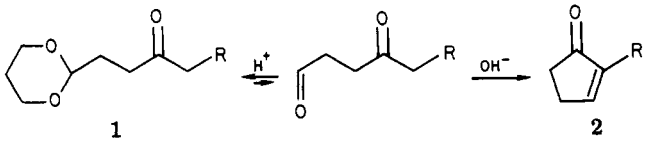
Scheme I



1 2

Furthermore, the base-catalyzed cyclization of γ-keto aldehydes gives much polymer, particularly where R is small.[3] Indeed where R is a methyl group, the cyclization could not be done in solution at all.[4]

Considered together, the characteristics of these two reactions would complement each other. To avoid polymerization in the aldol step, the concentration of keto aldehyde should be kept low. The acetal hydrolysis provides a very low concentration of keto aldehyde if little water is present. The second step is irreversible so it should ultimately drain the equilibrium step to completion if both steps are run concurrently. The dilemma is that the first step requires strong acid catalysis and the second requires a hydroxide base. Simple forms of these catalysts would of course neutralize each other, but we have found that R-276 Rexyn 300 (H-OH) ion-exchange resin,[5] which is a mixture of sulfonic acid beads and quaternary ammonium hydroxide beads, does catalyze both steps concurrently.

We have converted 2-(3-oxopentyl)-1,3-dioxane[6] (1, R = CH_3) to 2-methyl-2-cyclopenten-1-one[7] in 48% distilled yield in one operation by stirring with the mixed resin in hot methanol. In the same way, we have converted 2-(3-oxononyl)-1,3-dioxane[8] (1, R = n-C_5H_{11}) to 2-n-pentyl-2-cyclopenten-1-one[9] in 87% crude (56% distilled) yield.

In a typical procedure, 50 mmol of keto acetal, 55 g (34 mequiv) of resin, and 100 mL of methanol were heated at reflux with magnetic stirring for 1–2 h. This was cooled, filtered, and distilled to give the colorless cyclopentenone.

The thermal instability of the basic resin is a limitation in this process, so we are investigating other resins. We are also examining other reaction sequences which may be uniquely facilitated by this mixed catalysis.[10]

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We also thank the National Science Foundation for funds (Grant CHE 78-02081) to purchase a NMR spectrometer.

(1) A dioxolane would be more readily removed but the dioxane is preferred because of the superior characteristics of the Grignard reagent used to prepare the keto acetal.[2]

(2) Stowell, J. C. *J. Org. Chem.* **1976**, *41*, 560.

(3) This cyclization is considered extremely delicate and the methods described in the literature are rarely satisfactory: Larcheveque, M.; Valette, G.; Cuvigny, Th. *Tetrahedron* **1979**, *35*, 1745.

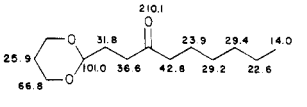
(4) Cavill, G. W.; Goodrich, B. S.; Laing, D. G. *Aust. J. Chem.* **1970**, *23*, 83. These authors did obtain some of the methylcyclopentenone at 370 °C in the gas phase.

(5) The mixed resin was obtained from Fisher Scientific Co.

(6) This keto acetal was prepared from propionyl chloride and the Grignard reagent from 2-(2-bromoethyl)-1,3-dioxane:[2] bp 97–99 °C (1.1 mmHg); ^1H NMR ($CDCl_3$) δ 1.05 (t, 3), 1.80 (m, 4), 2.45 (m, 4), 3.90 (m, 4), 4.58 (t, 1).

(7) The spectral characteristics of this compound are in accord with published values: Fischli, A.; Klaus, M.; Mayer, H.; Schonholzer, P.; Ruegg, R. *Helv. Chim. Acta* **1975**, *58*, 564.

(8) Prepared as in ref 2; ^{13}C NMR ($CDCl_3$):



(9) The spectral characteristics of this product are in accord with published values: Ravid, U.; Ikan, R. *J. Org. Chem.* **1974**, *39*, 2637.

