1226-46-6; **4** (R = H;R′ = OCH_3), 1141-07-7; **4** (R = R′ = H), 1450-31-3; **5** (R = R′ = OCH_3), 10019-24-6; **5** (R = R′ = CH_3), 5831-43-6; **5** (R = R′ = NMe_2), 1261-86-5; **5** (R = H;R′ = OCH_3), 68578-78-9; **5** (R = R′ = H), 632-51-9; **6** (R = R′ = OCH_3), 726-18-1; **6** (R = R′ = CH_3), 4957-14-6; **6** (R = H;R′ = OCH_3), 834-14-0; **6** (R = R′ = H), 101-81-5; **6** (R = R′ = NMe_2), 101-61-1; **7** (R = R′ = OCH_3), 42495-96-5; **7** (R = R′ = CH_3), 64725-53-7; **7** (R = H; R′ = OCH_3), 83476-34-0; **7** (R = R′ = H), 1726-02-9; **7** (R = R′ = NMe_2), 83463-89-2; $Na(C_2H_5)_3BH$, 17979-81-6; $FeCl_2$, 7758-94-3.

Paramagnetic Solvent Nuclear Magnetic Resonance Shifts in Radical Anion Solutions. 3. Kinetic Method for Measuring Molar Paramagnetic Solvent Shifts of Unstable Radical Anions

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Received April 30, 1982

The purpose of this paper is (1) to describe a method by which the molar paramagnetic solvent shift of an unstable, e.g., with respect to disproportionation, radical anion can be measured and (2) to show that the mode of radical anion preparation may have an effect upon the magnitude of the molar paramagnetic solvent shift.

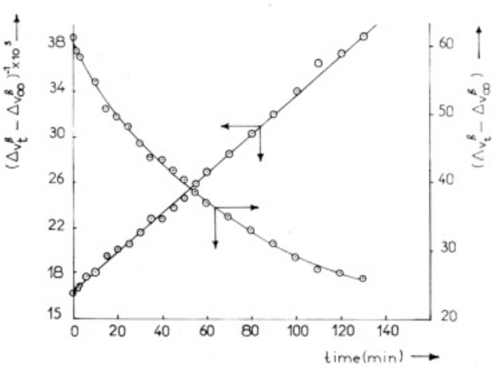

Figure 1. Decay curve of paramagnetism in an initially 0.48 M solution of lithium phenyltritylketyl in THF at 35 °C. The straight line is a plot of the same data according to the second-order rate law.

Solvent NMR shifts in radical anion solutions, in most cases, are linearly related to the formal concentration of the radical anion. This enables one to measure kinetics[1] by observing solvent shifts with respect to time in systems involving a stable radical anion either as a reactant or as a product. If the reaction in question obeys a rate law other than first order, it is necessary to know the molar shift of the radical anion; otherwise, the rate constant will be expressed in terms of units hertz/mole instead of moles/liter. In the case of stable radical anions the molar paramagnetic solvent shift can be determined readily.[2] However, there are cases in which a radical anion has a pronounced tendency toward disproportionation. This means that during the preparation of a concentrated solution of such a radical anion, which requires prolonged reaction of quivalent quantities of the alkali metal and the substrate, the radical anion disproportionates. In this category belongs the ketyl anion of phenyl trityl ketone, benzopinacolone. Attempted direct synthesis of lithium phenyltritylketyl according to eq 1 led to a reddish solution

$$Ph_3CCOPh + Li \rightarrow (Ph_3CCOPh)^{-}\cdot Li^{+} \quad (1)$$

which was feebly paramagnetic. When, however, the ketyl anion was generated by electron transfer from lithium naphthalene radical anion (eq 2), a bluish solution was

$$Li^{+}C_{10}H_8^{-}\cdot + Ph_3CCOPh \rightarrow (Ph_3CCOPh)^{-}\cdot Li^{+} + C_{10}H_8 \quad (2)$$

obtained instead, which gradually turned red within a few hours. This color change was accompanied by decay of the paramagnetism which was associated with the "blue" species, obviously the ketyl anion $(Ph_3CCOPh)^{-}\cdot Li^{+}$. In Figure 1 is given the decay curve of the solvent shift in a solution of lithium phenyltritylketyl in THF prepared according to eq 2. The electron-transfer reaction in eq 2 is instantaneous and quantitative due to the great difference[3] in the electron affinities of Ph_3CCOPh and $C_{10}H_8$, in favor of the former compound. In Figure 1 is also given a plot of the data according to the second-order rate law, which obviously is obeyed and agrees with the process (3) shown in eq 3. For further experimental evidence that

