yielding 3210 independent data. The final positional coordinates and equivalent isotropic thermal parameters for the non-hydrogen atoms are given in Table IX.

(3β,5β,14β,20*E*)-Methyl 3-[(2′,6′-dideoxy-3′,4′-*o*-(1′-methylethylidene)-β-D-*ribo*-hexopyranosyl)oxy]-14-hydroxyl-21-methylenepregn-21-carboxylate (IIIb), $C_{33}H_{52}O_7$, has M_r = 560.8, monoclinic space group $P2_1$, a = 17.621 (3) Å, b = 11.077 (3) Å, c = 8.115 (2) Å, β = 98.60 (2)°, Z = 2, d_c = 1.189 g cm^{-3}, μ(Mo Kα) = 0.881 cm^{-1}, R = 0.058 for 4073 observed data ($F > 4\sigma_F$). Data were measured to a $2\theta_{max}$ of 60° using Mo Kα radiation (λ = 0.71069 Å) on a Syntex P_3 diffractometer yielding 4826 independent data. The final positional coordinates and equivalent isotropic thermal parameters for the non-hydrogen atoms are given in Table X.

3-[(2′,6′-Dideoxy-3′,4′-*o*-(1′-methylethylidene)-β-D-*ribo*-hexopyranosyl)oxy](20*S*)-20,22-dihydrodigitoxigenin ((20*S*)-IVb), $C_{32}H_{50}O_7$, has M_r = 546.8, triclinic space group P_1, a = 7.887 (1) Å, b = 15.350 (2) Å, c = 6.303 (1) Å, α = 91.80 (1), β = 99.84 (1), γ = 93.53 (1)°, Z = 1, d_c = 1.211 g cm^{-3}, μ(Cu Kα) = 6.811 cm^{-1}, R = 0.046 for 3000 observed data ($F > 3\sigma_F$). Data were measured to a $2\theta_{max}$ of 150° using Cu Kα radiation (λ = 1.5418 Å) on an Enraf-Nonius CAD-4 diffractometer yielding 3058 independent data. The final positional coordinates and equivalent isotropic thermal parameters for the non-hydrogen atoms are given in Table XI.

Conformational Energy Calculations. Potential energy calculations for rotations of the C3-O3 and O3-C1′ steroid-sugar linkage bonds were done using the molecular mechanics program CAMSEQ[30] in conjunction with the modeling and graphics features of the NIH PROPHET computer system.[31] The potential energies were calculated at 10° rotation steps of each bond, while holding the geometry fixed as observed in the crystal structure. The final energies were then adjusted so the minimum value was zero.

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Supplementary Material Available: Tables of atomic coordinates and anisotropic thermal parameters and hydrogen atom coordinates and isotropic thermal parameters for Ib, IIa-c, IIIa,b, and (20*S*)-IVb (14 pages). Ordering information is given on any current masthead page.

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Origin of Benzophenone Ketyl in Reactions of Benzophenone with Lithium Dialkylamides. Implications for Other Possible Electron-Transfer Reactions†

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Abstract: A reaction scheme is presented for the formation of benzophenone ketyl in reactions of lithium dialkylamides containing β-hydrogen atoms with benzophenone. The key steps are fast concerted β-hydride reduction of benzophenone to give lithium benzhydrolate, rate-limiting deprotonation of the lithium benzhydrolate to give dilithium benzophenone dianion, and fast electron transfer from the dianion to benzophenone to give two molecules of ketyl. Benzophenone is supplied throughout the course of the reaction by a retro-aldol reaction of the lithium salt of aldol-like adduct **4** formed early in the reaction. The reaction scheme was confirmed by kinetic studies of the individual steps. The velocity of the retro-aldol reaction was orders of magnitude faster than that of ketyl formation. The deprotonation of lithium benzhydrolate by lithium diisopropylamide (LDA) in tetrahydrofuran at 22 °C occurred with an apparent second-order rate constant which was approximately equal to one-half of the apparent second-order rate constant for ketyl formation when benzophenone was treated with LDA under similar conditions. The possibility that related sequences of reactions could occur when weak organic oxidants are treated with reagents that can act as hydride donors and bases is discussed.

The reduction of benzophenone by lithium dialkylamides was first reported two decades ago by Wittig who concluded that the mechanism of the reaction involved a concerted β-hydride transfer from the base to benzophenone.[2] More recent studies, however, provided evidence that the reaction of amide bases with ketones may involve an electron-transfer step (single electron transfer, SET) from base to ketone. For example, Scott et al.[3a] observed that benzophenone ketyl coupling products were formed in the reaction of lithium diisopropylamide (LDA) with benzophenone. Although Scott made no mechanistic claims, it was clear that some route to the odd-electron radical anion existed. Ashby et al.[3b] studied the reactions of benzophenone and dimesityl ketone with LDA and concluded that the detection of ketyl by ESR (in up to 35% yield in the case of benzophenone) during the course of the reactions was evidence for an SET pathway. A pinacol product has also been reported by Paquette et al. from the reaction of LDA with an aliphatic diketone,[4] and an SET mechanism for the reaction of LDA with an ynone has been suggested.[5] Primarily because of the large percentage of ketyl detected in the reaction of LDA with benzophenone, this reaction had begun to assume the role of an archetypal SET process.

† Dedicated to Professor D. J. Cram on the occasion of his 65th birthday in admiration of his fundamental contributions in mechanistic carbanion chemistry.

