyl Chlorides (Series 2). The chemical shifts (δ, ppm) of **2-a**, **2-b**, **2-c**, **2-d**, **2-e**, and **2-f** at room temperature are given in Table 3. The signals of the benzyl α proton were not detectable, hidden by the signals of the aromatic protons.

Rotational Isomerism about the Amide C–N Bond: Calculations pertaining to equilibrium A⇌B were made from the signals of the methyl protons of **2-a** and **2-f**, and of the 1-methylene protons, H^1, of **2-b**, **2-c**, and **2-e**. In these compounds, as in the compounds of series **1**, the protons of the alkyl groups which are cis to the chlorine atom of the chloroformyl group (conformer A) are assumed to resonate at lower-field regions than those which are trans to the chlorine atom (conformer B). Calculated fractional populations (P_A, P_B) and free energies of activation (ΔG^*_A and ΔG^*_B) are shown in Table 4.

The *N*-methyl derivative (**2-a**) prefers conformation A, while the *N*-*t*-butyl derivative (**2-f**) prefers conformation B, which is consistent with that found for **1-a** and **1-f**. The values of P_A/P_B for **2-a**, **2-b**, and **2-f**, which were relatively precisely estimated, are greater than the values for the corresponding compounds of series **1**, **1-a**, **1-b**, and **1-f**, respectively. The free energies of activation for rotation about the C–N bond of the compounds of series **2** are smaller than the corresponding compounds of series **1**. These facts are attributed to the increase in repulsive interactions of the benzyl group with the chloroformyl group, especially its chlorine atom, in stable conformations A and B, by introduction of the α-Cl substituent. The free energies of activation are lowest for **2-f**. This is probably due to destabilization of conformations A and B by steric repulsion of the chloroformyl group with the bulky *t*-butyl group in addition to that with the α-chlorobenzyl group.

The δ value of the signal of the *t*-butyl protons of **2-f** in conformation B is 1.40 ppm, while that in conformation A is 1.67 ppm. Since the δ value of the signal of the *t*-butyl protons of **1-f** is 1.43 ppm, the aforementioned assignment of B to the most preferred conformation of **1-f** is consistent.

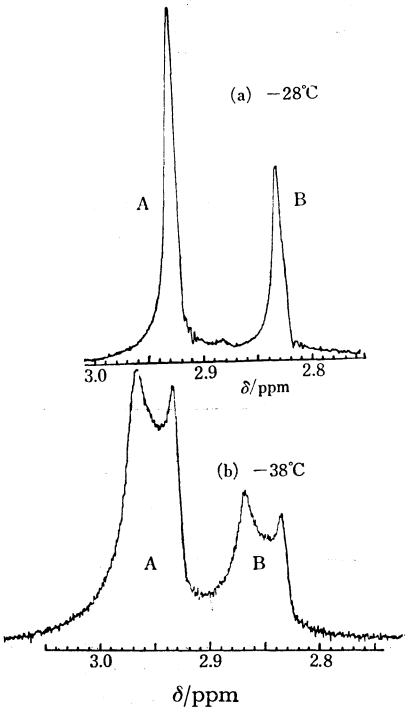


Fig. 3. NMR spectra of the methyl protons of *N*-methyl-*N*-(α-chlorobenzyl)carbamoyl chloride, **2-a**, (a) at −28 °C and, (b) −38 °C.

Rotational Isomerism about the α-Chlorobenzyl–Nitrogen Bond of 2-a: **2-a** shows two kinds of spectral change at low temperatures. The first one is due to the conformational interconversion A⇌B with the signal coalescence temperature at 24.5 °C. The second one is the splitting of each of the methyl signals for conformations A and B into two signals, shown in Fig. 3. The latter spectral change is ascribed to freezing of the interconversion of two relatively stable conformations about the α-chlorobenzyl–nitrogen bond. The values of ΔG^* for this conversion is estimated at about 10 kcal/mol. This comparatively large restriction to the conversion is probably caused by rigidity of the amide plane.

