Nucleophilic Addition of *o*-Tolyllithium Compounds to Di-*tert*-butyl Ketone. Thermal and Organolithium-Catalyzed Isomerization of *o*-Tolyldi-*tert*-butylcarbinol Rotamers

John S. Lomas, Pham Kim Luong, and Jacques-Emile Dubois*

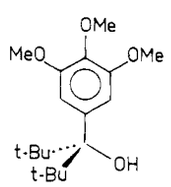
Laboratoire de Chimie Organique Physique de l'Université Paris VII, associé au C.N.R.S., 1, rue Guy de la Brosse, 75005 Paris, France

Received February 25, 1977

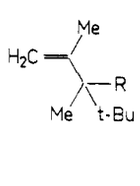
Addition of ring-substituted *o*-tolyllithium compounds to di-*tert*-butyl ketone gives rise to rotamers, syn- (sp) and anti-periplanar (ap) *o*-tolyldi-*tert*-butylcarbinols, the latter representing about 85–93% of the total, depending on the substituent. The ap isomer can be thermally isomerized to the sp form which, according to empirical force field calculations, is 6 kcal/mol more stable than the other. The IR and NMR spectra reveal marked similarities between the ap isomer and phenyldi-*tert*-butylcarbinol whereas the behavior of the hydroxyl group in the sp isomer is modified by the proximity of the *o*-methyl group. The enthalpy of activation for ap to sp rotation in dodecane varies from 25.1 to 26.6 kcal/mol whereas the activation entropy is −9 eu regardless of the substituent. The rotation rate of the parent compound is enhanced by a factor of about 10^5 by *n*-butyllithium in hexane, probably due to an increase in ground state strain in the lithium alkoxide ion pair. The mechanism of aryllithium addition to ketones is discussed: the formation of the ap alcohol is consistent with a four-center transition state with the aryl ring in the same plane as the carbonyl group and bisecting the *t*-Bu–C–*t*-Bu angle.

Restricted rotation about a single bond, other than a phenyl–phenyl bond, has been investigated primarily by the dynamic NMR method wherein barriers to rotation are measured by observing the temperature dependence of signals of protons which are exchanging environments. In this way barrier heights have been measured for rotation about a wide variety of bonds, including sp^3–sp^3 and sp^3–sp^2 carbon to carbon bonds.[1]

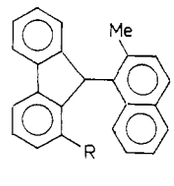
Recently, attention has been focused to some extent upon the isolation of rotamers, alternatively referred to as atropisomers or conformers. For this to be possible, two conditions at least must be satisfied. Firstly, the rotation energy barrier must be sufficiently high, about 15 kcal/mol or more, so that separation can be effected under normal experimental operating conditions, without significant isomerization. Further, the system must possess an asymmetric element which allows the differentiation of eventual rotational isomers. Thus, although the barrier to rotation about the phenyl to sp^3 carbon bond in 3,4,5-trimethoxypenyldi-*tert*-butylcarbinol (**1**) is high enough (about 20 kcal/mol),[1c,2] the rotamers are obviously identical, and rotation can only be discerned by NMR. The presence of two *tert*-butyl groups on an sp^3 carbon raises considerably the rotational energy barrier, as also occurs in the olefin **2** where $\Delta G^{\ddagger}$ goes from 9.1 to 11.2 to 15.4 kcal/mol for R = ethyl, isopropyl, and *tert*-butyl, respectively.[1e,3]



1



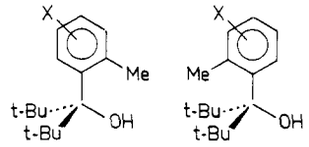
2



3 R = H
4 R = Me

Successful separation of rotamers has been achieved in the 9-arylfluorene series where not only are the barriers high, up to about 33 kcal/mol, but the introduction of an asymmetric element is straightforward.[4–7] Rotamers of 9-(2-methyl-1-naphthyl)fluorene (**3**) were partially separated by crystallization[7] and more recently **4** has been isolated in two crystalline forms.[5,8,9] It has been suggested[7] that the fact that two of the aryl groups bonded to the sp^3 carbon in question are bridged contributes to the enhancement of the energy barrier in such compounds and thus favors distinction between the two conformers. Mislow et al. have demonstrated,[10] however, that in suitably substituted triarylmethanes it is possible to isolate diastereomers with an interconversion barrier of some 30 kcal/mol, this interconversion occurring via a "one-ring flip" mechanism, which actually involves three simultaneous rotations about the phenyl to sp^3 carbon bonds.