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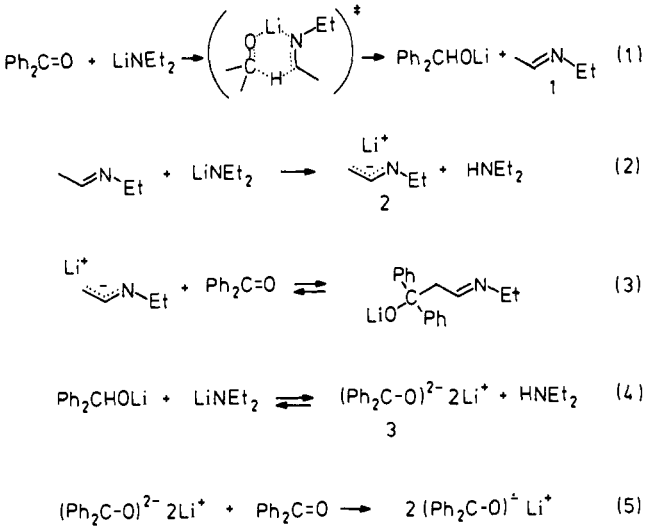
Scheme I



Despite the evidence which had accumulated suggesting that the benzophenone reduction by lithium dialkylamides involved an SET process, when we studied the reaction of benzophenone with a mechanistic probe designed to detect aminyl radicals, *N*-lithio-*N*-butyl-5-methyl-1-hex-4-enamine,[6a] we found no evidence that the probe had been oxidized to a radical.[6b] Clearly, if a large amount of ketyl was formed in an SET reduction then free aminyl radical should also have been formed. Thus, an SET process was not indicated. In our preliminary report describing the probe work, we speculated that ketyl could be formed by a series of secondary reactions occurring after the initial ketone reduction.[6b] In this paper we describe studies which confirm such a mechanistic scheme for ketyl formation. The kinetic studies reported herein coupled with our previous probe work provide a compelling argument against formation of ketyl and aminyl radicals by an SET process and support Wittig's original concerted β-hydride pathway, or at least a pathway in which no free intermediates are formed, for the primary reduction reaction.

When one restates the series of reactions that lead to benzophenone ketyl formation in general terms, one obtains a scheme which could be operative in reactions of a wide variety of **nu**cleophiles with oxidants that lead to oxidant-derived radical anions. Thus, it may be appropriate to question conclusions regarding SET processes which are based solely on the detection of such radical anions. We suggest that for some potential SET reactions, the two-electron pathway to radical anions which we present below should be shown not to be operative before an SET pathway is established.

The Two-Electron Route to Benzophenone Ketyl. Scheme I consists of a series of conventional reactions which could lead to ketyl formation in reactions of lithium dialkylamides with benzophenone. For convenience, we have illustrated the various steps with a representative base, lithium diethylamide (LDEA). Step 1 is a concerted β-hydride process which leads directly to lithium benzhydrolate and an imine (**1**). In step 2, imine **1** is deprotonated by base to give a 1-azaallyllithium reagent (**2**). Step 3 is a reversible aldol-like reaction between **2** and benzophenone. In step 4, the lithium benzhydrolate is deprotonated to give the dilithium benzophenone dianion (**3**). Finally, in step 5 the dianion **3** reacts with benzophenone to give two molecules of ketyl. Since step 3 is reversible, steps 4 and 5 need not be competitive with the early reactions in the sequence, but steps 2 and 3 must compete with step 1 for the scheme to be viable.

Results and Discussion

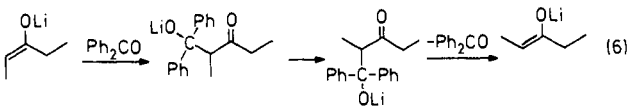
In order to verify that the processes in Scheme I occur in the reaction of benzophenone with lithium dialkylamides containing β-hydrogen atoms we have studied the rates of the individual steps of Scheme I where possible as well as the overall rate of ketyl formation. We chose to study reactions with LDA in depth since this base is so commonly used and since several purported SET reactions involve LDA. We also briefly studied reactions of LDEA. Much of the evidence supporting Scheme I already exists in the literature, and much of that evidence was reported by Wittig.

The Aldol Reaction (Steps 2 and 3). Wittig et al. have shown that steps 2 and 3 of Scheme I must occur in competition with the initial reduction since they isolated the aldol-like adducts **4a**

4a: R = CH_2CH_3 **4c**: R = $CH(CH_3)_2$
4b: R = c-C_6H_{11} **4d**: R = c-C_6H_{11}

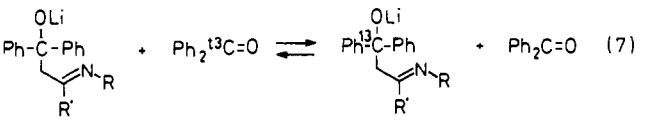
from the reaction of LDEA with benzophenone and **4b** from the reaction of lithium *N*-ethylcyclohexylamide with benzophenone.[2] The presence of the aldol-like products is a critically important point for understanding the observations made by others; we return to a discussion of this point below.

That step 3 can be reversible is predicted from the analogous, well established retro-aldol reactions seen with simple enolates. For example, Rathke has reported that stereoisomeric enolates from 3-pentanone can equilibrate by an aldol, retro-aldol sequence involving 3-pentanone itself as the electrophile.[7a] Similarly, the 3-pentanone enolate isomers react with benzophenone to give an equilibrium mixture of enolates, presumably via the sequence in eq 6,[7a] and isomeric 1-azaallyllithium reagents derived from di-



methylhydrazones can also equilibrate in the presence of benzophenone.[7b]

It was still necessary for us to establish that the rate of the reverse of step 3 in Scheme I, the retro-aldol process that can provide benzophenone during the course of the reaction, was fast enough to accommodate the scheme. We measured the rate in a qualitative manner. The label incorporation reaction shown in eq 7 could be monitored by ^{13}C NMR spectroscopy. Since the



equilibrium for step 3 lies on the side of aldolate product, especially in the presence of excess benzophenone, a measurement of the rate of incorporation of ^{13}C-labeled benzophenone into the aldolate product in eq 7 would give the rate of the retro-aldol reaction of step 3. Although the rate of incorporation could be measured accurately by this method, for our purposes it was sufficient to determine that the reaction was substantially faster than the overall rate of ketyl formation observed in other experiments discussed below. We note that this type of study could provide useful information for a variety of retro-aldol reactions which would be of both mechanistic and synthetic interest.