In light of a result of calculation of van der Waals energy by Allinger's modification[18a,b] of Hill's method[19] a qualitative potential energy curve for the rotation about the α-chlorobenzyl–nitrogen bond of **2-a** is

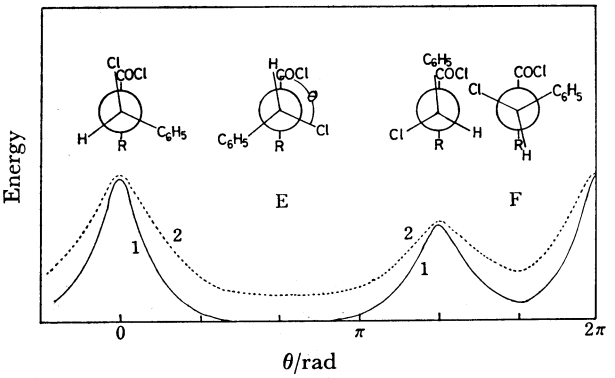


Fig. 4. Schematic potential-energy diagram for the rotation about the benzyl–nitrogen bond of *N*-alkyl-*N*-(α-chlorobenzyl)carbamoyl chlorides. θ represents the dihedral angle between the chlorine–carbon bond of the α-chlorobenzyl group and the chloroformyl–nitrogen bond. Curve 1——: **2-a**; curve 2·····: **2-c**.

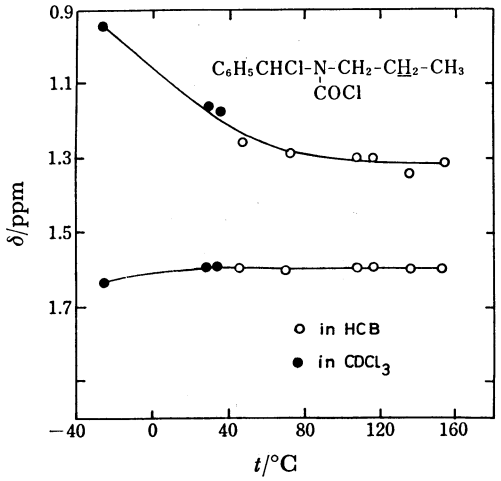


Fig. 5. Temperature-dependence of nonequivalent chemical shifts (from TMS) of the 2-methylene geminal protons of *N*-propyl-*N*-(α-chlorobenzyl)carbamoyl chloride, **2-c**. ●: in $CDCl_3$; ○: in hexachlorobutadiene.

depicted with a solid line (curve 1) in Fig. 4, which shows two stable conformations, E and F, intervened by potential energy barriers at $\theta=0$ and $4\pi/3$ rad. θ is the dihedral angle between the chlorine–carbon bond of the α-chlorobenzyl group and the chloroformyl–nitrogen bond. Of the two peaks of each of the methyl signals for A and B in Fig. 3(b), the more intense one at lower field is assigned to the more stable conformation, E, and the weaker one at higher field to the less stable conformation, F. In conformation E, the phenyl group and the chlorine atom of the α-chlorobenzyl group are close to the methyl group, and hence, must exert a downfield effect on it.

Nonequivalence of the 2-Methylene Protons of **2-c** *and* **2-e**: As is seen in Table 3, even above the coalescence temperature for the interconversion of conformations A and B, the geminal protons of the 2-methylene group, H^2, of **2-c** as well as those of **2-e**, give rise to two signals of equal intensity, that is, are nonequivalent, although the geminal protons of the other methylene groups appear

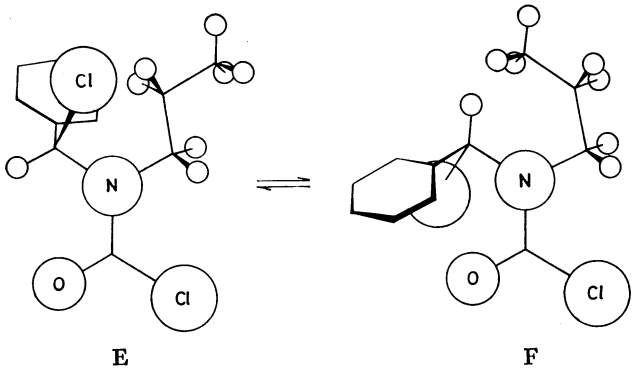


Fig. 6. Molecular model representation for a conversion between conformations E and F of *N*-propyl-*N*-(α-chlorobenzyl)carbamoyl chloride, **2-c**: rotation about the α-chlorobenzyl–nitrogen bond.

as equivalent. It is evident that these nonequivalences are originated from the chirality of the configuration about the α-carbon atom of the α-chlorobenzyl group.

These nonequivalences decrease with rising temperature. In the case of **2-c**, the difference in chemical shift between the two signals is about 80 Hz at −30 °C, and decreases to 40 Hz at 80 °C, as shown in Fig. 5. In spite of the shift, the splitting patterns of the nonequivalent signals do not essentially change. This fact indicates that rotation about any bond other than the amide C–N bond is not frozen even at the lowest temperature measured (−30 °C).

