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Use of 9-Methylfluorene as an Indicator in the Titration of Common Group IA and Group IIA Organometallic Reagents

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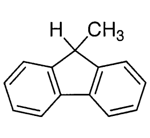
Received December 3, 2001

Abstract: 9-Methylfluorene was tested as an indicator in the titration of commonly used organometallic reagents. This indicator is readily prepared in three steps from fluorenone. In THF solution the deprotonated indicator is red and exhibits a sharp endpoint. The highly basic reagents *sec*-butyllithium and *tert*-butyllithium can be titrated in ether solution, where the color of the deprotonated indicator is yellow.

Organometallic reagents containing group IA and group IIA metals play important roles in organic chemistry. Often their use requires accurate knowledge of the concentration of the organometallic reagent in a solution. Many methods and indicators have been employed for the titrimetric determination of organometallic reagent concentrations.[1] An ideal indicator should have a single, cleanly removable proton with a pK_a lower than that of the conjugate acid of the titrand and higher than that of the conjugate acids of hydroxide or alkoxide impurities that contribute to the total base concentration. The rate of transfer of proton from the indicator to the titrand must be greater than the rate of transfer from titrant to deprotonated indicator. The indicator should be colorless in its protonated state and intensely colored when deprotonated in solution. It should also be readily available, stable in storage, recyclable, and nontoxic. We have examined the utility of 9-methylfluorene (**1**) as an indicator in titrimetric determinations of the concentrations of several group IA and group IIA organometallic reagents and report our results herein.[2]



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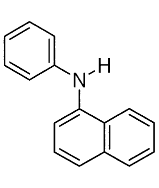

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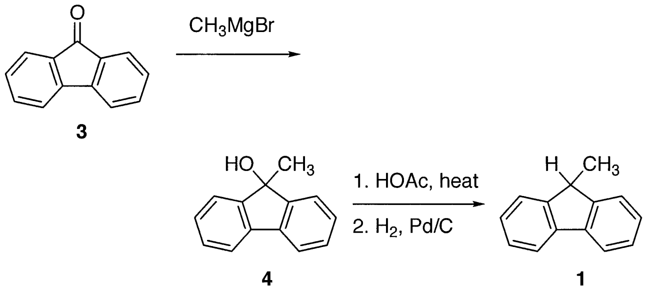
Compound **1** was prepared using published methods (see Scheme 1 and Supporting Information).[3] A description of the titration method appears in the Experimental Section. Results from titrations using **1**, and for comparison purposes *N*-phenyl-1-naphthylamine (**2**),[1i] are given in Table 1.

Tetrahydrofuran was commonly used as the solvent in titrations employing **1** as indicator. Ether was used as the solvent only when titrating very basic organometallics, such as *sec*-butyllithium and *tert*-butyllithium. An aliquot of the organometallic solution was added to solvent containing **1**, and in most cases a color change was observed immediately (vide infra). THF solutions of deprotonated **1** were deep red,[4] while ether solutions were bright yellow. These colored solutions were then titrated with a standard solution of *sec*-butanol in THF. In both THF and ether, visible endpoints were observed as a sharp change from colored to colorless or cloudy white solutions. In cases where the solution remained colorless, additional titrations could be performed in the same vessel by injecting another aliquot of the titrand and retitrating. Results obtained over several runs were consistent and, where comparable, in close agreement with parallel titrations using **2** as the indicator. Compound **2** gave a yellow to clear endpoint in THF or ether, which was often more difficult to distinguish than the endpoint of **1**.

SCHEME 1. Synthesis of 9-Methylfluorene (1)



Indicator **1** was more generally useful than **2** for the group IA organometallics tested. It worked well for determination of the concentrations of alkyllithium reagents, including *sec*-butyllithium and *tert*-butyllithium (Table 1, entries 1−7); of the amide bases lithium diisopropylamide, sodium hexamethyldisilazane, and potassium hexamethyldisilazane (entries 12−14); and of dimsylsodium and lithiated methyl phenyl sulfone (entries 15−16). In contrast, indicator **2** was more useful than **1** for the group IIA organometallics tested (entries