Among systems containing three independent (i.e., not bridged) substitutents to an sp^3 carbon and where conformational isomerism involves, in principle, rotation about one bond only, the aryldi-*tert*-butylcarbinols offer the best prospects for the isolation of rotamers. We have shown[11] that the introduction of an *o*-methyl substituent into a system akin to alcohol **1** not only provides an asymmetric tag, but also increases the rotational energy barrier to about 29 kcal/mol ($\Delta G^{\ddagger}$), thus making the separation of rotamers **5** and **6** a relatively simple affair.



5 **6**

a : X = 4-OMe
b : 4-Me
c : 5-Me
d : H
e : 5-Cl
f : 3,4,5-Me_3

This system presents several features which make it interesting for further study. The NMR and IR spectra are sensitive to the environment of the OH group, the rotation rate of the less stable alcohol is easily measured by GLC, and the isomers are very different in their stability. The condensation of *o*-tolyllithium with di-*tert*-butyl ketone gives primarily the less stable isomer; in attempting to check our original interpretation of this phenomenon we were led to examine the stability of the alkoxides generated by treatment of the alcohols by *n*-BuLi and, incidentally, to observe a novel organolithium-catalyzed rotation process.

Finally, we propose a simple model for the transition state of nucleophilic addition of an aryllithium compound to a carbonyl group.

Results and Discussion

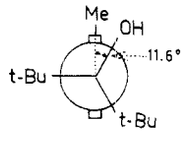
Aryldi-*tert*-butylcarbinols are most conveniently synthesized by the condensation of an aryllithium with di-*tert*-butyl ketone in diethyl ether at ambient temperature.[12] Normal work-up procedure (slow distillation at reduced pressure or preparative GLC on SE30 or Apiezon L at about 200 °C) led to the isolation of a stable alcohol **5** with appropriate IR and NMR spectral characteristics. When a crude reaction product

Table I. Spectroscopic Data for *o*-Tolyldi-*tert*-butylcarbinols, 5 and 6

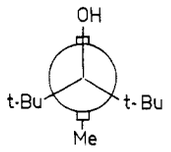
Compd	X	IR (CCl_4), cm^{-1}	NMR (CCl_4); ppm rel to internal Me_4Si						
			t-Bu (s, 18 H)	OH[a] (s, 1 H)	2-Me (s, 3 H)	Aromatic protons 3,4,5-H	6-H	$\Delta\nu$	X
5a	4-OMe	3643	1.09	1.73 (3.78)	2.56	6.52	7.34		3.72 (s, 3 H)
6a	4-OMe	3650, 3612	1.12	1.70 (4.29)	2.58	6.59	7.89	0.55	3.73 (s, 3 H)
5b	4-Me	3644	1.07	1.73 (3.82	2.56	6.89	7.28		2.30 (s, 3 H)
6b	4-Me	3650, 3613	1.11	1.69 (4.31)	2.57	6.86	7.84	0.56	2.25 (s, 3 H)
5c	5-Me	3643	1.13	1.77 (3.85)	2.57	6.89	7.28		2.30 (s, 3 H)
6c	5-Me	3649, 3613	1.12	1.72 (4.25)	2.57	6.86	7.80	0.52	2.30 (s, 3 H)
5d	H	3644	1.10	1.78 (3.84)	2.61	7.01	7.44		
6d	H	3650, 3613	1.13	1.75 (4.35)	2.62	7.01	8.01	0.57	
5e	5-Cl	3644	1.12	1.80 (4.13)	2.56	6.95	7.44		
6e	5-Cl	3649, 3611	1.12	1.85 (4.63)	2.57	6.98	8.00	0.54	
5f	3,4,5-Me_3	3641	1.11	1.78	2.51		7.11		2.16, 2.22 (6 H, 3 H)
6f	3,4,5-Me_3	3651, 3611	1.13	1.68	2.39		7.61	0.50	2.19, 2.27 (6 H, 3 H)