The shift may be elucidated by the change in population of the conformers about the α-chlorobenzyl–nitrogen bond, as follows. The potential energy curve of **2-c** as well as **2-e** about this bond may be similar to that of **2-a**, as a whole, but may be somewhat shallower, as shown with a dotted line (curve 2) in Fig. 4. In the more stable conformation E, the alkyl group is in close proximity of the phenyl group and the chlorine atom, both of which have large magnetic anisotropies and must impart large asymmetric field gradient to the 2-methylene protons. The terminal methyl or ethyl group of the alkyl group of the molecule in conformation E forces the protons of the 2-methylene group to face the chiral center, as a result of avoiding its repulsive interaction with the α-chlorobenzyl group (Fig. 6). When the molecule is in conformation F, the field gradient experienced by the same protons should be small because of the long distance from the chiral center. Therefore, increasing contribution of conformation F with rising temperature reduces the nonequivalence of the 2-methylene protons.

Nonequivalence of the Geminal Methyl Groups of **2-d**: The protons of the geminal methyl groups, H^2 and $H^{(2)}$, of **2-d** are also nonequivalent. Raising temperature causes a decrease in the separation of the signals accompanied by a gradual movement to higher fields, as shown in Fig. 7. This nonequivalence is not caused by the conformational interconversion A⇌B. The difference in chemical shift of H^1 between conformations A and B is not so large to permit the analysis of multiplets. As to the chemical shift of the methyl groups, there is no difference between conformations A and B of **2-d**, while the corresponding chemical shifts of **2-f**

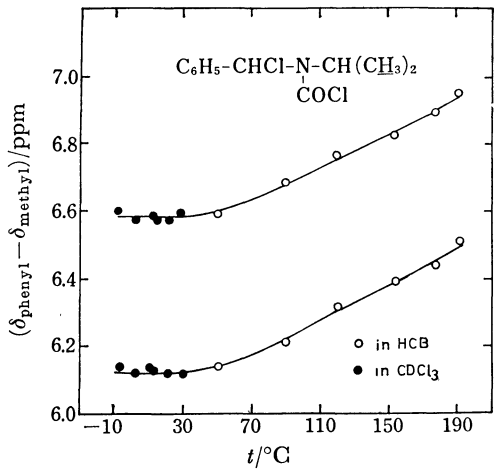


Fig. 7. Temperature-dependence of nonequivalent chemical shifts, $(\delta_{phenyl}-\delta_{methyl})$/ppm, of the geminal methyl protons of *N*-isopropyl-*N*-(α-chlorobenzyl)-carbamoyl chloride, **2-d**. ●: in $CDCl_3$; ○: in hexachlorobutadiene.

are separated 0.27 ppm from each other. This implies that both methyl groups of the isopropyl group can be apart from the chloroformyl group, while, at least, one of the methyl groups of the *t*-butyl group must be in close proximity to the chloroformyl group. The preferable conformation of **2-d** may resemble conformation E of **2-c** shown in Fig. 6. In this conformation, the nonequivalence of the two methyl signals may be largest, because one of the methyl groups approaches the chlorine atom, receiving a downfield effect from it, and the other methyl group comes just above the plane of the phenyl ring, receiving an upfield effect from it.

In the present cases, nonequivalent protons is three bonds removed from the chiral center. In a study of the NMR spectra of a series of compounds, $C_6H_5CH(CH_3)CH(CH_3)_2$, $C_6H_5CH(CH_3)O(CH_2)_nCH(CH_3)_2$ (n=0,1,2) and $C_6H_5CH(CH_3)O(CH_2)_2O(CH_2)_nCH(CH_3)_2$($n$=0,1), Whitesides *et al.*[20] have found that the nonequivalence of the geminal methyl protons does not decrease monotonically as the number of bonds separating the chiral center from the geminal methyl groups increases, and that it is unexpectedly large when these methyl groups are five bonds removed from the chiral center. The difference may originate from a greater flexibility of an ether molecule compared with the present carbamoyl chloride molecules, which bear a rigid amide plane and bulky phenyl and chlorine substituents.

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$1/2\tau=(\pi/\sqrt{2})\cdot(\Delta\nu_{AB}^2+6J_{AB}^2)^{1/2}$, at T_c.
$\Delta G^*=RT_c\ln(2\tau kT_c/h)$.

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