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(1) (a) Gilman, H.; Haubein, A. H. *J. Am. Chem. Soc.* **1944**, *66*, 1515−1516. (b) Gilman, H.; Cartledge, F. K. *J. Organomet. Chem.* **1964**, *2*, 447−454. (c) Eppley, R. L.; Dixon, J. A. *J. Organomet. Chem.* **1967**, *8*, 176−178. (d) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165−168. (e) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879−1880. (f) Duhamel, L.; Plaquevent, J.-C. *J. Org. Chem.* **1979**, *44*, 3404−3405. (g) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87−88. (h) Lipton, M. F.; Sorensen, C. M.; Sadler, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155−158. (i) Bergbreiter, D. E.; Pendergrass, E. *J. Org. Chem.* **1981**, *46*, 219−220. (j) Juaristi, E.; Martinez-Richa, A.; Garcia-Rivera, A.; Cruz-Sanchez, J. S. *J. Org. Chem.* **1983**, *48*, 2603−2606. (k) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509−510. (l) Aso, Y.; Yamashita, H.; Otsubo, T.; Ogura, F. *J. Org. Chem.* **1989**, *54*, 5627−5629. (m) Kiljunen, H.; Hase, T. A. *J. Org. Chem.* **1991**, *56*, 6950−6952. (n) Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, *64*, 3755−3756.

(2) Although the acidity of fluorene derivatives has been widely studied (e.g., see Bowden, K.; Cockerill, A. F. *J. Chem. Soc. B* **1970**, 173−179), their general utility as titrimetric indicators has not been described.

(3) Badger, G. M. *J. Chem. Soc.* **1941**, 535−538. Details of our synthesis based on this method appear in the Supporting Information for this note.

(4) The reported values of $\lambda_{\max}$ and ϵ for the cesium salt of **1** in THF are 376 nm (12350), 478 nm (980), 503 nm (1250), and 539 nm (890). See: Bors, D. A.; Kaufman, M. J.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 6975−6982.

10.1021/jo0111208 CCC: $22.00

TABLE 1. Titrations of Organometallic Solutions[a]

entry	organometallic	solvent	concentration, M[b,c]	titrated concentration, M	
				9-methylfluorene	*N*-phenyl-1-naphthylamine
1	BuLi	hexanes	1.6 (N)	1.56 ± 0.05[d]	1.56 ± 0.04[f]
2	BuLi	hexanes	1.6 (O, S)	1.29 ± 0.04[e]	1.31 ± 0.03[f]
3	BuLi	hexanes	1.6 (O)	1.65 ± 0.04[f]	1.65 ± 0.04[e]
4	*sec*-BuLi	cyclohexane	1.3 (O)	1.06 ± 0.11[f]	0.99 ± 0.08[f]
5	*tert*-BuLi	pentane	1.7 (O)	1.64 ± 0.13[e]	no result[g,h]
6	MeLi	ether	1.6 (N)	1.59 ± 0.06[f]	1.66 ± 0.09[f]
7	PhLi	cyclohexane/ether	1.8 (N)	1.63 ± 0.05[d]	1.63 ± 0.07[d]
8	MeMgCl	THF	3.0 (O)	no result[i]	1.65 ± 0.29[d,j]
9	*tert*-BuMgCl	THF	1.0 (N)	no result[i]	no result[i]
10	phenyl MgBr	ether	3.0 (O)	no result[i]	3.07 ± 0.11[d]
11	vinyl MgBr	THF	1.0 (O)	1.08 ± 0.08[f]	1.01 ± 0.02[f]
12	LDA	heptane/THF	2.0 (N)	2.04 ± 0.06[f]	1.93 ± 0.10[f]
13	$NaN(SiMe_3)_2$	THF	1.0 (N)	0.97 ± 0.05[e]	no result[k]
14	$KN(SiMe_3)_2$	toluene	0.5 (N)	0.78 ± 0.06[e]	no result[g]
15	$NaCH_2S(O)CH_3$	THF	~0.5[l]	0.35 ± 0.08[d]	no result[g]
16	$LiCH_2SO_2Ph$	THF	~0.25[m]	0.17 ± 0.02[d]	no result[g]

[a] Titrations were performed using THF as solvent except for *sec*-BuLi and *tert*-BuLi, which were performed in ether. [b] Original molarity according to the label. [c] N = new bottle, O = previously opened bottle, S = sediment present. [d] Average of 4 titrations. [e] Average of 5 titrations. [f] Average of 6 titrations. [g] Addition of organometallic to indicator in THF gave a yellow solution that never exhibited an endpoint. [h] Ref 1i reports the titration of *tert*-BuLi using *sec*-BuOH in xylenes. [i] Addition of organometallic gave no color change. [j] Endpoint difficult to distinguish. [k] Addition of organometallic gave a black solution. [l] Anticipated concentration; prepared by reaction of NaH with an excess of dry DMSO. [m] Anticipated concentration; prepared by reaction of BuLi with an excess of methyl phenyl sulfone in dry THF.

