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RESTRICTED ROTATION OF SUBSTITUTED N,N-DIMETHYLNICOTINAMIDES.

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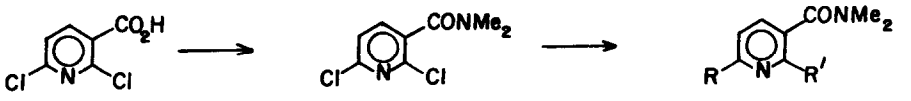
During our recent attempts directed toward the synthesis of pyridine-linked nucleotide models, we investigated the chemical and physical properties of substituted N,N-dimethylnicotinamides. Since very limited ^{1}H[1] and ^{13}C[1a,2] studies of N,N-dimethylnicotinamide have been reported, the effect of substituents on rotational barriers needed to be ascertained. Numerous studies of the related N,N-dimethylbenzamides have been reported;[1a,3] however, limited substituent effects have been evaluated. Summary of these previous works indicates that amides generally possess partial double-bond character of the C-N bond and upon protonation, the increased amide C-N double-bond character is confirmed by the free energies of activation for rotation about the amide bond. We herein report that with selected 2,6-disubstituted N,N-dimethylnicotinamides, these rotational barriers of the diastereotopic methyl groups are lowered upon protonation.

Treatment of 2,6-dichloronicotinic acid 2[4] with excess thionyl chloride afforded the acyl chloride, which upon dissolution in anhydrous CH_2Cl_2, was cautiously added to dimethylamine hydrochloride in triethylamine at 0°C to give (95%) N,N-dimethylamide 3: mp 68.5-69°C. To a suspension of sodium hydride in xylene, ethanol, followed by 3, were added and the mixture was refluxed for 15 hours under nitrogen.[5] The resultant viscous oil was chromatographed (ThLC) to give 1a [bp 140°C (1 mm); 60%; NMR ($CDCl_3$) δ 1.34 (t, 2-pyr-$OCH_2\underline{CH_3}$, J=7Hz, 3H), 1.36 (t, 6-pyr-$OCH_2\underline{CH_3}$, J=7Hz, 3H), 2.93 (bs, NMe^A, 3H), 3.08 (bs, NMe^B, 3H), 4.32 (q, 6-pyr-OCH_2, J=7Hz, 2H), 4.40 (q, 2-pyr-OCH_2, J=7Hz, 2H), 6.29 (d, 5-pyr-H, J=8Hz, 1H), 7.53 (d, 4-pyr-H, J=8Hz, 1H); IR (neat) 1630 (C=O) cm^{-1}] and 1b [mp 65-65.5°C; 27%; NMR ($CDCl_3$) δ 1.36 (t, $OCH_2\underline{CH_3}$, J=7Hz, 3H), 2.87 (s, NMe^A, 3H), 3.09 (s, NMe^B, 3H), 4.44 (q, $O\underline{CH_2}$, J=7Hz, 2H), 6.92 (d, 5-pyr-H, J=7.8Hz, 1H), 7.55 (d, 4-pyr-H, J=7.8Hz, 1H); IR (KBr) 1630 (C=O) cm^{-1}]. Unambigious structure proof of 1b was accomplished by dehalogenation via treatment with $PdCl_2$[6] affording (49%) 1c, as the major product [bp 115°C (1.5 mm); NMR δ 8.18 (dd, 6-pyr-H, J=5,2Hz, 1H); IR (neat) 1630 (C=O) cm^{-1}] along with 19% unreacted starting material and 2-hydroxy-N,N-dimethylnicotinamide 1d [mp 153-154°C ($CHCl_3$-CCl_4); 11%].[7]

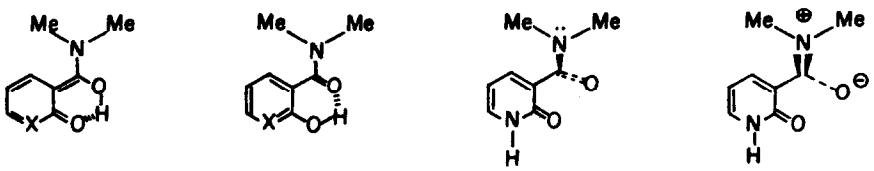


2 3

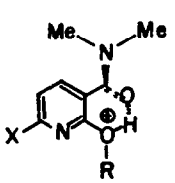
1g R=R'=OEt
b R=Cl;R'=OEt
c R=H;R'=OEt
d R=H;R'=OH

