7 or 8 are genuine intermediates in the reaction, or whether they simply represent resonance contributors to the transition state of a single step displacement on oxygen.

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Role of Hexamethylphosphoramide in Facile, High-Yield One-Electron Reductions by Organometallic Compounds

Sir:

It was recently reported that trimethylsilylsodium is a good one-electron reducing agent in hexamethylphosphoramide (HMPA) solution.[1] We wish to report that HMPA facilitates the one-electron reduction of a variety of compounds by organolithium and -magnesium compounds.[2] For example, 0.1 *F* HMPA solutions of methyl-, *n*-butyl-, or *tert*-butyllithium or benzylmagnesium chloride will quantitatively reduce 10^{-4} *M* biphenyl to its radical anion in less than 10 min.

Investigations of the reactions of *n*-butyllithium with biphenyl and anthracene in mixed solvent systems indicate that the concentration of HMPA is the most important variable in determining the extent of one-electron reduction observed. No apparent reaction occurs between *n*-butyllithium and biphenyl in tetrahydrofuran (THF) solution within 1 hr. Incremental replacement of THF by HMPA leads to a concurrent increase in the formation of biphenyl radical anion (Table I). The amount of reduction which occurs is not related to any particular stoichiometric ratio of HMPA to *n*-butyllithium or biphenyl, but is dependent on the HMPA concentration.

Table I. Yield of Biphenyl Radical Anion as a Function of HMPA Concentration[a]

[HMPA], *M*	Yield, %[b]	[HMPA], *M*	Yield, %
0.0	*c*	2.95	10.0
0.95	*c*	4.35	38.0
1.91	3.0	5.40	100.0

[a] THF was the cosolvent, [biphenyl] = 1.10×10^{-3} *M*, [*n*-butyllithium] = 0.10 *F*. [b] Calculated using an extinction coefficient of 4.0×10^4 at 407 nm (J. Jagar-Grodzinski, M. Field, S. L. Yang, and M. Szwarc, *J. Phys. Chem.*, **69**, 628 (1968); M. Szwarc, "Carbanions, Living Polymers, and Electron Transfer Processes," Interscience, New York, N. Y., 1968, p 174). [c] Not detected by visible or epr spectra.

This conclusion was confirmed by a detailed study of the reaction between anthracene and *n*-butyllithium. Anthracene does not react rapidly with *n*-butyllithium in diethyl ether solution in the dark.[5] However, in THF solution,[6] in diethyl ether–tetramethylethylenediamine (TMEDA),[7] and in diethyl ether–HMPA solvent mixtures rapid reaction occurs. The reaction products are anthracene radical anion and the alkylate, 10-*n*-butyl-9-lithio-9,10-dihydroanthracene. The alkylate is the major product in THF solution and the diethyl ether–TMEDA and diethyl ether–HMPA (when HMPA/*n*-butylithium < 15) solvent mixtures (Table II). When diethyl ether or THF is successively replaced by larger quantities of HMPA (HMPA/*n*-butyllithium > 15), the amount of anthracene radical anion observed increases at the expense of the alkylate (Table II). The anthracene radical anion is not formed by decomposition of the alkylate nor is the amount observed a function of any particular stoichiometric ratio of HMPA to *n*-butyllithium or anthracene. Only when the HMPA concentration is high (and HMPA/*n*-butyllithium is large) does electron transfer become the major reaction. A reasonable hypothesis is that the high dielectric constant of HMPA ($E = 30/20°$)[8] favors these electron transfer reactions.

Table II. Yields of Anthracene Radical Anion and Alkylate as a Function of HMPA Concentration[a]

[HMPA], *M*/Solvent[b]	Yield, %[c] Alkylate	Radical	[HMPA], *M*/Solvent	Yield, % Alkylate	Radical
0.00/T	>99	<1[d]	0.82/E	90	10
1.39/T	77	23	1.39/E	85	15
1.43/T[e]	72	28	1.48/E	83	17
2.15/T[e]	45	55	1.80/E	70	30
2.78/T	32	68	1.80/E[f]	71	29
4.17/T	13	87	2.46/E	50	50
5.21/T	7	93	3.77/E	15	85
0.16/E	87	13	4.17/E	16	84
0.33/E	81	19	5.07/E	8	92
0.33/E[f]	87	13	1.71/E[g]	>99	<1[d]
0.35/E	86	14	4.30/E[g]	89	11

[a] Unless noted otherwise, [*n*-butyllithium] = 0.10 *F* and [anthracene] = 8.2×10^{-4} *M*. [b] T = THF, E = diethyl ether. [c] Yield of radical anion calculated using an extinction coefficient of 2.4×10^4 at 366 nm (see references in Table I, footnote *b*). Yield of alkylate calculated using an extinction coefficient of 2.4×10^4 at 455 nm (HMPA containing solutions) or 425 nm (TMEDA containing solutions). The alkylate has two equally intense absorptions at 395 and 444 nm in THF solutions (ref 6a). [d] Not detected in sufficient quantity to accurately measure. [e] [*n*-Butyllithium] = 0.05 *F*. [f] [Anthracene] = 16.0×10^{-4} *M*. [g] TMEDA rather than HMPA added.