[a] Figures in parentheses are for Me_2SO solutions.

containing the 4-methoxy derivative **5a** was exposed for several weeks at summer room temperature (25 ± 5 °C), the alcohol **5a** was obtained in the form of well-defined triclinic crystals containing two molecules per unit cell. The complete crystallographic study, carried out by Hough,[13] gives full details of the molecular geometry, whose most important features are the angle between the plane of the aryl group and the C–O bond (11.6°) and the proximity of the *o*-methyl carbon to the carbinol oxygen atom (2.66 Å). This establishes unambigously that **5a** has the syn-periplanar (sp) conformation,[14] shown in **5A.** From the IR and NMR spectral similarities (Table I) it can be deduced that the other alcohols are of the same structural type as the 4-methoxy derivative.



5A

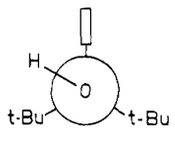


6B

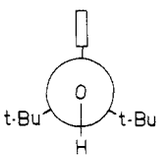
Whereas gas chromatography at the elevated temperatures required for such involatile compounds on regular 5-ft columns reveals only one product in the crude reaction mixture, it is possible by operating with very short, lightly loaded columns to reduce the oven temperature and the retention times to such an extent that the presence of a second product, **6,** of higher retention time than the stable isomer **5** becomes apparent. Moreover, this thermally unstable isomer proves to be the major component of the reaction mixture prior to distillation. This product can by isolated by adsorption chromatography on an alumina column packed in pentane or light petroleum; the stable isomer is eluted before the unstable one. Although it has not yet been possible to carry out a crystal study on this isomer, it is clear from spectral data and force-field calculations that it must have the anti-periplanar (ap) conformation,[14] **6B.**

Spectral Behavior. The NMR and IR spectra of the two conformers (Table I) are consistent with the structures assigned to the stable and unstable isomers, sp and ap, respectively. Thus, in Me_2SO the NMR absorption of the hydroxyl proton of alcohol **5** is at δ 3.78–3.85, whereas that of alcohol **6** is at δ 4.25–4.35, except for X = 5-Cl, where both values are substantially higher. A value of δ 4.16 has been reported for phenyldi-*tert*-butylcarbinol.[15b] Now, it is known that the downfield shift of the absorption of the hydroxyl proton in Me_2SO is related to the accessibility of the hydroxyl group;[15] the observed downfield shifts indicate then that the hydroxyl group is less accessible in **5** than in **6.**

The IR absorption of the OH stretch in isomer **5** is a narrow band (10^{-2}M solution in CCl_4) at 3643 cm^{-1} characteristic of free OH, whereas in the other isomer **6** there are peaks at 3612 and 3650 cm^{-1}. In this respect also, isomer **6** is rather similar to phenyldi-*tert*-butylcarbinol, which has bands at 3617 and 3644 cm^{-1}; the first of these was attributed to π-complexed OH,[16] but this implies a spatial relationship between the OH group and the aryl ring which was subsequently rejected.[15b] It is reasonable to attribute the two bands to conformations such as **6C** and **6D.**[15b] The absence of the low-frequency band in **5** corresponds then to the exclusion of conformation **C** due to the proximity of the *o*-methyl and the hydroxyl hydrogen atom which would arise therein.