$$(Ph_3CCOPh)^{-}\cdot + (Ph_3CCOPh)^{-}\cdot \rightarrow (Ph_3CCOPh)^{2-} + Ph_3CCOPh \quad (3)$$

the decay of the paramagnetism is due to the disproportionation reaction and not due to an alternative one, see the following discussion as well as the Experimental Section. A rate constant of 0.175 L Hz^{-1} min^{-1} at 35 ± 0.5 °C was extracted from the data. In order to convert the rate constant into the appropriate units of L mol^{-1} min^{-1}, it was necessary to know the molar paramagnetic solvent shift of the lithium phenyltritylketyl. This was done by extrapolation of the kinetic line. Thus we could obtain a rather accurate estimate of the shifts at the moment of mixing the reagents and from them the molar shifts. The molar shifts referred to the two proton bands of THF were $\Delta\nu_m^{\alpha} = 178$ and $\Delta\nu_m^{\beta} = 162$ Hz/mol (at 80 MHz and after being corrected for the naphthalene ASIS). The latter molar shift was used to convert the rate constant to units of L mol^{-1} s^{-1}, which now is $k = 1.80 \times 10^{-5}$ L mol^{-1} s^{-1}. This kinetic method of measuring molar paramagnetic solvent shifts is applicable to radical anions which decay with a half-life of the order of 1 min or longer.

In the first paper of this series[2] we stated that if a radical anion tends to disproportionate, then its preparation by mixing equimolar quantities of the dianion and the neutral aromatic molecule, i.e., by inverse disproportionation, e.g., eq 4, would lead to the equilibrium mixture. On the basis

$$(Ph_3CCOPh)^{2-}K_2^{2+} + Ph_3CCOPh \nrightarrow 2(Ph_3CCOPh)^{-}\cdot K^{+} \quad (4)$$

of the above-given information, the phenyl trityl ketone dianion appeared to be an ideal system for proving or disproving the correctness of our statement. We chose to employ potassium phenyl trityl ketone dianion because of its greater chemical stability (with respect to solvent cleavage) as compared to the relevant stability of $(Ph_3CCOPh)^{2-}Li_2^{2+}$. Thus a solution prepared according to eq 4 and being 0.40 N in "active alkalinity" exhibited a shift of only 11.6 Hz at 80 MHz. This small shift remained constant throughout the period of our observations, which lasted 1 h, and it was found unchanged after

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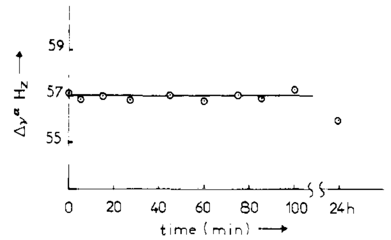
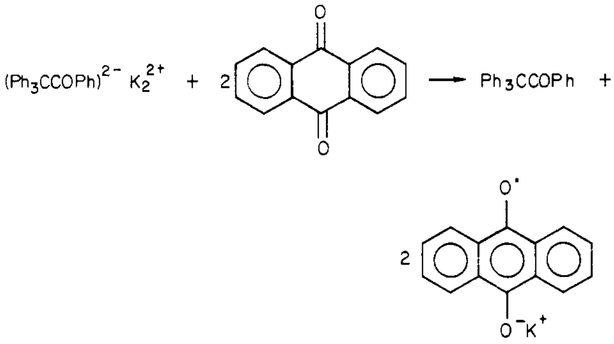


Figure 2. Shift vs. time plot in a 0.49 M solution of lithium benzophenone ketyl in THF at 35 °C generated by electron transfer from $Li^+C_{10}H_8^-\cdot$ to benzophenone.

24 h. Obviously, no "equilibrium relaxation" takes place upon mixing equivalent amounts of a dianion and the neutral substrate if the radical anion has a pronounced tendency toward disproportionation. Otherwise, we should be able to observe a substantial shift as in the case of generating the radical anion according to eq 2. In order to substantiate the above result, i.e., to ascertain that we had in solution a dianion (mainly), we added an equivalent quantity of fluorenone, which has an electron affinity greater than that of phenyl trityl ketone. The solution, which turned immediately brownish; was found strongly paramagnetic, and on the basis of the solvent shift we estimated a potassium fluorenone ketyl concentration, which agreed within 10% with the total alkality of the solution. Further[4] substantiation of our results was obtained by isolating the regenerated neutral ketone from the dianion of the phenyl trityl ketone by electron transfer to anthraquinone (eq 5).



