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LITHIUM DIALKYLAMIDES. ^{13}C PARAMETERS AND SLOW PROTON TRANSFER

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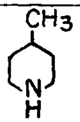
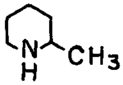
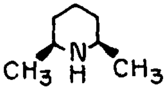
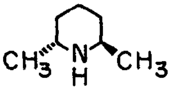
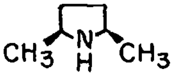
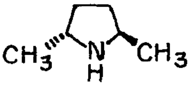
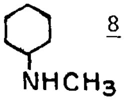
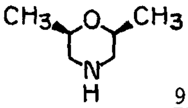
Abstract: The changes in ^{13}C chemical shifts for the structural change $R_2NH \rightarrow R_2N\text{-}Li$ have been measured for a series of dialkylamines. These lithiation shifts are largest at the alpha carbon (3.7 - 9.7 ppm) and decrease in the order $\alpha > \beta > \gamma > \delta$. The rates of lithium-hydrogen interchange between R_2NH and $R'_2N\text{-}Li$ have been determined. The activation energies are large (9 - 17 kcal/mole) and increase as the size of R or R' increases. The slow exchange permits the direct measurement of acidity differences between pairs of amines using ^{13}C nmr.

In spite of the current widespread use of lithium dialkylamides in organic chemistry, spectroscopic studies on these compounds have been almost non-existent (1, 2). In the only paper involving ^{13}C studies, specifically of lithium diisopropyl amide (LDA), Newcomb and Reeder (1) report the intriguing observation of individual signals for the alpha carbons of LDA and diisopropylamine (DIPA) which are separated by about 6 ppm at room temperature. This finding is surprising in two respects, the shift at the alpha carbon on lithiation being large and downfield and the proton transfer from DIPA to LDA being so slow. The minimum value for $\Delta G^{\ddagger}$ for this process, assuming a $T_c \geqslant 50°C$, would be 16 kcal/mole (3). In this report we wish to examine a number of lithiation shifts for potential utility and to measure the rate of slow proton transfer as a function of structure.

Lithiation Shifts: All ^{13}C shielding parameters, measured on 1M solutions using an FT-80 spectrometer, are reported in Table 1. Any dubious signal assignments were confirmed by off-resonance decoupling experiments. We will refer to the difference in the shift for a specific carbon in the lithiated amine relative to the amine ($\delta_{R_2N\text{-}Li} - \delta_{R_2NH}$) as a lithiation shift. It can be seen that all the lithiation shifts for the carbons attached (alpha) to nigrogen are positive (shift downfield on lithiation) and range from 3.7 to 9.7 ppm. The positive lithiation shifts are in the opposite direction to that expected on the basis of charge density effects. Nevertheless, the trend is not unusual in the sense that downfield shifts are seen for ^{13}C shieldings as a result of deprotonation of carboxylic acids (5), of phenols (6) and upfield shifts for the protonation of amines (7, 8). None of these phenomena have yet been accounted for satisfactorily by theory. The magnitudes of the lithiation shifts in 1 - 9 in general reflect the distance of the carbon from the nitrogen atom in that $\alpha > \beta > \gamma > \delta$ with only a few exceptions. The range of β shifts (2.5 to 4.7 ppm) though appreciable fails to indicate any stereochemical dependence (compare 4 with 5) as might be anticipated on the basis of changing $\eta \rightarrow \sigma^*$ interactions in axial versus equatorial methyl groups (9). The range of γ lithiation shifts (1.5 to 3.9 ppm) and δ shifts (1 to 1.5 ppm) are appreciable and

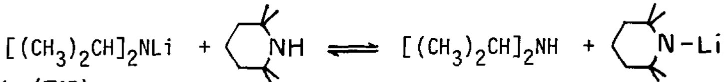
TABLE 1: ^{13}C Shifts[a] in Dialkylamines and Their Lithio Derivatives

Compound		Chemical Shifts					
		C_α	C_β	C_γ	$C_\beta'(C_5)$	$C_\alpha'(C_6)$	CH_3
$[(CH_3)_2CH]_2NH$ 1	1-H	46.7	24.6				
	1-Li	52.9	28.6				
 2	2-H	48.6	37.6	33.4			24.0
	2-Li	57.1	42.3	35.4			25.5
 3	3-H	54.2	36.7	27.0	28.2	49.07	24.3
	3-Li	59.9	40.7	29.0	32.5	55.3	28.0
 4	4-H	54.1	36.0	26.9			24.3
	4-Li	61.3	40.4	29.1			28.8
 5	5-H	47.6	34.7	21.3			22.1
	5-Li	51.3	38.8	25.2			25.9
 6	6-H	56.3	35.2				23.1
	6-Li	63.1	37.9				25.0
 7	7-H	54.8	36.5				23.7
	7-Li	60.1	38.8				26.0
 8	8-H	60.2	34.8	26.5	28.2	(C_δ)	34.9
	8-Li	57.4	38.5	28.0	29.2		41.0
 9	9-H	54.2	74.4				20.3
	9-Li	63.9	67.9				20.5

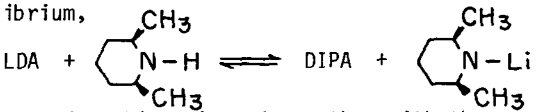
[a] All shifts are reported on the δ scale and were measured on 1 M solutions in THF using the α-carbon of solvent (δ = 69.00) as reference.

potentially useful as an aid to spectral assignments.