6C



6D

Another feature of importance is the NMR shift of the ortho proton, which is about 0.55 ppm further downfield in isomer **6** than in the stable isomer **5.** A rather smaller difference, 0.22 ppm in the same direction, was found[2] between the two nonequivalent ortho protons in carbinol **1.** The nonequivalence of the ortho protons has been attributed to two competing effects:[1c] (i) the downfield shifts caused by the hydroxyl group, the syn ortho hydrogen being shifted about 0.6 ppm further than the anti; (ii) the downfield shift caused by overcrowding; the shift for the ortho hydrogen between the two *tert*-butyl groups is greater by 0.4 ppm. It seems likely that the very high downfield shift of the syn ortho hydrogen in alcohol **6** is due to an enhanced downfield contribution by the hydroxyl group, which will be much closer to this proton than it is in the phenyl, as opposed to *o*-tolyl, derivatives.

In conclusion, the spectral data are consistent with considerable steric hindrance by the *o*-methyl group of the hydroxyl group in the isomer **5** (sp), whereas isomer **6** (ap) resembles phenyldi-*tert*-butylcarbinol in that there is an accessible hydroxy function.

Estimation of the Ground-State Energies by Empirical Force-Field Calculations. Whereas most studies of restricted rotation about single bonds are concerned with conformers of similar energy, in the present case the thermal equilibrium between the ap and sp alcohols lies so heavily in

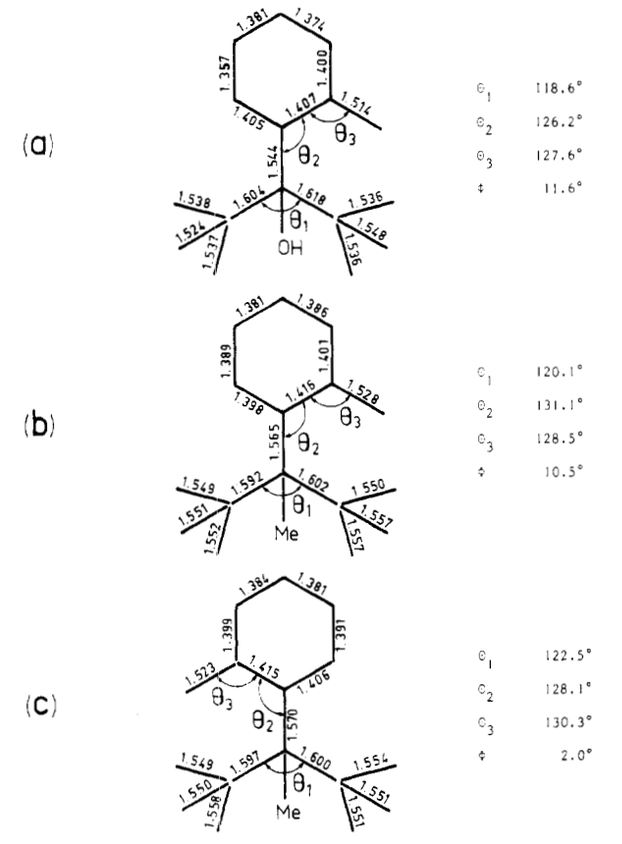
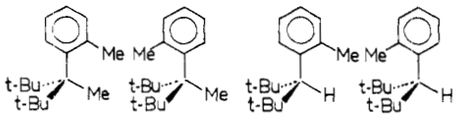


Figure 1. Molecular geometry of *o*-tolyldi-*tert*-butylcarbinols: (a) sp isomer from crystal data on **5a**; (b) force-field calculation on **5d** with OH replaced by Me; (c) force-field calculation on **6d** with OH replaced by Me. Φ is the angle between the benzene ring and the C–OH or C–Me bond. The layout of these structures is purely schematic and is designed to display the critical bond distances and angles.[26]

favor of the sp isomer that the ap isomer is not detectable by GLC (<0.1%); the energy difference between the conformers must then be at least 4–5 kcal/mol. A more precise estimate was obtained by empirical force field (molecular mechanics) calculations. This approach has been applied mainly to the calculation of the strain energies of saturated hydrocarbons, but has been extended to systems containing functional groups by Allinger, Boyd, Mislow, Schleyer, and others.[17]

Alcohols pose certain problems related to the nonspherical electron density distribution about the nucleus[18a] and have only recently been handled explicitly by the force-field approach.[18b] However, in cases where we are interested only in steric energy differences rather than in absolute values of the heat of formation, an OH group,[19] or even a tosylate[20] or a *p*-nitrobenzoate[21] group, can be treated as a hydrogen atom or a methyl group. A modified Boyd–Allinger force field for the treatment of benzenoid hydrocarbons is included in the Andose–Mislow program STRAIN which we used.[22]

Since we are concerned with conformation isomers in which the numbers of different bond and atom types are constant, the problem of determining the best values for group increments,[23] zero-point energy corrections,[24] etc., does not arise.