(10) While this work was in progress, another example of sequential catalytic reactions appeared: Pittman, C. U., Jr.; Liang, Y. F. *J. Org. Chem.* **1980**, *45*, 5048.

Registry No. 1 (R = CH_3), 70710-36-0; 1 (R = C_5H_{11}), 57345-99-0; 2 (R = CH_3), 1120-73-6; 2 (R = C_5H_{11}), 25564-22-1; propionyl chloride, 79-03-8; 2-(2-bromoethyl)-1,3-dioxane, 33884-43-4.

John C. Stowell,* Henry F. Hauck, Jr.
Department of Chemistry
University of New Orleans
New Orleans, Louisiana 70122
Received February 4, 1981

Evidence for Single Electron Transfer in the Reactions of Alkali Metal Amides and Alkoxides with Alkyl Halides and Polynuclear Hydrocarbons

Summary: Evidence for single electron transfer as the major pathway in reactions previously considered to be classic S_N1 and S_N2 pathways has been obtained. In this connection, the reaction of KOBu-*t* with trityl bromide has been shown to proceed through the trityl radical, and the reaction of LiN(*i*-Pr)$_2$ with a primary alkyl iodide probe gave evidence of proceeding by single electron transfer, as indicated by the cyclized nature of the product as a result of a radical intermediate.

Sir: Recently we reported that the reactions of various main group metal hydrides with alkyl halides, polynuclear hydrocarbons, and dimesityl ketone proceed mechanistically via a single electron transfer (SET) pathway.[1-3] Although metal hydrides in general have been regarded previously as nucleophilic sources of hydride ion in reactions with the above organic substrates,[4-6] the occurrence of SET has been clearly established by spectroscopic (visible and EPR) studies as well as by product-formation studies using cyclizable probes. In view of these results, we have decided to extend our studies to include nucleophiles other than hydride ion and to involve reactions previously thought to proceed by classic S_N1 or S_N2 pathways, e.g., reactions involving alkali metal amides and alkoxides with alkyl halides. In this study we report the observation of radical intermediates in reactions involving typical nucleophiles such as alkoxides and dialkylamides, not only with alkyl halides but also with polynuclear hydrocarbons.

Lithium diisopropylamide (LiN-*i*-Pr$_2$), lithium *tert*-butoxide (LiOBu-*t*), and potassium *tert*-butoxide (KOBu-*t*) react rapidly with trityl chloride or bromide (Ph_3CX, when X = Cl or Br) in THF to give an orange-red solution. These solutions have been found to be EPR active and show an EPR spectrum consistent with that previously reported for the trityl radical ($Ph_3C\cdot$, Figure 1). The concentration of this radical increases with time over a period of 24 h (estimated intensity 10–20%), beyond which the intensity of the radical decreases. The product of the reaction of trityl bromide with LiN-*i*-Pr$_2$ is triphenylmethane which is consistent with the formation of a radical

(1) E. C. Ashby, A. B. Goel, and R. N. DePriest, *J. Am. Chem. Soc.*, **102**, 7779 (1980).

(2) E. C. Ashby, A. B. Goel, R. N. DePriest, and H. S. Prasad, *J. Am. Chem. Soc.*, **103**, 973 (1981).

(3) E. C. Ashby, R. N. DePriest, and A. B. Goel, *Tetrahedron Lett.*, submitted for publication.

(4) H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, Menlo Park, CA, 1972.

(5) H. C. Brown and S. Krishnamurthy, *J. Org. Chem.*, **45**, 849 (1980).

(6) C. W. Jefford, D. Kirkpatrick, and F. Deloy, *J. Am. Chem. Soc.*, **94**, 8905 (1972).

(7) F. C. Adam and S. I. Wieseman, *J. Am. Chem. Soc.*, **80**, 2057 (1958).