The rotational barriers around the C-N bond of these amides were initially determined via VTNMR measurements. Free energies of activation ($\Delta G^{\ddagger}$) were ascertained from the coalescence temperatures of the diastereotopic N-methyl signals and are shown in the Table I. Slightly higher C-N rotational barriers for 1a, 1b, and 3, which possess substituents that inflict steric hindrance to conjugation of the amide function with the ring, are indicative of greater C-N amide double-bond character. The rotational barriers of several 2-substituted N,N-dimethylbenzamides have been demonstrated to have a similar magnitude to those shown for these nicotinamides. One exception is for 1d, in which the related 2-hydroxy-N,N-dimethylbenzamide (4b) has a $\Delta G^{\ddagger}$ of 12.27 Kcal/mol[3e], a value less than that for the related unsubstituted compound. Although intramolecular hydrogen bonding would cause planarity of the ring and the carbonyl group in resonance forms such as 4a and 5a, no such stabilization of the ring system is likely in the case of 1d, since it probably exists predominantly in the pyridone (6↔7) form. Further comparison of 1a-c indicates that with different 6-substituents, the rotational barrier is increased by electron-withdrawing groups (1c > 1b > 1a); similar correlations have been shown with 4-substituted N,N-dimethylbenzamides.[1a]

Protonation of these N,N-dimethylnicotinamides was conducted by dissolution of 1 (10% w/v) in $CDCl_3$, followed by introduction of HCl gas. Traces of acid caused considerable alteration in rotational energy barriers,[3d,8,9] in that the predominant conjugate acid, derived from amide O-protonation, increases C-N double-bond character. At the same time with a kinetically significant concentration also in equilibrium with amide N-protonation, the barrier to rotation is diminished.[9] Further, with addition of traces of pyridine, catalysis by acid can be eliminated and the pyridine absorptions are shifted to lower field via subsequent salt formation.



4a (X=N) 5a (X=N) 6 7
b (X=CH) b (X=CH)



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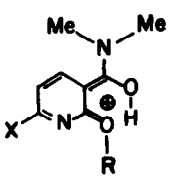

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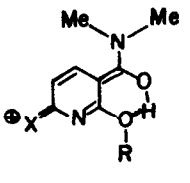

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TABLE I. Free Energies of Activation for the Restricted Rotation Around the C-N Bond in Selected N,N-Dimethylnicotinamides.

Substituents			Coalescence		$\Delta G^{\ddagger}$
R	R'	Solvent	Temp; T_c (°K)	$\Delta\nu$ (Hz)	(Kcal/mol)
Cl	Cl (3)	HCB[a,c]	363	12.0	18.99
H	OEt (1c)	HCB[a,c]	340	12.2	17.74
Cl	OEt (1b)	HCB[a,c]	333	14.0	17.27
OEt	OEt (1a)	$CDCl_3$[b]	328	12.0	17.10
H	OH (1d)	$CDCl_3$[b]	323	7.5	17.13
H	Me[d]	$C_2D_2Cl_4$	345	26.4	17.48
H	H[d]	$CDCl_3$	301	10.0	15.75

[a]Hexachlorobutadiene. [b]T_c in HCB was < 313°K. [c]T_c in $CDCl_3$ was > 343°K.
[d]Ref. 1b

TABLE II. Free Energies of Activation for the Restricted Rotation Around the C-N Bond upon Protonation.

Compound	Solvent	Coalescence Temp; T_c (°K)	$\Delta\nu$ (Hz)	$\Delta G^{\ddagger}$ (Kcal/mol)
3 + H^+	HCB[a]	353	12.0	18.45
1c + H^+	HCB[a]	333	12.0	17.37
	$CDCl_3$	337	14.0	17.48
1b + H^+	$CDCl_3$	<308	~12	<16
1a + H^+	$CDCl_3$	<308	~12	<16

[a]Hexachlorobutadiene

Rotational barriers of 1 were lowered (Table II) by addition of traces of HCl gas. Since shifts of the pyridine peaks were negligible, the diminished C-N amide bond character must result from favorable O-protonation and resonance structures, such as 8, 9, and 10, contribute to the stabilization of the resultant 6-membered chelate ring. In the case of 1c and 3, the minimal lowering of the rotational barrier is illustrative of the lack of p-quinoid-type resonance delocalization.

Work toward the determination of the exact nature of protonation of substituted nicotinamides is currently in progress.[10]

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