	5-Me	6-Me	5-H	6-H
Steric energy (kcal/mol)	40.1	46.7	14.1	20.0

Table II. Rate Constants (±1–3%) for the Rotation of (ap)-*o*-Tolyldi-*tert*-butylcarbinols 6 in Dodecane (10^4k, s^{-1})

Compd	95 °C	112 °C	130 °C	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
6a	0.847	4.24	18.3	25.1 ± 0.5	−9.3 ± 1.2
6b	0.779	3.78	16.9	25.2 ± 0.5	−9.3 ± 1.3
6c	0.603	3.04	13.6	25.5 ± 0.4	−9.0 ± 0.9
6d[a]	0.564	2.75	12.6	25.9 ± 0.4	−8.2 ± 0.9
6e	0.483	2.29	11.2	25.7 ± 0.4	−8.9 ± 1.0
6f	0.131	0.645	3.40	26.6 ± 0.6	−9.0 ± 1.5

[a] 0.126×10^{-4} s^{-1} at 80 °C (ref 11).

Errors could arise, however, from the tendency of Allinger's hydrogens to be too large and the carbons too small,[24] though, once again, such errors could be expected to cancel out.

The results show that the sp form **5** is approximately 6 kcal/mol more stable than the ap form **6**, whether the OH group is approximated by methyl (46.7 − 40.1 = 6.6 kcal/mol) or by hydrogen (20.0 − 14.1 = 5.9 kcal/mol).[25] Though there is no reason to expect the geometry of the hydrocarbons to reproduce that of the alcohols, it is nevertheless noteworthy that when OH is approximated by a methyl group the calculated geometry[26] of the sp form, **5**-Me, agrees reasonably well with the crystal data (Figure 1). There are, however, serious discrepancies when a hydrogen atom is used (not shown). The calculated geometry of the ap form, **6**-Me, is given for comparison. Outstanding features of both isomers are the very long carbon to *tert*-butyl bonds,[27,28] the very high angle, θ_1, subtended by the *tert*-butyl groups to the central carbon atom,[27,28] and the deformation of the two carbon to benzene bond angles,[29] θ_2 and θ_3. The dihedral angle, Φ, between the aryl ring and the C–O bond is closely similar to that found in 1-(4-methoxyphenyl)-2,2,6,6-tetramethylcyclohexanol[27] (12.9°); the molecular mechanics calculations offer no support for an angle of 45° we previously advanced on the basis of kinetic and model studies.[30] Complete rotation of the aryl group about the phenyl to sp^3 carbon axis in 10° steps revealed no minima other than those corresponding to the ap and sp conformations. The syn-planar conformation of **5**-Me (Φ = 0°) is, however, only 0.2 kcal/mol less stable than the sp conformation (Φ = 10.5°), indicating that interchange between the two sp forms must be very fast.

Substituent Effects Upon Thermal Isomerization Rates in Dodecane. It was anticipated that meta and para substituent effects on the rotation rate would be negligible, since the reaction involves no charged species. In fact, the substituent effects are small, but not insignificant, since the 4-OMe derivative is some 1.5 times more reactive than the parent alcohol and the 5-Cl derivative is 20% slower (Table II). The differences in reactivity are so small that linear free energy relationships are hardly meaningful; there is little to choose between σ ($\rho = -0.41$, $r = 0.940$) and σ^+ ($\rho = -0.24$, $r = 0.970$). The activation parameters are very similar from **6a** to **6e**, but $\Delta H^{\ddagger}$ tends to decrease with increasing electron donation, whereas no trend in the entropy term (−9 eu) is detectable.