Possibly the most useful application of these shifts lies in the fact that they provide, in conjunction with the slow rate of intermolecular exchange, a method for measurement of pK_A differences between pairs of dialkylamines. Consider the equilibrium,



for which $K_{eq} = \frac{K_A\,(TMP)}{K_A(DIPA)}$ (10). This equilibrium mixture gives rise to identifiable signals for all four species. Measurements of peak intensities (with corrections made for relaxation time effects) provide the value $K = 0.026 \pm 0.003$ and thus log K or $\Delta pK_A = 1.6 \pm 0.05$. This shows lithium tetramethyl piperidide to be 1.6 pK units more basic than the more commonly used LDA. Thus Olofson's contention that LTMP should be used as a proton-specific strong base (11) is further reinforced by its greater basicity in THF. We have also determined K to be 2.9 ± 0.5 for the equilibrium,



Thus $\Delta pK = 0.5 \pm 0.05$ for this pair and together with the previous measurement shows the order of acidities cis-2,6-dimethylpiperidine > DIPA > TMP over a range of 2 pK units. The extension of these measurements to other dialkylamines, with the aim of identifying bases of greater basicity and synthetic ability is being examined.

Amide-Amine Exchange Rates: Because the appearance of separate signals for LDA and DIPA signified a barrier of more than 16 kcal/mole, we chose to measure the proton-lithium interchange by direct observation of the attainment of equilibrium at low temperature. For example, a mixture of DIPA and LiTMP prepared at -78° was monitored by ^{13}C to measure the decrease in signal intensity with time from which as Table 2 shows $\Delta G^{\ddagger}$ for the reaction (at -47°C)

$$\text{DIPA} + \text{LiTMP} \rightleftharpoons \text{LDA} + \text{TMP}$$

was found to be 16.8 kcal/mole. The barrier to proton lithium interchange was found to be lower by some 2 kcal/mole for the reaction between LDA and cis-2,6-dimethylpiperidine. That the rates are strongly affected by the size of the alkyl groups was further demonstrated by measurement of $\Delta G^{\ddagger} = 9.3$ kcal/mole for the degenerate exchange process,

$$(CH_3CH_2)_2\overset{*}{N}\text{-Li} + (CH_3CH_2)_2NH \rightleftharpoons (CH_3CH_2)_2\overset{*}{N}\text{-H} + (CH_3CH_2)_2N\text{-Li}$$

using the standard DNMR technique of measuring the coalescence temperature (3). The steric effect on exchange rates is therefore large if one compares these rates with those for CH_3NHK and methylamine, $\Delta G^{\ddagger} = 6.5$ kcal/mole (12) and for NH_2K and NH_3, $\Delta G^{\ddagger} = 7.4$ kcal/mole (13). The large barriers probably reflect other factors in addition to simple steric effects. For example, rupture of the aggregates of $LiNR_2$ (14) may be involved in the slow step. Aggregation which undoubtedly plays a significant role on lithiation shifts and basicities as well, must receive attention to allow proper understanding of lithiated amines.

Acknowledgement

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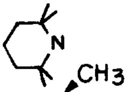
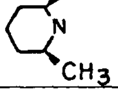
TABLE 2: Amide-Amine Exchange Rates

$$R_2NH + R'Li \rightleftharpoons R_2NLi + R'H$$

R	R'	$k(\mathrm{lm^{-1}sec^{-1}})$	$\Delta G^{\ddagger}$(kcal/mole)	T(°C)	Method
$(CH_3)_2CH$		2.5×10^{-4}	16.8 ± 0.3	-47	chemical exchange
$(CH_3)_2CH$		1.4×10^{-3}	14.7 ± 0.3	-65	chemical exchange
CH_3CH_2	$(CH_3CH_2)_2N$	177 (1.75 M)	9.3 ± 0.3	-77	DNMR
CH_3CH_2	$(CH_3CH_2)_2N$	311 (1.0 M)	9.6 ± 0.3	-65	DNMR

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(3) $\Delta G^{\ddagger}$ is calculated using the standard formula $\Delta G^{\ddagger} = 4.57\, T_C\, (10.32 + \log \frac{T_C}{k})$ where k at the coalescence temperature $(T_c) = 2.22\, \Delta\nu$ (4).

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