Two aldol-like products, **4a** and **4d**, were employed in these studies. Aldimine adduct **4a** is known to form in the reaction of LDEA with benzophenone;[2] and **4d** was a manageable ketimine adduct that we substituted for adduct **4c** which would be the expected aldol-like product from the reaction of LDA with benzophenone. For the lithium salts of both **4a** and **4d**, the equili-

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bration shown in eq 7 was >90% complete in less than 60 min at 22 ± 2 °C. The velocities of these retro-aldol reactions were orders of magnitude greater than the overall velocity of ketyl formation (vide infra).

Since step 3 is reversible, a low steady-state concentration of free benzophenone was present after the initial processes (steps 1–3) in reactions of benzophenone with lithium dialkylamides. Some of this benzophenone must have been reduced to lithium benzhydrolate via step 1, but the rate constant for this step was small. After the first few minutes, we could not detect a significant change in the yield of benzhydrol (<1%) during the next 24 h at 22 °C.

Deprotonation of Lithium Benzhydrolate. Formation of the dilithium benzophenone dianion (**3**) by deprotonation, step 4 of Scheme I, is the most unusual step in the sequence. Potentially, it could also be the most difficult to study since at equilibrium the reagents on the left of eq 4 could be favored. Yet step 4 could still be the rate-limiting process in the formation of ketyl provided that the velocity of step 5 is greater than that of the reverse of step 4. Our experimental results suggest that the pK_a of lithium benzhydrolate is close to but somewhat higher than that of a dialkylamine.[8]

When benzhydrol was added to an LDA or LDEA solution, the reaction mixture slowly turned the characteristic deep red color of the benzophenone dianion.[9] In ^{13}C NMR studies with LDA as base, new signals which we ascribed to the dianion grew in as the reaction proceeded. By ^1H NMR spectroscopy we could observe a reduction in intensity of the benzhydrolate methine proton signal relative to those of the aryl protons and could estimate the amount of dianion formed. For example, about 7% of dianion was present when lithium benzhydrolate was treated with a fourfold excess of LDA for 12 h at 25 °C. However, it was clear that the rate of formation of dianion was rapidly decreasing over this period which suggested that an equilibrium was being approached. Since it was apparent that we would have difficulties in measuring the ratio of products accurately at low conversion using NMR spectroscopy, we abandoned this method of analysis.

The benzophenone dianion concentration could be determined accurately by a method which incorporated a GC analysis. Whitesides et al.[9] have shown that treatment of this dianion with oxygen gives benzophenone quantitatively. Thus, we allowed benzhydrol to react with LDA and periodically removed aliquots from the reaction mixtures, treated the aliquots with oxygen, and analyzed the products by capillary GC. There is a *caveat*. In the basic reaction mixture, under oxygen, benzhydrol suffered slow autooxidation to give benzophenone; related autooxidations of weakly acidic hydrocarbons are known.[10] However, the oxidation of the dianion was complete in less than 1 min at 25 °C, and in a set of control reactions we determined that the potentially complicating autooxidation process occurred with a velocity of approximately 0.1% of the benzhydrol concentration per minute. Thus, the effect of the autooxidation was minimal in these studies. In confirmation of this conclusion the oxidation of a reaction mixture at time zero gave 0% benzophenone.

The results of the deprotonation reactions are given in Table I. Again the results indicated that there was an approach to equilibrium situation as can be seen by comparing the apparent second-order rate constants calculated according to eq 8. The

$$d[\text{dianion}]/dt = k_2[\text{LiNR}_2][\text{Ph}_2\text{CHOLi}] \quad (8)$$

deprotonation process most likely is complex in the order of base,

Table I. Formation of Dilithium Benzophenone Dianion via Deprotonation of Lithium Benzhydrolate by LDA at 22 °C

[LDA][a]	[Ph_2CHOLi][a]	time, h	[$(Ph_2CO)^{2-}$][b]	k_2,[c] M^{-1} s^{-1}
0.27	0.063	1	0.0036	6.1×10^{-5}
0.27	0.063	2	0.0039	3.3
0.28	0.05	3	0.0040	3.0
0.27	0.063	3	0.0047	2.7
0.27	0.063	4	0.0051	2.2
0.28	0.07	12	0.0043	0.56
0.34	0.07	22	0.0069	0.39
0.28	0.07	24	0.0050	0.31
0.28	0.07	55	0.0059	0.16

[a] Concentrations (M) at time zero. [b] Concentration (M) at time t. [c] Apparent second-order rate constant calculated by using eq 8; see text and ref 16 for details.

and attempting to solve an approach to equilibrium rate problem with unknown order of reactants (but at least second order on both sides) appeared to be overwhelming. This kinetic problem was further complicated because the reactions were so slow that decomposition of solvent by LDA became important at long (several days) reaction times, and thus we were unwilling to estimate an equilibrium constant. As a first approximation of the rate constant for the deprotonation step, we used the simple apparent second-order rate constant calculated via eq 8 at short (≤4 h) reaction times. The assumption that the deprotonation process is a simple second order reaction both in this deprotonation and in the ketyl formation (vide infra) leads to a cancellation of errors which minimizes problems arising from the assumption. Thus, we conclude that k_2 for deprotonation of lithium benzhydrolate by LDA at 22 ± 2 °C in THF is $4 \pm 2 \times 10^{-5}$ M^{-1} s^{-1}. A one point determination for k_2 for deprotonation by LDEA (3 h, 22 °C) was 3×10^{-5} M^{-1} s^{-1}.