The radical anions of many aromatic hydrocarbons and compounds such as nitrobenzene[9] have been formed by reaction with organolithium or -magnesium compounds in HMPA solution. Since overreduction does not appear to be a problem, a large excess of the organometallic reagent can be used. The radical anion is formed rapidly and its destruction by trace amounts of

(1) H. Sakurai, A. Okade, H. Umino, and M. Kira, *J. Amer. Chem. Soc.*, **95**, 955 (1973).
(2) One-electron transfers by organolithium compounds in low yield in THF solution[3] and upon photolysis in diethyl ether solution[4] have been observed.
(3) G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Amer. Chem. Soc.*, **86**, 1807 (1964), and references therein.
(4) H. J. S. Winkler and H. Winkler, *J. Org. Chem.*, **32**, 1695 (1967).
(5) H. J. S. Winkler, R. Bellinger, and H. Winkler, *J. Org. Chem.*, **32**, 1700 (1967).
(6) (a) D. Nicholls and M. Szwarc, *J. Amer. Chem. Soc.*, **88**, 5757 (1966); *Proc. Roy. Soc., Ser. A*, 301, 223, 231 (1967); (b) R. G. Harvey and C. C. Davis, *J. Org. Chem.*, **34**, 3607 (1969).
(7) The TMEDA–*n*-butyllithium complex is very reactive. See C. G. Eberhardt and W. A. Butte, *ibid.*, **29**, 2928 (1964); C. G. Screttas and J. F. Eastham, *J. Amer. Chem. Soc.*, **87**, 3276 (1965); R. G. Harvey, L. Nazareno, and H. Cho, *ibid.*, **95**, 2376 (1973).
(8) H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6**, 1046 (1967).
(9) G. R. Stevenson, L. Echegoyen, and L. R. Lizardi, *J. Phys. Chem.*, **76**, 1439 (1972), have reported the epr spectra of nitrobenzene radical anion as its lithium, sodium, and potassium salts in HMPA solution.

water or oxygen is eliminated under these conditions. In a typical preparation a quartz epr flat cell is attached to a Y cell[10] and the assembly is flushed with dry nitrogen. The cell is charged with 0.75 ml of HMPA, 50 μl of 1.6 *F* *n*-butyllithium in HMPA,[11] and 25 μl of 6.5×10^{-3} *M* biphenyl in HMPA by syringe. Both the epr [$a_{p\text{-H}} = 5.26$ G, $a_{o\text{-H}} = 2.58$ G, $a_{m\text{-H}} = 0.40$ G, line width = 40 mG] and electronic spectra of the solution are recorded in the flat cell.

The spectra obtained for the lithium salts of the hydrocarbon radical anions indicate that they are the expected "free ions."[12] However, epr and electronic spectra indicate that the magnesium salts exist as associated ion pairs in HMPA solution. For example, lithium anthracenide has epr parameters ($a_{\text{H-9}} = 5.24$, $a_{\text{H-1}} = 2.72$, and $a_{\text{H-2}} = 1.48$ G) and absorbs at 366 nm, whereas magnesium anthracenide has epr parameters ($a_{\text{H-9}} = 5.20$, $a_{\text{H-1}} = 2.71$, and $a_{\text{H-2}} = 1.48$ G) and absorbs at 340 nm.

The observations reported here suggest that many radical anions previously prepared with great difficulty can be easily prepared by one-electron reduction with readily available organometallic compounds in HMPA solution.

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(10) The Y cell is one side of Russell's H cell.[3]

(11) For most applications the organometallic reagent can be used as the more readily available hydrocarbon or ether solutions.

(12) M. Szwarc, "Carbanions, Living Polymers, and Electron Transfer Processes," Interscience, New York, N. Y., 1968, Chapters 5 and 6.

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Utilization of Carbon-13–Carbon-13 Coupling in Structural and Biosynthetic Studies. An Alternate Double Labeling Method

Sir:

We wish to report a new method utilizing ^{13}C–^{13}C coupling in structural and biosynthetic studies.[1,2] When a microbial metabolite of polyacetate origin is labeled with doubly labeled acetate ($^{13}CH_3{}^{13}CO_2H$), the ^{13}C–^{13}C coupling should be observed with the metabolite between the C–C bonds which had formed the acetic acid molecule. However, the coupling should not be observed between the C–C bonds formed by the condensation of acetic acid. In the proton-decoupled cmr spectrum of the labeled compound, each signal appears as a triplet, whose center peak is caused by the natural abundance peak.

