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SHORT COMMUNICATIONS

Quantitative analysis of organolithium reagents

Of the many analytical procedures* proposed for the analysis of organolithium reagents, the most widely used and accepted method is the Gilman double titration procedure[1,3]. This procedure requires titration of one aliquot with standard acid to yield total base concentration, RLi + ROLi, and treatment of a second aliquot with benzyl chloride[3] or 1,2-dibromoethane[1] followed by titration with standard acid to yield ROLi concentration. RLi concentration is then obtained by difference.

As developed by Gilman[1,3] the analyses are performed in a heterogeneous ether/water system. In the course of some kinetic studies in this laboratory it was found that the presence of hydrocarbons increased the difficulty of accurately determining the end point. We suggest that this problem can be obviated by the use of monoglyme instead of ether. However, a much more fundamental and serious problem was encountered: specifically, the tertiary lithium alkoxides react, albeit slowly, with benzyl chloride or 1,2-dibromoethane. As a result, the analyses obtained for tertiary alkyllithium reagents were too high. Therefore, an analytical procedure was developed which requires a single titration and yields results which are comparable to the Gilman procedure for aryllithium compounds, and which we believe to be superior for alkyllithium compounds.

This analytical procedure has its genesis in the observation of Price and Whiting[4] that organic acids, including weak acids, could be titrated with sodium dimethyl sulfoxide ("dimsylsodium") in DMSO solution using diphenylmethane or triphenylmethane as indicator. The present method involves the titration of a known amount of a standard organic acid with the organolithium solution of unknown titer in DMSO/monoglyme/hydrocarbon solution with triphenylmethane as indicator. The acid of choice is benzoic acid because of the relative ease of observation of the yellow to red (alkyllithium) or green to red-brown (phenyllithium) end point and because a monoglyme solution of this acid can be standardized by an aqueous base titration. However, many of the early studies and data reported here were obtained using acetophenone as the acid. The overall reactions occurring in the system are as follows:

$$RLi + C_6H_5CO_2H \rightarrow C_6H_5CO_2Li + RH$$

and at the end point when the standard acid is consumed:

$$RLi + (C_6H_5)_3CH \rightarrow RH + (C_6H_5)_3C^-Li^+ \text{ (red)}$$

In the absence of DMSO a white precipitate rather than a color change was observed.

Analyses by this procedure were compared with analyses by the Gilman double titration method and in the case of phenyllithium by a gravimetric procedure

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* For a comprehensive listing of references to analytical procedures through 1964 see refs. 1 and 2.

using triphenyltin chloride as precipitant[1]. Typical results are shown in Table 1.

The results in Table 1 show that for phenyllithium the three methods of

TABLE 1

ANALYTICAL RESULTS

Organo-lithium	*Solvent*	*Oxide conc.*	*Concentration of organolithium*[a]			
			This procedure, standard acid[b]			*Gilman*[c]
			(1)	(2)	(3)	
methyl	ether benzene	0.581		0.451 ± 0.003		
n-butyl	hexane heptane	0.139	0.930 ± 0.008			1.06 ± 0.02
sec-butyl	hexane heptane	0.365		0.292 ± 0.002	0.291 ± 0.002	
tert-butyl	pentane benzene	0.042		0.329 ± 0.004		
tert-butyl	pentane decalin	0.60	0.706 ± 0.007[d]			
tert-butyl	pentane decalin	0.345	0.969 ± 0.010	0.966 ± 0.015		1.23 ± 0.02
tert-butyl	pentane decalin	0.40	0.696 ± 0.005[e]			
tert-butyl	pentane decalin	0.60	0.715 ± 0.018[e]			
phenyl	benzene ether	0.322	0.804 ± 0.008			0.818 ± 0.007[f]

[a] All concentrations are in moles/liter and all errors shown are average experimental errors. [b] (1) acetophenone; (2) benzoic acid solution standardized by an aqueous base titration (appropriate blanks on monoglyme solvent); (3) β-naphthol. [c] Coupling reagent 1,2-dibromoethane. [d] Average of six determinations; all other values from triplicates. [e] Duplicate analyses of the same tert-butyllithium solution, lithium tert-butoxide added to second run. (Solid present.) [f] $(C_6H_5)_4Sn$: 0.810 ± 0.005.

analysis agree within experimental error. However, for *n*-butyl- and tert-butyllithium, the values determined by the Gilman titration are significantly higher than those by the triphenylmethane titration. These difficulties are believed to be due to problems in the Gilman procedure resulting from analyzing hydrocarbon solutions and from the reaction of the oxides present with the 1,2-dibromoethane. The results in Table I also show that titration of an alkyllithium against pure acid and against a monoglyme solution of benzoic acid, which was standardized by an aqueous base titration to the phenolphthalein end point, gave experimentally identical values for the concentration of alkyllithium. These results indicate that the reaction of the organic acid with the alkyllithium is quantitative and that the end point and the equivalence point are experimentally identical.

Inasmuch as Steiner and Gilbert[5] have observed that the pK_a's of alcohols in dilute solution in DMSO and tetrahydrofuran are in the same range as triphenylmethane and that the stoichiometries observed in the titrations of alcohols with dimsyl reagents were a function of the cation present, it was necessary to establish that the alkoxides would not interfere with the present procedure. This was done by two methods; in the first case, a tert-butyllithium solution at the titration end point

was saturated with lithium tert-butoxide and allowed to stand for two hours; in the second case, aliquots of a tert-butyllithium solution were analyzed in the absence and presence of a large quantity of added tert-butoxide. Within the precision of the method no effect of added tertiary alkoxide was observed. In addition, no color change was observed when a freshly prepared solution of triphenylmethane in DMSO was saturated with lithium tert-butoxide.

The indicator solution was prepared by dissolving 0.50 g of triphenylmethane in a mixed solvent of 400 ml of DMSO and 100 ml of monoglyme. This solution was then dried to the first permanent red color by addition of an alkyllithium solution and stored in a serum-capped bottle. The red color gradually disappeared as oxygen and water from the glass of the bottle reacted, but this was of little consequence since the indicator solution was again dried within the titration vessel.

For the titration, a 50-ml Erlenmeyer flask fitted with a septum and containing a magnetic stirring bar was evacuated, flamed, and flushed with purified nitrogen three times. Ten ml of the indicator solution was added with a syringe and dried by titration with an alkyllithium solution to the first permanent red color. The flask was immediately charged with either weighed, pure acid or an accurately measured aliquot of a standard solution of the acid in monoglyme. The amount of acid was chosen so that the titration would consume 2.00 to 2.50 ml of base solution. Needle inlet and exhaust ports were inserted and purified nitrogen admitted in a constant stream. The solution was immediately titrated to the red end point with the unknown organolithium solution, added from a 2.50-ml Hamilton gas tight syringe. The syringe was fitted with a screw-driven plunger and a magnifying reading glass, and the needle delivery tip was placed into the solution. The syringe had an inherent delivery accuracy of ± 0.02 ml. Rapid stirring and nitrogen cover were maintained at all times. Triplicate analyses were performed.

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