The Electron-Transfer Process (Step 5). The equilibrium shown in eq 5 is known to lie on the side of ketyl.[11a-c] While we are unaware of a measurement of the rate constant for the electron transfer in eq 5, this process is expected to be exceedingly fast since it should suffer steric constraints similar to those present in the electron transfer from benzophenone ketyl to benzophenone, a reaction known to occur with a rate constant of ca. 2×10^8 M^{-1} s^{-1} at 25 °C.[11d] In an attempt to measure the rate of step 5, we generated dilithium benzophenone dianion in THF (<0.1 M), cooled the mixture to −78 °C and added a 0.1 M solution of benzophenone. As expected, the reaction could not be studied by conventional methods since it proceeded faster than mixing. The minimum limit on the rate constant at −78 °C was $k > 1 \times 10^2$ M^{-1} s^{-1} from which one can reasonably assume that at 22 °C the rate constant would be $k > 1 \times 10^5$ M^{-1} s^{-1}.[12]

Reactions of Lithium Dialkylamides with Benzophenone. There is an important feature of previous studies of these reactions which

(8) The pK_a's of diisopropylamine (35.7) and diphenylmethane (35.9) in THF are close to one another (see Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Chem. Soc., Chem. Commun.* **1983**, 620–621). Apparently, any inductive effect of OLi in reducing the acidity of lithium benzhydrolate at the methine position is almost completely offset by a stabilizing effect of the ion triplet (dilithium benzophenone dianion) in THF; ion triplet stability has been discussed by Streitwieser (see Streitwieser, A., Jr.; Swanson, J. T. *J. Am. Chem. Soc.* **1983**, *105*, 2502–2503).

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(12) Scheme I requires that dianion reacts rapidly (in step 5) with the steady-state concentration of benzophenone provided in the reverse of step 3. Is our minimum value for k for step 5 large enough to ensure that step 5 will be faster than the reverse of step 4? By using an experimental rate constant for the reverse of step 3 of $k > 7 \times 10^{-4}$ s^{-1}, an assumed $\Delta G^{\ddagger}$ for the forward of step 3 of 10 kcal/mol and the known concentrations (ca. 0.05 M) of aldol adduct in the reactions discussed in Table II, one estimates that the steady-state concentration of free benzophenone in these studies was about 1×10^{-5} M. From this value for benzophenone concentration, the pseudo-first-order rate constant for reaction of dianion in eq 5 is $k > 1$ s^{-1}. Now, since we know that the rate constant for the forward reaction in eq 4 is $k = 4 \times 10^{-5}$ M^{-1} s^{-1} and we may estimate an equilibrium constant for eq 4 of ca. 1×10^{-3}, we can use the known concentrations of diisopropylamine (ca. 0.05 M) to calculate a pseudo-first-order rate constant for protonation of dianion (reverse of eq 4) of $k = 2 \times 10^{-3}$ s^{-1}. In other words, we conclude that, in reactions where benzophenone and LDA were mixed, >99.8% of the dianion formed in step 4 must have reacted with the free benzophenone; step 5 under our conditions was at least 3 orders of magnitude faster than the reverse of step 4. This conclusion was confirmed by the kinetic results shown in Table II. It was apparent that protonation of dianion (reverse of step 4) was of little kinetic importance.

Table II. Formation of Benzophenone Ketyl in Reactions of Benzophenone with LDA at 22 °C

LDA:Ph_2CO[a]	% redn[b]	[LDA][c]	[Ph_2CHOLi][c]	time, h	[ketyl][d]	method[e]	$k_2/2$,[f] M^{-1} s^{-1}
1:1	50	0	0.104	18	0	ESR	
2:1	51	0.16	0.067	4	0.010		3.6×10^{-5}
				12	0.018		2.4
				30	0.019		1.0
3:1	53	0.20	0.047	4	0.007		2.9
				12	0.015		2.3
				30	0.019		1.3
				60	0.012		0.4
4:1	57	0.24	0.042	4	0.006		2.3
				12	0.013		1.8
				30	0.019		1.2
				60	0.007		0.2
3:1	58	0.26	0.070	14	0.020	OX	1.3
	56	0.17	0.046	18	0.012		1.4
	58	0.26	0.070	21	0.024		1.1
4:1	58	0.19	0.036	12	0.008		1.6
				21	0.010		1.2
				36	0.017		1.4
				60	0.019		1.0
6:1	66	0.33	0.044	7.5	0.012		1.8
				21	0.017		1.0
	61	0.34	0.043	21	0.014		0.8

[a] Initial ratio of LDA to benzophenone. [b] Percent reduction of benzophenone determined immediately after mixing by a time zero aqueous quench of a reaction aliquot followed by GC analysis. [c] Initial measured concentrations (M) of reagents immediately after mixing. [d] Concentration (M) of ketyl at time t. [e] ESR indicates analysis by the ESR method. OX indicates analysis by the oxidation method. See text for details. [f] One-half of the apparent second-order rate constant for formation of ketyl according to eq 9; see text and ref 16 for details.

should be clarified first. A most striking contrast is seen in the conclusions concerning the rates of the reductions. Wittig stated that lithium dialkylamide reductions of benzophenone were complete in one min at 0 °C,[2b] and Creary, Kowalski, et al. clearly demonstrated that the primary reactions of benzophenone with lithium diisopropylamide (LDA) were essentially complete within a few minutes at −78 °C.[13,14] In the latter work benzophenone was allowed to react with LDA for a short time, and then methyllithium was added to trap any free ketone. Subsequent quenching gave benzhydrol, 1,1-diphenylethanol and a considerable amount of benzophenone. The benzophenone detected at the conclusion of the reaction sequence must have been trapped as an unreactive intermediate during the reaction. It is quite likely that this unreactive intermediate was the lithium salt of the aldol-like adduct **4c** based on Wittig's observation of adducts **4a** and **4b** and our finding that upon GC analysis the aldol-like adducts **4a** and **4d** were *quantitatively cleaved to give benzophenone*. The detection of benzophenone (formed by pyrolysis of **4**) in a GC analysis may have led to some confusion in the studies by Scott and co-workers[3a] and Ashby and co-workers.[3b] Both groups apparently concluded that the reduction of benzophenone by LDA was a rather slow reaction.

At the onset of the studies it was clear that an accurate method for assaying the amount of ketyl formed in reactions was required. Ketyl can be observed by various spectroscopies, but these methods are difficult to use for quantiative measurements. In ESR spectroscopy substantial errors can arise in the quantitation of radicals,[15a] and in IR spectroscopy the benzophenone ketyl is known not to obey Beer's Law in ether.[15b] Further, the known[15c] concentration dependent aggregation and dimerization of ketyl could complicate quantitation in a spectroscopic method.