(5)

Contrary to the behavior of lithium phenyltritylketyl lithium benzophenone ketyl, generated in a manner examplified by eq 2, showed no shift change with time (see Figure 2). In a period of 24 h the shift decreased by only 1 Hz. This information indicates that lithium benzophenone ketyl exhibits almost no tendency to disproportionate or to undergo aggreation to other diamagnetic species. By this method a $\Delta\delta_m{}^\alpha = 1.42$ ppm/mol was obtained (lit.[2] $\Delta\delta_m{}^\alpha = 1.40$ ppm/mol).

Experimental Section

Solvent ^1H NMR shifts were measured with a Varian FT-80 NMR spectrometer. Due to the great stability of the instrument, no external marker was used. Benzene-d_6 was sealed in thin-walled capillaries and used to obtain a lock. Shifts are referred to the resonance positions of THF proton bands in neat solvent. THF was purified as described previously.[5] Benzopinacolone was synthesized according to the literature[6] and the starting material, benzopinacol, by rapid acidification of lithium benzophenone ketyl with 6 N HCl.

Attempted Preparation of Potassium Phenyltritylketyl by Inverse Disproportionation. To a solution of potassium phenyl trityl ketone dianion prepared[2] from 1.74 g (5.0 mmol) of phenyl trityl ketone, 0.395 g (10 mol) of potassium metal, and 10 mL of THF were added 1.74 g (5.0 mmol) of phenyl trityl ketone and 10 mL of THF. The mixture, which remained reddish, was found, by double titration using ethylene bromide,[1b] to be 0.40 M in active alkalinity and 0.02 M in nonactive alkalinity. This solution exhibited a solvent shift of 11.6 Hz. To the remainder solution was added 1.8 g (10 mmol) of fluorenone. The resulting brownish solution now exhibited a solvent shift of 72 Hz; i.e., the concentration of potassium fluorenone ketyl was 72/240 = 0.30 M, 240 Hz/mol being the (80 MHz) molar shift of this ketyl anion.[2] The total alkalinity in the same solution was 0.33 M. Thus over 90% of the total alkalinity was mainly in the form of potassium phenyl trityl ketone dianion.

Regeneration of Neutral Phenyl Trityl Ketone from the Corresponding Dianion. To a solution of potassium phenyl trityl ketone dianion (5 mmol), prepared as described in the previous paragraph, were added 2.1 g (ca. 10 mmol) of powdered anthraquinone and 10 mL of THF. The resulting mixture was stirred under argon until it turned green (ca. 3 h). The content of the reaction flask was transferred quantitatively with the aid of 250 mL of distilled water into a wide-mouthed Erlenmeyer flask. The hydrolyzed mixture was stirred until the anthraquinone semidione was air-oxidized, i.e., until discharge of the reddish color in solution. The precipitated organic solids were isolated by filtration and air-dried. This material was stirred with 100 mL of methylene chloride, and the insoluble anthraquinone was filterred off. Anthraquinone precipitated almost completely from the fitrate by gradual reduction of the volume to ca. 20 mL and cooling with an ice–water bath. Another filtration afforded a filtrate which on evaporation to constant weight gave 1.45 g of a solid product. After this was washed with ca. 5 mL of cold ether, a material was obtained which weighed 1.2 g (mp 158–165 °C) and exhibited an IR spectrum identical with that of phenyl trityl ketone (lit.[6] mp 179–180 °C).

Quenching Dilithium Phenyl Trityl Ketone Dianion. A solution of the title dianion was prepared from 1.74 g (5.0 mmol) of phenyl trityl ketone, 0.070 g of lithium chips and 10 mL of THF at 0–5 °C. The dianion solution was stirred under argon for 1 h at room temperature (ca. 30 °C), and then its protonation was attempted with a 400% excess of *sec*-butyl alcohol. The reddish color of the solution did not discharge upon the addition of the alcohol, but it did discharge rapidly on addition of water. The product of this reaction, a white solid, was analyzed by NMR for possible fragmentation products, mainly triphenylmethane. Only traces of triphenylmethane were found.[7]