0022-3263/81/1946-2429$01.25/0

Table I. Reaction of LiN-*i*-Pr_2 with Polynuclear Hydrocarbons in THF at 24 °C[a]

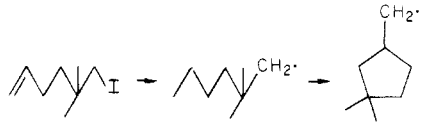
hydrocarbon	10^{-4} M	time, days	color	% radical anion[b]	EPR data: g value	EPR data: no. of lines
anthracene	300	15	light blue	5	2.0029	43
benzo[*a*]pyrene	1	7	violet	30	2.0031	93
chrysene	4	10	blue-green	8	2.0035	111
2,3-benzanthracene	1	7	yellow	40	2.0032	65
phenanthrene	4	10	blue	5	2.0030	73
perylene	1	5	blue	60	2.0029	59

[a] LDA was used in 20-fold excess. [b] Percentages of radical anion intermediate were calculated from the values of the extinction coefficient as well as by integrating the EPR spectra. Values are within ±5% of the reported values.

intermediate. On the other hand, potassium *tert*-butoxide reacts with trityl bromide to give mainly the ether product, Ph_3COBu-*t*, with a small amount of $(t\text{-}BuOC_6H_4)CPh_2$ (eq 1) (characterized by GC/MS and NMR). This reaction is an example of the classic Williamson ether synthesis.[8]

$$Ph_3CBr + KO\text{-}t\text{-}Bu \rightarrow [Ph_3CBr]^{\cdot-} + [KO\text{-}t\text{-}Bu]^{\cdot+} \rightarrow Ph_3C^{\cdot} + Br^- + [KOBu]^{\cdot+} \rightarrow Ph_3CO\text{-}t\text{-}Bu + \text{(t-BuO, H, Ph, Ph)C=C} + KBr \quad (1)$$

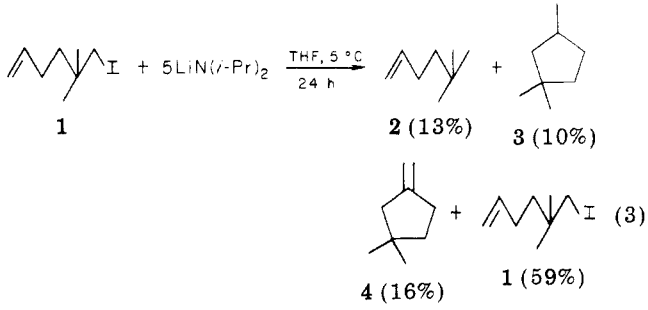
The alkyl iodide 2,2-dimethyl-1-iodo-5-hexene (1) has been used as a mechanistic probe for the detection of single electron transfer reactions.[3] It has been shown that the primary alkyl radical intermediate derived from 1 cyclizes rapidly to give the cyclic radical intermediate (eq 2). In



(2)

1

the present study, the reactions of 1 with LDA and lithium *n*-butylamide (LiN(H)-*n*-Bu) were investigated. The results are summarized in eq 3 and 4. Thus the formation



1 2 (13%) 3 (10%) 4 (16%) 1 (59%) (3)

$$1 + 5LiN(H)n\text{-}Bu \xrightarrow[60\ h]{THF,\ room\ temp} 2\ (35\%) + 3\ (14\%) + 4\ (22\%) + 1\ (28\%) \quad (4)$$

of cyclic product 3, a product derived from radical intermediates (eq 2), is a clear indication of single electron transfer as described in Scheme I.

Note that the production of cyclic hydrocarbon 4 could be the consequence of either disproportionation of the radical intermediate or the reaction of base ($LiNR_2$) with an intermediate (7) formed as a result of a radical chain process.[9] We are currently conducting experiments in order to determine the extent of reaction of radical 6 in H atom abstraction from solvent and disproportionation of radical 6 as described in the above reaction.

(8) R. T. Morrison and R. N. Boyd, "Organic Chemistry", 3rd ed., Allyn & Bacon, Inc., Boston, MA, 1973.
(9) J. F. Bunnett, *Acc. Chem. Res.*, 11, 413 (1978).