(1) For earlier studies of ^{13}C–^{13}C couplings in organic molecules, see: K. D. Summerhays and G. E. Maciel, *J. Amer. Chem. Soc.*, **94**, 8348 (1972); F. J. Weigert and J. D. Roberts, *ibid.*, **94**, 6021 (1972); A. M. Ihrig and J. L. Marshall, *ibid.*, **94**, 1756 (1972).

(2) For biosynthetic studies in which ^{13}C–^{13}C couplings were observed from singly labeled precursors, see: M. Tanabe, T. Hamasaki, H. Seto, and L. F. Johnson, *Chem. Commun.*, 1539 (1970); M. Tanabe, T. Hamasaki, Y. Suzuki, and L. F. Johnson, *J. Chem. Soc., Chem. Commun.*, 212 (1973); A. I. Scott, C. A. Townsend, K. Okada, M. Kajiwara, P. J. Whitman, and R. J. Cushley, *J. Amer. Chem. Soc.*, **94**, 8267 (1972).

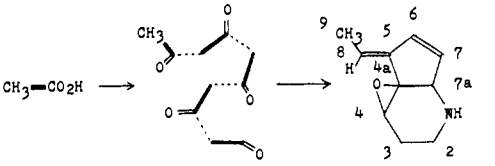

Figure 1. Dihydrolatumcidin and its biosynthetic pathway.

Information on the other C–C bonds formed by the condensation of acetic acid molecule may be obtained by labeling the metabolite using mixed labeled acetate (1:1 mixture of $^{13}CH_3CO_2H$ and $CH_3{}^{13}CO_2H$). Although four combinations between these two differently labeled acetates are possible, only one ($CH_3{}^{13}CO\cdots{}^{13}CH_2COR$) gives the desired ^{13}C–^{13}C coupling.[3] The results obtained by using doubly and mixed labeled acetate are complementary to each other and will give the complete sequence of the carbon skeleton of the metabolite. In addition to polyketides, the above mentioned "alternate double labeling method" can be applied to steroids and terpenes which are biosynthesized fron acetate *via* mevalonate.

From the biosynthetic point of view, one of the advantages of using doubly labeled acetate is that this method makes it possible to know the occurrence of any C–C bond fission during biosynthesis. The direction of the elongation of a polyketide chain can also be detected (R_1CH_2–$CO\cdots CH_2R_2$ or $R_1CH_2\cdots CO$–CH_2R_2).[5]

In order to test the "alternate double labeling method," we chose as a model compound dihydrolatumcidin (I) ($C_{10}H_{13}ON$), a metabolite of *Streptomyces reticuli* var. *latumcidicus*,[6] whose structure[7] and biosynthesis[8] had been previously established (Figure 1).

The proton-decoupled cmr spectrum of I labeled with doubly labeled acetate (90% enriched) exhibited very strong peaks due to ^{13}C–^{13}C coupling (Figure 2a). Likewise, the ^{13}C–^{13}C coupling with weaker intensity appears in the spectrum of I (Figure 2b) labeled with mixed labeled acetate (both 90% enriched). It should be noticed in this spectrum that C_{4a} and C_5 couple respectively to two carbons and that C_2 and C_9 do not couple to any carbon.

The coupling constants, chemical shift, and multiplicity on the off-resonance decoupling spectrum obtained with an unlabeled sample are summarized in Table I. From these data and the known chemical shift of carbons,[9] the following carbon sequences are very easily obtained from the sample labeled with doubly labeled acetate: $NC_{(2)}H_2C_{(3)}H_2$, $C_{(4)}HX$-

(3) In addition to the 1,2 couplings, 1,3 couplings ($^{13}CH_3CO\cdots{}^{13}CH_2COR$) may also occur. In this case, discrimination between the 1,2 and the 1,3 couplings becomes very important in the correlation of carbon signals. Fortunately, since the 1,2 coupling is much larger than the 1,3 or 1,4 coupling, with the exception of cyclopropane derivatives,[4] the magnitude of the coupling constant is very useful in making the assignment.

(4) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N. Y., 1972, p 370.

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(6) Y. Sakagami, I. Yamaguchi, H. Yonehara, Y. Okimoto, S. Yamanouchi, K. Takiguchi, and H. Sakai, *J. Antibiot., Ser. A*, 11, 6 (1958).

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