Kinetic Run. A solution of lithium naphthalene radical anion (5.00 mL of a 1.00 M solution in THF) was thermostated at 35 °C and then added to a suspension of 1.74 g (5.0 mmol) of phenyl trityl ketone in 4.0 mL of THF at 25 °C. Time started being counted from the point of mixing the reagents. An aliquot of the bluish solution was injected into an NMR tube[2] at constant temperature (35 °C), and then it was transferred into the thermostated probe at the same temperature. The fisrt kinetic point was recorded 10.00 min after mixing the reagents. The THF band due to β protons was followed with time. $\Delta\nu_\infty{}^\beta$ was equal to 12.6 Hz. The LSQ line of $(\Delta\nu_t{}^\beta - \Delta\nu_\infty{}^\beta)^{-1}$ vs. time is $(\Delta\nu_t{}^\beta - \Delta\nu_\infty{}^\beta)^{-1} \times 10^3 = 16.444 + 0.1746t$ ($r = 0.999$). Extrapolating to $t = -10.00$ min, one obtains the shift at the moment of mixing. This value was $\Delta\nu_0{}^\beta = 81$ Hz, and dividing this shift by the concentration of the paramagnetic species, which was 0.48 M, we obtained the

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(4) A referee noticed that our raw kinetic data can be plotted acceptably according to the first order rate law. Indeed, a plot ln $(\Delta\nu_t{}^\beta - \Delta\nu_\infty{}^\beta)$ vs. time exhibits a very shallow upward concavity, and the LSQ analysis indicates an $r = 0.997$, vs. $r = 0.999$ for a second-order plot. Therefore, our data could not preclude the possibility of actually observing the unimolecular decomposition of the lithium phenyltritylketyl anion, perhaps as follows: $(Ph_3CCOPh)^-\cdot Li^+ \rightarrow Ph_3CLi + (PhC{=}O)$. [The observed paramagnetism upon the addition of fluorenone could be due to the reaction Ph_3CLi + fluorenone $\rightarrow$ $(\text{fluorenone})^-\cdot Li^+ + (Ph_3C\cdot)$.] However, we were aware of the fact that $(Ph_3CCOPh)^-\cdot$ does not decompose from a private communication from J. J. Eisch to C.G.S. (1976). Our own experimental evidence agrees with Eisch's findings.

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(6) Bachmann, W. E. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, p 73.

(7) These traces of triphenylmethane could result from the possible base-catalyzed fragmentation of the carbinol $Ph_3CCH(OH)Ph$. This type of C–C cleavage is most pronounced in the case of pentaarylethanols; see, e.g.: Fuson, R. C.; Tomboulian, P. *J. Am. Chem. Soc.* 1957, *79*, 956.

molar shift $\Delta\nu_m{}^{\beta} = 169$ Hz/mol, which after correction for the naphthalene ASIS was 162 Hz/mol (2.03 ppm/mol). Similarly, the ASIS-free $\Delta\nu_m{}^{\alpha}$ was found to be equal to 178 Hz/mol (2.23 ppm/mol).

Registry No. $Li^+C_{10}H_8{}^{-\cdot}$, 7308-67-0; Ph_3CCOPh, 466-37-5; $Li^+(Ph_3CCOPh)^{-\cdot}$, 83802-04-4; $(Ph_3CCOPh)^{2-}2K^+$, 83802-05-5; THF, 109-99-9; fluorenone, 486-25-9; anthraquinone, 84-65-1.

Direct Geminal Dialkylation of Ketones Using Organotitanium Reagents. A Simple Entry into Synthetic Tetrahydrocannabinoids

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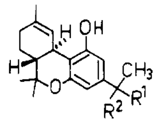
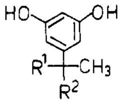
Received June 8, 1982

Replacing the *n*-pentyl side chain of natural or synthetic tetrahydrocannabinoids[1] by more lipophilic *tert*-alkyl groups has a profound influence on the pharmacological properties.[1-4] Many syntheses of natural or synthetic Δ^1-tetrahydrocannabinoids (e.g., 1) as well as their $\Delta^{1(6)}$ isomers make use of acid-mediated condensation of 5-substituted resorcinols (e.g., 2) with such terpenes as *p*-mentha-2,8-dien-1-ol (4).[1,2] Since the meta substitution pattern in 2 prohibits simple Friedel–Crafts *tert*-alkylation, several multistep procedures have been developed, most of them leading to dimethyl derivatives 3 which are then converted into 2.[1,2,4] We describe a new and variable way to synthesize compounds 3 using the titanium reagents[5] 5 and 6.



