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THE EFFECT OF ADDITIVES ON ORGANOLITHIUMS

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Abstract: The effect of additives on the "apparent" acidities of weak carbon acids as measured versus lithiated amides is found to be small ($<$ 2 pK units). TMEDA is found to be the most effective in accelerating the rates of deprotonation of triphenylmethane.

The beneficial effects of amines such as tetramethylethylenediamine (TMEDA), and 1,4-diazabicyclo[2.2.2]octane (DABCO), as catalysts for reactions involving alkyllithiums have been known for over two decades (1,2). More recently, strongly basic alkyllithiums as metalating agents have frequently been replaced by the less basic lithiated amines (3) such as lithium diisopropylamide [LDA(4)] lithium 2,2,6,6-tetramethylpiperidide [LTMP(5)] and lithium *bis*-trimethylsilylamide (6). Tetrahydrofuran is most frequently the solvent of choice (3). Further modulation of the reactivity of these amides has been achieved by the addition of hexamethylphosphoramide [HMPA] and N,N'-dimethylpropylene urea [DMPU(8)]. These additives caused a significant increase in metallation rates, most probably as a result of their abilities to influence aggregation effects (9,10). Changing the metal counterion, long known to have an important effect on reactivity (11,12) has been achieved in reactions of LDA, by the addition of an equivalent of potassium t-butoxide (13,14). It has been assumed, without direct evidence, that the effect of these "additives" is solely kinetic (14) and that the basicity of the amide is not significantly altered by the type of solvated counterion. In view of the practical significance of this assumption (15), we have undertaken the measurement of the acidities of five carbon acids, in equilibrium with the appropriate lithiated amine, each in the presence of a variety of additives, for the purpose of determining their effects on the position of the equilibrium [1], as well as on the rates of metalation.

$$RH + LiNR'_2 \rightleftharpoons RLi + HNR'_2 \qquad [1]$$

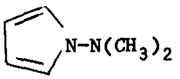
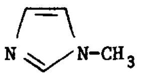
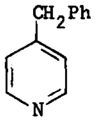
The value of K in the equilibrium has been determined by ^{13}C NMR as described previously (16). The value for -log K then provides the ΔpK or the acidity difference between the two weak acids RH and R'_2NH. The carbon acids studied include thioanisole, N,N-dimethylaminopyrrole, N-methylimidazole, diphenylmethane, and 4-benzylpyridine. The first two acids were assessed relative to 2,2,5,5-tetramethylpiperidine (pK_a = 37.3) the next two relative to diisopropylamine (pK_a = 35.7) the 4-benzylpyridine relative to bis-trimethylsilylamine (pK = 35.8). Table 1 presents the results, arbitrarily describing the effect of each addition as influencing the pK of the carbon acid only. The general trend in all cases can be summarized as follows: the variation of pK_a of the carbon acid as a result of inorganic salt, tertiary amine or coordinating agent is never more than 2.1 pK units. In fact, only thioanisole and N,N-dimethylaminopyrrole, each versus tetramethylpiperidine, varied by more than one pK unit. Consequently, one does not alter the thermodynamic acidity in a significant way by the use of additives.

The importance of additives thus remains in their ability to increase kinetic acidity. We have compared the influence of these additives on the rates of deprotonation of triphenylmethane by LDA. Also included are comparative rates for two other hindered amines. It can be seen, from the results in Table 2, that useful rate enhancements are provided by HMPA, DMPU, and TMEDA. Of the three, the cheapest and the safest, TMEDA, is also the most effective. And for bases more hindered than LDA, TMEDA should be used routinely. In addition to catalysing the deprotonation, it can be expected, on the basis of recent work, that these three additives will also have a significant influence on regioselectivity (17,18) and stereoselectivity (19,20).

The forty-fold increase in the rate of deprotonation of triphenylmethane by LDA in the presence of TMEDA has proven useful. Our intial measurement of the pK_a of triphenylmethane (21) was, in fact, in error as the slow deprotonation by LDA ($t_{\frac{1}{2}}$ = 13 hr) allowed some unmeasured competitive hydrolysis to occur. The deprotonation, catalysed by TMEDA revealed the fact that a true equilibrium had not been reached. We have redetermined the pK_A for triphenylmethane using thiophene, pK_A = 33.0 (22), as reference acid. The revised value of 32.9 replaces the earlier estimate of 34.6.

TABLE 1

pK$_A$ VALUES IN THF-Et$_2$O[a]

Additive	CARBON ACID				
	PhSCH$_3$		Ph$_2$CH$_2$		
None	38.1[b]	37.1[c]	35.3[d]	33.7[c]	25.1[e]
LiCl	38.9	37.7	35.6	-[f]	25.2
LiBr	38.2	38.1	34.9	-	25.3
TMEDA	37.5	37.3	34.6	33.7	24.8
DABCO	37.6	37.2	35.0	34.0	24.6
HMPA	37.4[g]	37.7[g]	-[g,h]	34.0[g]	25.2
DMPU	-[i]	-[i]	34.3[j]	-	24.8
K t-BuO	36.8[g]	36.4[g]	34.5[g]	33.7[g]	24.6
K t-BuO[k]	36.9[g]	37.1	34.8	-	-

[a] The lithiated amine was produced by adding methyllithium in ether (1.1 ml) to a solution of amine in THF(2 ml). An equivalent of carbon acid and additive were then added and solution examined by ^{13}C NMR. [b] Ref. 21, versus TMP. [c] Ref. 22 versus diisopropylamine. [d] Ref. 21 versus diisopropylamine. [e] Ref. 23 versus bistrimethylsilylamine. [f] broad peaks prevented accurate measurement. [g] determined at -60°C to avoid decomposition. [h] Equilibrium not attained. [i] Additional peaks suggested addition to DMPU. [j] The pK was essentially the same (34.2) at -70°C. [k] Solid Li t-BuO filtered off before measurement.

TABLE 2

EFFECT OF "ADDITIVES" (1 eq.) ON HALF LIFE (mins.) FOR DEPROTONATION OF TRIPHENYLMETHANE

LDA	LDA-LiBr	LDA-DABCO	LDA-DMPU	LDA-HMPA	LDA-TMEDA
784	863	695	41	27	18

LTMP	LTMP-TMEDA	R$_3$SiNR$_2$[a]
2020	148	5800

[a] The base was lithiated i-propyl trimethylsilylamine (24).

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