Alternatively, one could use a chemical analysis for determining ketyl concentration. Whitesides et al.[9] have shown that ketyl reacts with aqueous basic solutions to give a 1:1 mixture of benzophenone and benzhydrol and that ketyl reacts with oxygen to give benzophenone quantitatively. Thus, if half of a reaction mixture that contains ketyl is quenched with aqueous base and the other half is treated with oxygen, the difference observed in the percentage yields of benzophenone and benzhydrol from the two quenches is a direct measure of the percentage of ketyl in the original reaction mixture. However, this analytical method is also not problem free. When reaction mixtures that contained ketyl and excess lithium dialkylamide base were treated with oxygen and permitted to stand at room temperature, the relative amount of benzophenone increased slowly with time due to the autooxidation reaction discussed above. It was unfortunate that in this case the ketyl oxidation itself was not as fast as the dianion oxidation (vide supra); the process required a few minutes to proceed to completion and thus the autooxidation reaction (proceeding at ca. 0.1% of benzhydrol concentration per minute) complicated the results. At long reaction times when the ketyl concentration could be as high as 30% of the total initial benzophenone concentration, the autooxidation reaction (with a 15 min oxygenation time) would lead to a small error in our estimate of ketyl concentration (i.e., an apparent increase in ketyl yield of 1–2% at most), and the corrected ketyl concentration could be computed with confidence. However, at short reaction times, the autooxidation could produce an error in measured ketyl concentration as large as the actual concentration, and we could not trust the accuracy of the calculated ketyl yields.

We resolved our quantitation problems by using both ESR and chemical analyses. Since the error in ESR measurements arises in the absolute quantitation but not the relative quantitation of successive measurements in the same tube, we followed reactions by ESR spectroscopy recording spectra of the ketyl at high modulation at various times. The areas of the signals could be compared to determine the *relative* amounts of ketyl present in each measurement. Then, at high ketyl concentrations, we used the double quenching method of Whitesides and determined the absolute amount of ketyl by the differences in the benzhydrol and benzophenone ratios determined by capillary GC. (Recall that the aldol-like products **4** were shown to break down quantitatively to give benzophenone upon GC injection.) The absolute yields of ketyl determined by the chemical analysis method were then used to calculate an ESR response factor for the ketyl which permitted us to quantitate all of the ESR measurements. In three

(13) The contribution by Kowalski, Creary, et al.[14] was cited in our previous communication,[6b] but due to the required brevity of the format the intention of our reference was not clear. Their studies *supported* a β-hydride pathway for the reaction of LDA with benzophenone, and their paper established that the primary reactions of LDA with benzophenone were *facile*,[14] a point explicitly stated before we shortened our contribution.[6b] We had hoped that, even after editing, the reader would appreciate the significance of their studies upon being directed to their work, but our poor phrasing implied that our results contradicted theirs. This was definitely not the case.

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determinations of this response factor we found a variance of <10%. Thus, the absolute ESR quantitation was reproducible, and we believe it was accurate to within 25% of the stated amount of ketyl. In some experiments we followed the formation of ketyl using only the double quench method and GC analysis, but with this method we were not willing to assay the reacting system at short reaction times when the ketyl concentration was low.

Table II contains the results of our rate studies of ketyl formation using both methods of analysis. Solutions of benzophenone were added to base solutions at 22 ± 2 °C in doubly capped reaction vessels under argon. Initially, the reactions showed a faint color, but over a period of hours the characteristic blue color of lithium benzophenone ketyl increased in intensity in those reactions where an excess of base was present. Aliquots were removed at time zero and then periodically from the reaction vessels and were analzyed as discussed above. Under our conditions the primary reactions between amide base and benzophenone were complete within a minute. The initial ratio of benzhydrol to benzophenone detected by an aqueous quench and GC analysis reflected the amounts of lithium benzhydrolate and the lithium salt of aldol-like product **4** present in the reaction mixture. As the ratio of base to benzophenone was increased, the relative amount of initial reduction increased slightly. The fact that increasing the LDA to benzophenone ratio from 1:1 to 6:1 resulted in only a small increase in the percentage of β-hydride reduction relative to aldol formation clearly demonstrated that the forward reaction in step 3 of Scheme I was substantially faster than the reduction in step 1.

For each time t point in Table II we were measuring the amount of ketyl formed, and we knew the amount of base and lithium benzhydrolate from the time zero quenches. If Scheme I correctly explains the reaction sequence then the rate of ketyl formation should be twice the rate of lithium benzhydrolate deprotonation, the rate-limiting step in Scheme I. Thus, we could calculate an apparent k_2 for ketyl formation at each point according to eq 9.

$$d[\text{ketyl}]/dt = 2d[\text{dianion}]/dt = 2k_2[\text{LiNR}_2][\text{Ph}_2\text{CHOLi}] \quad (9)$$

Again in eq 9 we have assumed that the deprotonation reaction is a simple second-order process; obviously errors in our assumption of the order of the rate law for deprotonation here will cancel in a comparison with the k_2's determined from eq 8. Unlike the case with the deprotonation studies, the reverse of step 4 (protonation of the dianion) did not seem to be important here. Apparently as dianion formed it was predominantly diverted to ketyl by reaction with benzophenone rather than reprotonated to give lithium benzhydrolate.

From the data in Table II it is clear that the amount of ketyl reached a maximum and then began to decrease after ca. 30–40 h. By this time decomposition of the solvent by base was a major source of impurities in the reaction mixture. This reaction of base with solvent led to a lowering in the actual concentration of base, so it is not surprising that the apparent rate constants determined at longer reaction times were lower than those determined at short reaction times, and we do not consider the data at >40 h to be useful for kinetic discussions. On balance, we believe the rate constants were remarkably consistent over a reasonably broad range of reactant ratios given that they are one-point second-order rate constants determined with low concentrations of reagents and at low conversion. The consistency is especially apparent for those constants measured at one specific time where the errors in our kinetic assumptions in eq 9 will tend to cancel.