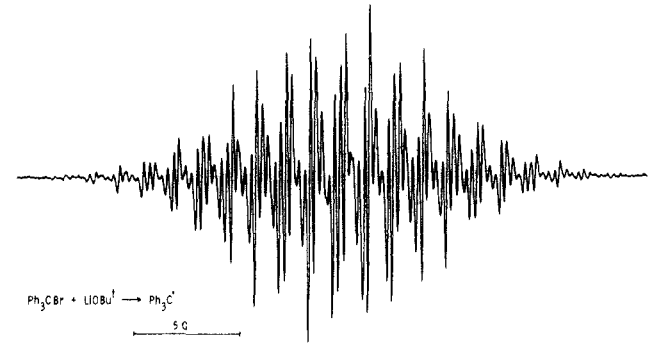
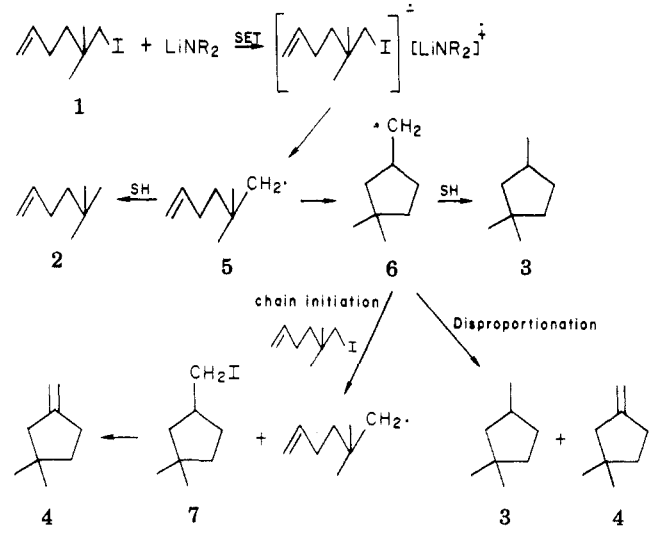
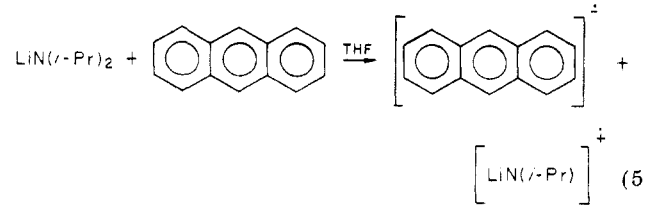


Figure 1. EPR spectrum of the intermediate ($Ph_3C\cdot$) formed in the reaction of trityl bromide with lithium diisopropylamide, lithium *tert*-butoxide, and potassium *tert*-butoxide in THF at room temperature.

Scheme I



Polynuclear hydrocarbons have also been found to be excellent probes for the observation of SET since the radical intermediates are stable and show strong and well-defined visible and EPR spectra. Reactions of LDA with perylene, 2,3-benzathracene, benzo[*a*]pyrene, phenanthrene, chrysene, and anthracene (eq 5) in THF have



(5)

been carried out. Although the reactions proceed slowly, radical formation has been observed in all of the reactions

by EPR spectroscopy. The EPR spectra in all cases have been found to be consistent with the respective radical anion EPR spectra reported previously.[2] The intensity of the EPR signals increases continuously with time and the amount of the radical intermediate after a specific time interval is given in Table I. Similarly, LiOBu-*t* and KOBu-*t* have also been found to generate radical anions with polynuclear hydrocarbons, but at a much slower rate compared to that of LDA.

In conclusion, the above preliminary results represent the first definitive proof that reactions of alkali metal amides and alkoxides with organic substrates such as alkyl halides and polynuclear hydrocarbons can proceed via a single electron transfer pathway, although these reactions heretofore have been generally considered to be classic S_N1 or S_N2 processes.