1



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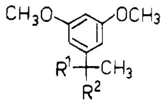

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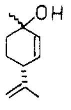

4

CH_3TiCl_3

5

$(CH_3)_2TiCl_2$

6

Our strategy is based upon the formal replacement of the carbonyl oxygen atom in ketones 7 by two alkyl groups. Such geminal dialkylation has been accomplished in other systems by a simple three-step sequence:[6] (1) Grignard addition, (2) formation of the tertiary alkyl chloride, and (3) methylation by using 5 or 6. Unfortunately, in the present case the corresponding cumyl chlorides are rather sensitive. We have therefore developed a one-pot procedure. Addition of the alkyllithium to 7 in hexane followed *by the reaction of the lithium alcoholates 8 with a 1:1 mixture of 5 and 6 in methylene chloride (method A) results in smooth formation of 3* (Table I). In spite of the fact that this unusual C–C bond-forming reaction probably involves intermediate carbocations, position specificity pertains. Undesired Wagner–Meerwein rearrangements or retro-Friedel–Crafts reactions are not observed. If the amount of methylating reagent is reduced, the yields of 3 are lower. In order to introduce two new methyl groups, direct geminal dimethylation[7] of 7 by employing 6 is the method of choice (method B, Table I).

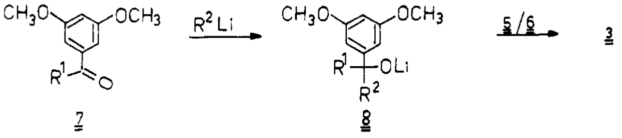

Table I. Direct Geminal Dialkylation of Ketones 7

R^1	R^2	method	isolated 3 (% yield)
CH_3	C_2H_5	A[a]	3a (77)
CH_3	n-C_4H_9	A	3b (80)
CH_3	n-C_6H_{13}	A	3c (73)
n-C_4H_9	n-C_4H_9	A	3d (68)
n-C_4H_9	CH_3	B[b]	3b (91)
n-C_6H_{13}	CH_3	B	3c (73)

[a] Alkyllithium was reacted with the ketone (−40 °C, 1 h), and a mixture 1.5 parts of $(CH_3)_2Zn$ and 2.0 parts of $TiCl_4$ in CH_2Cl_2 (this generates a 1:1 mixture of 5 and 6) was added at −40 °C. The reaction mixture was allowed to come to −10 °C (2 h) and then poured onto ice–water. Extraction and Kugelrohr distillation afforded 3. [b] The ketone was reacted with 6 in CH_2Cl_2 at −40 to −10 °C (2 h) according to the literature procedure.[7]

Demethylation of 3 to form 2 can be accomplished by using acids or trimethylsilyl iodide.[2,4] Condensation of resorcinols of the type 2 has been carried out with *p*-toluenesulfonic acid to form the $\Delta^{1(6)}$ isomer of 1, which can be easily isomerized to 1.[2]

Thus, the present methodology for the construction of quarternary carbon atoms represents a variable entry into synthetic tetrahydrocannabinoids of the type 1.

Experimental Section

Materials. Ketones 7 were prepared according to literature procedures (7, R^1 = methyl;[8] 7, R^1 = *n*-butyl or *n*-hexyl[9]).

Preparation of a Mixture of CH_3TiCl_3 (5) and $(CH_3)_2TiCl_2$ (6). Stock solutions of a 1:1 mixture of 5 and 6 were prepared by adding 150 mm of $(CH_3)_2Zn$[10] to 200 mmol of $TiCl_4$ in 300 mL dry CH_2Cl_2 under an atmosphere of nitrogen at −30 °C.

Geminal Dialkylation of Ketones 7 (Method A). To 10 mmol of ketones 7 in 10 mL of dry hexane was added 10.5 mmol of alkyllithium in hexane at −40 °C under nitrogen. After 1 h the precipitated lithium alcoholate 8 was taken up in 40 mL of dry CH_2Cl_2. At −40 °C, 36 mL of the above stock solutions, of 5 and 6 were added, and the mixture was stirred for 2 h while the temperature was allowed to come to −10 °C. [Instead of using stock solutions of 5 and 6, one can add the corresponding amounts of $(CH_3)_2Zn$ and $TiCl_4$ simultaneously to 8; this has no effect on the yields.] The mixture was poured onto ice–water, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2.

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