The important rate constants are those determined at relatively short reaction times. It can be seen that despite all of the errors and approximations in our methods, the rate constants for deprotonation of lithium benzhydrolate by LDA are essentially equal to one-half of the rate constants for ketyl formation in the reaction of benzophenone with LDA as predicted by Scheme I. Specifically, at 4 h one-half of k_2 for ketyl formation was $2\text{–}4 \times 10^{-5}$ M^{-1} s^{-1} which compares favorably with the k_2 for LDA deprotonation of lithium benzhydrolate of $(4 \pm 2) \times 10^{-5}$ M^{-1} s^{-1}.[16]

In the case of LDEA where little data was collected the same relationship apparently held. In two determinations at 4 h at 22 °C, the values for one-half of k_2 for ketyl formation were 0.8×10^{-5} and 2.0×10^{-5} M^{-1} s^{-1} (2:1 and 4:1 initial ratios of LDEA to benzophenone, respectively) which are close to the k_2 for deprotonation of 3×10^{-5} M^{-1} s^{-1}.

As a final test of Scheme I, we measured the rate of ketyl formation in an experiment designed to approximate the conditions which would be predicted to exist immediately after benzophenone and LDA were mixed if Scheme I is the correct mechanistic route. Specifically, we treated benzhydrol with a fivefold excess of LDA, and then added to this mixture 0.5 molar equiv (relative to benzhydrol) of the aldol product **4d**. *Benzophenone ketyl was produced despite the fact that no benzophenone per se was employed.* One-half of the apparent second order rate constant for ketyl formation at 22 °C (one point) measured at 15 h using eq 9 was 0.6×10^{-5} M^{-1} s^{-1} which compares favorably with the rate constants in Table II measured at about the same time.

Conclusion

From a comparison of the second-order rate constants for formation of ketyl when benzophenone was treated with excess LDA with those for deprotonation of lithium benzhydrolate with this base, it is apparent that the series of reactions in Scheme I explains the formation of ketyl and that the rate-limiting step for this process is the deprotonation of lithium benzhydrolate. This conclusion coupled with the results of our previous mechanistic probe study[6b] establishes that no free intermediates are formed in the actual reduction of benzophenone by lithium dialkylamide bases containing β-hydrogen atoms and supports Wittig's original conclusion[2] that the reduction occurs by a concerted β-hydride pathway. We now understand the details of the reactions well enough to explain most of the observations of others. Wittig et al. observed no ESR signals because they consistently used 1 equiv of base and employed short reaction times.[2] Kowalski, Creary, et al. observed partial reduction of benzophenone because a substantial portion of the benzophenone was trapped as the lithium salt of adduct **4c**; some of the diphenylethanol they obtained when excess methyllithium was added as a trapping agent may have formed after this aldolate decomposed by a retro-aldol process.[14] Finally, ketyl coupling products and ESR signals from ketyl were detected by Scott's and Ashby's groups when excess base was employed and the reactions were allowed to proceed for an extended period.[3] Questions concerning some details of these reactions certainly remain; i.e., what is the pathway for formation of high weight products in the reaction of benzophenone with lithium tetramethylpiperidide which contains no β-hydrogen atoms? and indeed what are the identities of these high weight products?[3a] Nevertheless, we believe that establishing an SET pathway in reactions of aryl ketones with amide bases now requires

(16) Various kinetic analyses for the data in Tables I and II were considered. Since one cannot predict the order of base in the deprotonation reactions and since the concentrations of base changed only slightly during the period of the measurements, we found it instructive to solve for pseudo-first-order rate constants. The rate constants are of the form in eq i. If one

$$k' = k\,[\text{LDA}]^x \quad (i)$$

assumes a first-order dependence on [LDA] in the deprotonations then, of course, one obtains values for k which are nearly identical with those derived from the true second-order expressions in eq 8 and 9. However, it is likely that dialkylamide bases are aggregated in THF, and it is possible that these aggregates must dissociate before deprotonation. In such a case the dependence on [LDA] would be only partial order, for example, $^1/_2$ order if dimeric base must dissociate in an (unfavorable) prior equilibrium to give reactive monomeric base. When we used the data in Table II and solved for k in eq i letting $x = 1$, $^1/_2$, and $^1/_4$, the percent deviation for the rate constants at a given time became progressively smaller. Specifically, for the four points collected at 4 and 7.5 h in Table II, the maximum differences in k were 50%, 30%, and 10% of the value of the largest rate constant when the order of [LDA] was 1.0, 0.5, and 0.25, respectively. Despite the limited data, this suggests to us that LDA is indeed aggregated in THF and must dissociate to an active form for the deprotonation of lithium benzhydrolate. In any event, by using an eq 8 and 9 we present our *weakest* case unless multiple order of base is involved in the deprotonation, a model for which we are aware of no supporting evidence.

Scheme II

$$(B\text{-}H)^- + Ox \longrightarrow (Ox\text{-}H)^- + B \quad (10)$$

$$(Ox\text{-}H)^- + (B\text{-}H)^- \longrightarrow (Ox)^{2-} + H\text{-}B\text{-}H \quad (11)$$

$$(Ox)^{2-} + Ox \longrightarrow 2\,(Ox)^{\cdot-} \quad (12)$$

more than the detection of ketyls or their coupling products.