Acknowledgment. We acknowledge support of this work by the National Science Foundation (Grant No. HPS 7504127).

Registry No. 1, 77400-57-8; lithium diisopropylamide, 4111-54-0; lithium *tert*-butoxide, 1907-33-1; potassium *tert*-butoxide, 865-47-4; trityl chloride, 76-83-5; trityl bromide, 596-43-0; trityl radical, 2216-49-1; lithium butylamide, 41487-32-5; 2,2-dimethyl-5-hexene radical, 71880-21-2; 1,3,3-dimethylcyclopentane radical, 77400-58-9; anthracene, 120-12-7; benzo[*a*]pyrene, 50-32-8; chrysene, 218-01-9; 2,3-benzanthracene, 92-24-0; phenanthrene, 85-01-8; perylene, 198-55-0; anthracene radical anion, 34509-92-7; benzo[*a*]pyrene radical anion, 34505-58-3; chrysene radical anion, 34488-57-8; 2,3-benzanthracene radical anion, 34512-30-6; phenanthrene radical anion, 34510-03-7; perylene radical anion, 34505-65-2.

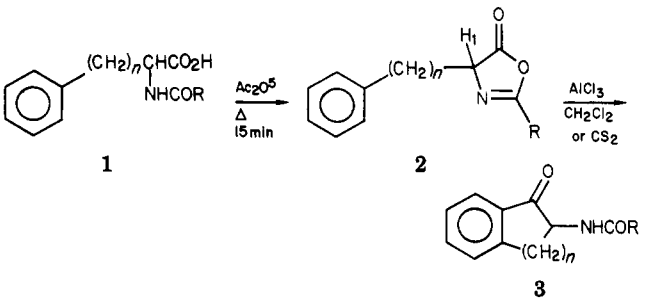
E. C. Ashby,* A. B. Goel, R. N. DePriest
School of Chemistry
Georgia Institute of Technology
Atlanta, Georgia 30332
Received January 29, 1981

Chiral α-Amino Ketones from the Friedel–Crafts Reaction of Protected Amino Acids

Summary: The Friedel–Crafts reaction employing *N*-methoxycarbonyl-protected α-amino acids is described. This method yields chiral α-amino ketones which can be further used to prepare doubly chiral vicinal amino alcohols.

Sir: Both acyclic and cyclic vicinal amino ketones and alcohols constitute widely studied structural classes of interest as medicinal agents and as intermediates in natural product syntheses.[1,2] One of the most important features of such biologically active compounds is the chirality present at the asymmetric centers; therefore, useful chiral synthetic procedures are continually sought. In this communication, we describe the novel and preparatively useful approach to chiral α-amino ketones via a Friedel–Crafts reaction of N-protected amino acids. This retention of chirality was dependent upon the utilization of the *N*-methoxycarbonyl derivative.

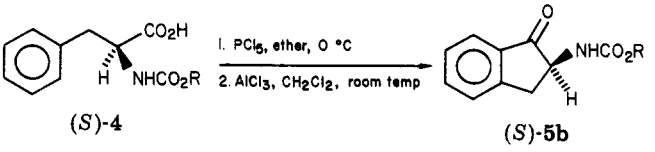
The synthesis of α-amino ketones **3** via azlactones[3,4] worked well (55–90%) for the formation of a five-, six-, or seven-membered ring. However, their known rapid racemization due to the high acidity[6] of H_1 in **2** negated their use in the formation of chiral **3**.[7]



1 2 3

a, n = 1, R = CH_3; **b**, n = 1, R = Ph; **c**, n = 2, R = CH_3; **d**, n = 2, R = Ph; **e**, n = 3, R = CH_3

Recent publications indicated that the replacement of the R substituent of **2** by an OR moiety yielded derivatives less prone to racemization.[9] In addition, these syntheses proceeded through the corresponding acid chloride, an intermediate potentially useful in a Friedel–Crafts cyclization. However, the $AlCl_3$-catalyzed reaction of the acid chloride of Cbz-protected L-phenylalanine (**4a**)[9] produced only intractable tars presumably due to the generation of benzyl carbonium ions from the Cbz substituent.