8−11). Neither **1** nor **2** was useful for determination of the concentrations of lithium hexamethyldisilazane, lithiated phenylacetylene, or the lithium enolate of cyclohexanone. The last two failures can be attributed to the comparable thermodynamic acidities of phenylacetylene, cyclohexanone, and the indicators.[5,6] The apparent failure of most Grignard reagents and lithium hexamethyldisilazane to deprotonate **1** is more difficult to rationalize. A significant kinetic barrier to deprotonation of **1** must exist and may be attributable to differences in ion-pairing and organometallic aggregation for these reagents.[7] Compound **2** was an adequate indicator for the less basic organolithiums, for LDA, and for three of the four Grignard reagents tested. However, its yellow endpoint was often obscured by residual coloration of the solution.

9-Methylfluorene offers some advantages over other indicators used in organometallic titrations. It has a single removable proton with a pK_a of 22,[5] which is lower than those of the conjugate acids of organometallic species normally titrated and higher than those of the conjugate acids of hydroxide or alkoxide impurities that contribute to the total base concentration.[8] It is colorless in its protonated state and intensely colored when deprotonated in THF or ether solution. The titration endpoint is easily discernible. 9-Methylfluorene is expected to be stable in storage and recyclable when warranted. Although it is presently commercially unavailable, it is readily prepared in three steps from inexpensive fluorenone.[3]

Experimental Section

HAZARDOUS CHEMICAL WARNING: 9-Methylfluorene has been shown to be mutagenic; see ref 9. Tetrahydrofuran and diethyl ether were distilled from sodium metal and benzophenone prior to use. *sec*-Butanol was distilled from calcium hydride and stored over 3 Å sieves. A standard solution was prepared by weighing dry *sec*-butanol (4−5 g) into a 100 mL class A volumetric flask that had been dried in an oven for several days and diluting to the mark with freshly distilled THF.

Titration Procedure. A flame-dried 25 mL three neck round-bottom flask under argon was charged with indicator (ca. 15 mg) and THF or ether (5 mL). The flask was fitted with two rubber septa and a class A 10 mL buret that had been dried in an oven and inserted through a third rubber septum. The buret was filled with the standard solution of *sec*-butanol in THF. The organometallic solution to be titrated (1.00 mL) was then added via syringe. The organometallic solutions containing indicator normally turned red (THF) or yellow (ether) for **1** and yellow for **2**. The standard solution of *sec*-butanol in THF was added dropwise until the color just disappeared. The concentration of the organometallic was then calculated from the volume of the standard solution dispensed. If the organometallic was not colored to begin with, another aliquot of organometallic could be added and the titration repeated (often several times) in the same flask. If the organometallic was colored, or for highly basic organometallics, such as *sec*-butyllithium and *tert*-butyllithium, multiple titrations were performed in separate flasks to facilitate observation of the endpoint.

Note Added after ASAP: A typographical error was introduced in the first paragraph of the version posted ASAP 11/15/2002; the corrected version was posted 11/27/2002.

Supporting Information Available: Details of the synthesis of **1** from fluorenone. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The reported pK_a value for **1** in THF is 21.85. See ref 4.

(6) Values of pK_a reported for phenylacetylene and cyclohexanone vary. See: (a) Cram, D. J. *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965. (b) Jones, J. R. *The Ionization of Carbon Acids*; Academic Press: New York, 1973. (c) Bates, R. B.; Ogle, C. A. *Carbanion Chemistry*; Springer-Verlag: Berlin, 1983, and references cited in the these books.

(7) Parris, G. E.; Ashby, E. C. *J. Am. Chem. Soc.* **1971**, *93*, 1206−1213, and references therein.

(8) This was demonstrated by adding potassium *tert*-butoxide to a solution of 9-methylfluorene in THF. No color was observed over 48 h.

(9) For studies bearing on the toxicological properties of 9-methylfluorene, see: (a) Rice, J. E.; Rivenson, A.; Braley, J.; LaVoie, E. J. *J. Toxicol. Environ. Health* **1987**, *21*, 525−532. (b) Veith, G. D.; Mekenyan, O. G.; Ankley, G. T.; Call, D. J. *Chemosphere* **1995**, *30*, 2129−2142.