We caution against generalizing our results too broadly for reactions of lithium dialkylamides. Electron-transfer processes in reactions of hindered lithium dialkylamide bases with various substrates are supported by the results of several groups. Creary observed that pivaloin triflate was reduced by lithium tetramethylpiperidide (LTMP).[17] Our group observed reductions of an oxaziridine by LDA, LDEA, and LTMP,[18] and more recently we have found that two mechanistic probes support an electron-transfer pathway for this reduction.[6a,19] Ashby's group has reported evidence for electron transfers in reactions of amide bases with an alkyl iodide probe and with polynuclear aromatics.[20] Newkome and Hager found evidence of an electron transfer process in a study of the reaction of LDA with pyridine.[21] Eleveld and Hogeveen concluded that the reaction of lithium dialkylamides with molecular oxygen proceeded via an SET pathway, although a major point in their mechanistic argument was that LDA reacted with benzophenone by an SET process.[22] Only in the cases of the reactions of polynuclear aromatics and pyridine would we suggest that a reaction scheme similar to Scheme I might lead to radical anion products. Further, the deprotonation step in Scheme I (eq 4) seems unreasonable for aliphatic alkoxides, and we would not invoke Scheme I as the pathway to the pinacol product obtained by Paquette's group.[4] Of course, Scheme I is not viable when the amide base does not contain β-hydrogen atoms.

Nevertheless, it is instructive to consider the two-electron pathway to odd-electron products in more detail, especially because the acceptable criteria for implicating an SET pathway are loosely defined. We can rewrite the sequence of reactions in Scheme I in general terms to obtain Scheme II which is a possible pathway for formation of oxidant-derived radical anions in reactions of weak organic oxidants with any agent which can serve as both a hydride donor and a base. As in the specific case of the benzophenone–amide reaction, the processes in Scheme II are conventional reactions which often could be subjected to independent kinetic studies. The mode of hydride reduction in eq 10 is not specified since the reducing agent could be a conventional hydride donor, i.e., a metal hydride, or a β-hydride donor like an alkoxide or a Grignard reagent. The nature of the oxidant in eq 10 also is not specified, since we see little reason to distinguish between oxidants like carbonyl compounds and polynuclear aromatics. Scheme II is a viable pathway when the rate of deprotonation of the initial reduction product in eq 11 is similar to that of the hydride reduction in eq 10 or when some combination of reactions traps the initial oxidant reversibly (as in eq 2 and 3 of Scheme I). Inevitably, the rate of electron transfer in eq 12 will be fast; further, the potential equilibrium in eq 12 must favor formation of radical anions in the reactions of interest or else the radical anions would not have been detected in the first place.

There are examples in the literature where radical anion formation has been explained by a sequence of reactions similar to those in Scheme II in that a substrate-derived dianion acted as a one-electron reducing agent, but the formation of dianion occurred by different routes. Specifically, nucleophilic addition of potassium *tert*-butoxide to nitrobenzene followed by deprotonation[23a] and double deprotonation of arenes by mixed base[23b] both give dianions that can transfer an electron. These pathways were not proposed as general schemes, but if the basic concept of Scheme II can account for radical anion formation across the broad spectrum of reactivity represented by the reaction of nitrobenzene with potassium *tert*-butoxide,[23a] the reaction of benzophenone with LDA (this work), and the reactions of simple arenes with *n*-butyllithium–potassium *tert*-pentoxide,[23b] then we suggest that it warrants general consideration.

It is interesting to note that the mode of radical anion formation in Scheme II, i.e., electron donation from a dianion to a neutral, was discussed in some of the earliest papers describing formation of radical anions in reactions of base–nucleophiles with organic oxidants. In his pioneering works reported as early as two decades ago, Russell outlined such a pathway as well as related alternative mode for radical anion formation wherein a nucleophile adds to a nitroaromatic and the salt thus formed transfers an electron to a neutral nitroaromatic.[24] Unfortunately, Russell's conclusions apparently have been overlooked by recent workers (including our group).

Thus, Scheme II is a possible pathway for a wide variety of reactions where oxidant-derived radical anions are detected directly, by coupling products, or by probes. It offers a hydride reduction or deprotonation as the rate-limiting step to radical anion formation as opposed to the direct electron-transfer step of an SET process. How often Scheme II will prove to be the actual reaction pathway in what are now thought to be SET processes is hard to predict. However, the relatively low value for the pK_a of lithium benzhydrolate which we have established in this work coupled with the fact that the detection of an aryl ketyl has been a primary piece of evidence supporting an SET process in a variety of reactions[25] suggests to us that the two-electron route to odd-electron products will not be limited to a few cases. We suggest that consideration of Scheme II as a route to odd-electron products will be useful in future mechanistic studies of possible SET reactions not just as an alternative mechanistic rationale but, more importantly, because the component reactions can be studied independently. If one can preclude Scheme II by kinetic studies then the case for an initial SET process will be strengthened.

Experimental Section

General. All reactions were performed in flame-dried reaction vessels under argon. Syringe transfers were performed by using standard techniques. Argon was dried by passing it through a drierite tower. Chemicals were supplied by Aldrich Chemical Co. unless noted. Tetrahydrofuran (THF) was dried by distillation from potassium–benzophenone ketyl before use. Diethylamine and diisopropylamine were distilled from calcium hydride (CaH_2). Benzophenone and benzhydrol were recrystallized from hexane. *n*-Butyllithium (in hexane) and methyllithium (in ether) were titrated before use.[26] ^1H NMR spectra were obtained on a Varian EM-390 spectrometer at 90 MHz. ^1H-decoupled ^{13}C NMR spectra were recorded at 20 MHz on a Varian FT-80 spectrometer; benzene-d_6 was used for an internal lock signal; chemical shifts were measured relative to the upfield signal of THF (defined as 25 ppm). ESR spectra were recorded on a Varian E-4 spectrometer at 2 mW power and high modulation; the double integral of the first derivative ESR spectrum was determined by a numerical integration method.[27] GC analyses were performed on a Varian 2440 instrument equipped with a capillary injector and a flame ionization detector using a 25 m BP-10 (Scientific Glass Engineering) fused silica column; signal integration was achieved

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with an HP 3390A integrator. Melting points were measured with a Thomas-Hoover capillary apparatus; temperatures are uncorrected.

N-(3-Hydroxy-3,3-diphenylpropylidene)ethylamine (**4a**) was prepared by the method of Wittig and Frommeld;[2b] mp 122-124 °C (lit.[2b] mp 124-125 °C).

N-(3-Hydroxy-1-methyl-3,3-diphenylpropylidene)cyclohexylamine (**4d**) was prepared by a modification of the method of Wittig and Suchanek[28] using THF instead of ether as the solvent; mp 90-91 °C (lit.[28] mp 91-93 °C).