(*S*)-4 (*S*)-5b

a, R = benzyl; **b**, R = CH_3

Thus, the methoxycarbonyl derivative **4b**,[10] via its acid chloride,[11] produced **5b**[12] in 55–75% yields. The respective chiral precursors gave (*R*)- or (*S*)-**5b**[12] after an aqueous hydrochloric acid workup. Chiral shift NMR analysis[8] with $Eu(hfbc)_3$ revealed none of the opposite enantiomer, indicating a chiral purity of ≥98% for each isomer.[13]

(1) (a) Wasson, B. K.; Gibson, W. K.; Stuart, R. S.; Williams, H. W. R.; Yates, C. H. *J. Med. Chem.* **1972**, *15*, 651. (b) Howe, R.; Crowther, A. F.; Stephenson, J. S.; Rao, B. S.; Smith, L. H. *Ibid.* **1968**, *11*, 1100. (c) Morrow, D. F.; Johnson, P. C.; Tonabi, H.; Williams, D.; Wedding, D. L.; Craig, J. W.; Majewski, R. F.; Braselton, J. P.; Gallo, D. G. *Ibid.* **1973**, *16*, 736. (d) "Antihypertensive Agents"; Engelhardt, E. L., Ed.; American Chemical Society: Washington, DC, 1976. (e) Torchiana, M. L.; Porter, C. C.; Stone, C. A. *Arch. Int. Pharmacodyn.* **1968**, *114*, 118.

(2) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3088. Bowman, R. E.; Evans, D. D.; Guyett, J.; Hagy, H.; Weale, J.; Weyell, D. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 438.

(3) Carter, H. E. *Org. React.* **1946**, *3*, 198.

(4) (a) Cioranescu, E.; Buchen-Barladeanu, L. *Izv. Akad. Nauk SSSR, Otiel. Khim. Nauk* **1961**, 149; *Chem. Abstr.* **1961**, *55*, 18653. (b) Balaban, A. T.; Bally, I.; Frangopol, P. T.; Bacescu, M.; Cioranescu, E.; Buchen-Barladeanu, L. *Tetrahedron* **1963**, *19*, 169.

(5) The acetyl derivatives (R = CH_3) were generated in situ by heating the parent amino acid on a steam bath with acetic anhydride for a few minutes as indicated.

(6) Goodman, M.; Levine, L. *J. Am. Chem. Soc.* **1964**, *86*, 2919.

(7) The known, partially chiral (*R*)-**2b** was cyclized to give **3b**, $[\alpha]^{25}_D$ 11.0° (*c* 0.60, dioxane). The optical rotation of (*S*)-**2b** used was $[\alpha]^{25}_D$ 19.78° (*c* 0.45, dioxane) which implies, at best, a 28% enantiomeric excess.[6] Chiral shift NMR analysis[8] indicated an enantiomeric excess for **3b**, so formed, of only 5–10%.

(8) McClure, D. E.; Arison, B. H.; Baldwin, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 3666.

(9) Jones, J. H.; Witty, M. J. *J. Chem. Soc., Chem. Commun.* **1977**, 281. Jones, J. H.; Witty, M. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3203.

(10) Petri, E. M.; Staverman, A. J. *Recl. Trav. Chim. Pays-Bas* **1952**, *71*, 385.

(11) Heating should be kept to a minimum during the concentration process to remove ether and $POCl_3$. Prolonged heating led to the loss of methyl chloride and formation of the *N*-carboxy anhydride derivative.[10] Routinely, solvent was removed at 25–30 °C (25 torr) and the crude acid chloride used immediately in the cyclization step.

(12) All new compounds exhibited spectral and microanalytical or high-resolution mass spectral properties completely consistent with the assigned structures.

0022-3263/81/1946-2431$01.25/0