Diphenyl-*1*-^{13}C-methanone was prepared in 81% yield by the method of Nicodem and Marchiori[29] using 90% labeled benzoic acid (Merck) and was purified by silica gel chromatography with 1:1 hexane-methylene chloride elution.

Deprotonations of Lithium Benzhydrolate. The following procedure is representative. Into an oven-dried, 40-mL centrifuge tube which was flushed with argon and fitted with two No-Air septa was added 0.71 g (7.0 mmol) of diisopropylamine. THF (15 mL) was added and the solution was cooled to -78 °C. To the solution was added 4.50 mL of 1.56 M *n*-butyllithium in hexane. The solution was allowed to stand for 20 min at -78 °C then was warmed to 22 ± 2 °C. Benzhydrol (0.25 g, 1.4 mmol) in 1 mL of THF was added by syringe. Aliquots of the reaction mixture were removed periodically and quenched with oxygen. This was done by capping a 10-mL scintillation vial with a septum, flushing with oxygen, and then adding the aliquot and gently mixing. Saturated ammonium chloride solution (1 mL) was added after 1 min. After separation of the phases the THF layer was analyzed by GC.

Reactions of Benzophenone. The following procedure is representative. Into an oven-dried, 40-mL centrifuge tube which had been flushed with argon and fitted with two No-Air septa was added 0.68 g (6.7 mmol) of diisopropylamine. THF (15 mL) was added and the solution was cooled to -78 °C. To the solution was added 4.3 mL of 1.56 M *n*-butyllithium in hexane. The solution was allowed to stand for 20 min at -78 °C then was warmed to 22 ± 2 °C. Benzophenone (2.2 mL of a 0.95 mmol/mL solution) was added by syringe. Within 5 min a sample was removed from the reaction mixture, added to aqueous ammonium chloride solution, and analyzed by GC. Aliquots were removed periodically and analyzed by either of two methods.

(1) Analysis by oxidation: At a given reaction time an aliquot of the reaction mixture was quenched by addition to a 50% sodium hydroxide solution. A second sample was added to a vessel containing oxygen and allowed to react for 10-15 min before addition of saturated aqueous ammonium chloride. The percentage of benzhydrol and benzophenone in each sample was measured by a GC analysis. The difference in the percentage of the benzophenone detected in the two analyses represented 50% of the ketyl present after correction for autooxidation of benzhydrol. (See text for details.)

(2) Analysis by ESR: At a given time a 1-mL sample was removed and added to a 5-mm tube. The ESR spectrum of the sample was measured at 2 mW power and high modulation. The area of the curve was measured and related to those measured for a series of ketyl concentrations which had been determined by the oxidation method. All spectra were determined with constant instrument settings with the exception of the receiver gain; this effect was accounted for in the area measurements.

Rate of the Retro-Aldol Reactions. To a 10-mm NMR tube which had been flushed with argon was added 103 mg (0.33 mmol) of **4d**. After the addition of 2.5 mL of dry THF and cooling to -78 °C, 0.22 mL of 1.5 M methyllithium in ether was added. The solution was warmed to 22 ± 2 °C, and 60 mg (0.33 mmol) of the ^{13}C-labeled benzophenone was added. Spectra were obtained every 30 min, and the ratio of the carbonyl peak (δ 194.5) to the quaternary carbon (δ 79.6) was measured. A similar experiment was performed with **4a**.

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Synthesis, Chiroptical Properties, and Electron Self-Exchange Reactivity of a Rigid Pentacyclic Metal Ion Cage System with D_3 Symmetry

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Abstract: The rigid pentacyclic metal ion cages Δ-(4,9,15,20,25,30*R*)- and Λ-(4,9,15,20,25,30*S*)-[(1,12-dinitro-3,10,14,21,24,31-hexaazapentacyclo[10.10.10.0^{4,9}.0^{15,20}.0^{25,30}]dotriacontane)cobalt(III)](3+) (Δ(*R*,*R*)$_3$ and Λ(*S*,*S*)$_3$-[Co(diNOchar)]$^{3+}$) have been synthesized by the reaction of nitromethane and formaldehyde with the corresponding [Co(chxn)$_3$]$^{3+}$ substrate (chxn = (*R*,*R* or *S*,*S*)-*trans*-1,2-cyclohexanediamine). Reduction with Zn and HCl yields the cobalt(II) complexes and also reduces the nitro substituents to amino groups. Reoxidation with H_2O_2 and O_2 then gives the Δ(*R*,*R*)$_3$- and Λ(*S*,*S*)$_3$-[Co(diAMchar)]$^{3+}$ ions quantitatively. The cage complexes are configurationally and conformationally rigid and substitutionally inert in both the cobalt(II) and cobalt(III) oxidation states, and the amino derivatives are stable in aqueous solutions of strong acid or strong base at elevated temperatures (>200 °C). Reversible reduction potentials and ^1H NMR, ^{13}C NMR, and chiroptical spectra are reported for all of the complexes prepared. The cobalt(II,III) electron self-exchange rate constant for the Δ(*R*,*R*)$_3$-[Co(diAMchar)]$^{2+}$, Λ(*S*,*S*)$_3$-[Co(diAMchar)]$^{3+}$ reaction is 1.1 M^{-1} s^{-1}, which is roughly 10^5 greater than that for [Co(en)$_3$]$^{2+/3+}$ and that inferred for the [Co(chxn)$_3$]$^{2+/2+}$ system.

We have recently developed a template approach to the encapsulation of some inert transition-metal ions, notably Co(III),[1] Pt(IV),[2] and Rh(III).[3] The procedure involves condensation of formaldehyde and either nitromethane or ammonia with the [M(en)$_3$]$^{n+}$ species at pH ~10 to yield the metal ion cage complexes (**1**, **2**).[4] The chiral cobalt center and six chiral nitrogen donors imply 16 possible diastereoisomers, only one of which is found.

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