The temperature dependence of the NMR spectrum of 9-chloro-9-mesitylfluorene was once attributed to ionization of the C–Cl bond, followed by recombination within a tight ion pair,[6] but this has been shown to be incorrect.[5] Clearly our data are consistent with no process in which ionic species are formed, but would be considered to support a radical mechanism if there were other evidence in its favor. We have found that *o*-tolyldi-*tert*-butylcarbinols *decompose* in a radical reaction to aryl *tert*-butyl ketones,[31] but at much higher temperatures ($k_1 = 0.4 \times 10^{-4}$ s^{-1} at 237 °C for the parent compound).[32] There is then no plausible mechanism for isomerization except rotation about the phenyl to sp^3 carbon

Table III. Equilibrium Constants (sp isomer, 5d) and Apparent Rate Constants (ap isomer, 6d) for the Equilibration of o-Tolyldi-tert-butylcarbinol by n-Butyllithium in n-Hexane at 25 °C

[n-BuLi], M	$K = [sp]_{eq}/[ap]_{eq}$	$10^3(k_A + k_S)$, s^{-1}	$10^3 k_A$, s^{-1}	$10^3 k_S$, s^{-1}
0.08	10.1			
0.16	6.88	2.78	2.43	0.35
0.48	3.44	3.86	2.99	0.87
0.80	2.27	5.62	3.90	1.72
1.12	1.78	7.65	4.90	2.75
1.60	1.57	9.65	5.90	3.75

axis accompanied, perhaps, by concerted movement of the tert-butyl groups.

Not unexpectedly, the prehnityl derivative **6f** is slower, by a factor of 6, than would be predicted on the basis of additivity of substituent effects, the difference appearing to reside entirely in the enthalpy term. The presence of four methyl groups on adjacent carbon atoms will tend to make the 2-methyl group more rigid. Opening of the C_1–C_2–Me angle will be more difficult and the barrier to rotation consequently higher. This point is illustrated by force-field calculations on aryldi-tert-butylethanes. In the prehnityl derivative the calculated C_1–C_2–Me angle is 124.8 (sp) and 125.0° (ap), whereas the corresponding values for **5**-Me and **6**-Me are 128.5 and 130.3°, respectively.

Alkoxide Rotation Catalyzed by n-Butyllithium in n-Hexane. In experiments designed to compare the stabilities of the alkoxides corresponding to **5d** and **6d** (see below), we observed that the rotation of the alkoxides proceeds much more rapidly than that of the alcohols. The alkoxide ion is generated by reaction of the alcohol with an organolithium compound. We would therefore expect the rotation rate of the ap and sp alcohols in n-butyllithium to be that of the corresponding alkoxide ions, AO^- and SO^-:

$$AO^- \underset{k_S}{\overset{k_A}{\rightleftharpoons}} SO^-$$

The rate of equilibration of the ap alcohol **6d**, $k_A + k_S$ proves, however, to be n-BuLi concentration dependent, as is the value of the apparent equilibrium constant, $K = k_A/k_S$ (Table III and Figure 2). These observations suggest that the alkyllithium is directly involved in the rotation process and that its role is not limited to mere proton abstraction. The rate constant for the ap → sp reaction in n-hexane, extrapolated to zero n-BuLi concentration, is approximately 2×10^{-3} s^{-1} at 25 °C. This is to be compared with the value of 1.08×10^{-8} s^{-1} calculated for the rotation of the ap alcohol **6d** in dodecane at 25 °C from data at higher temperatures. Tentatively, this rate increase, by a factor of approximately $10^{5.3}$, can be attributed to ground-state steric effects, as in the case of 9-X-9-mesitylfluorenes and related systems.[4,6,33] In these molecules steric interaction between X and the aryl group enhances the energy of the ground state when X increases in size from H to OH to Cl, but this interaction is absent in the transition state for rotation. Similarly, the effective size of the $-O^-Li^+$ ion pair will be greater than that of the hydroxyl group; the ground-state energies of the alkoxides must therefore be higher than those of the alcohols. In the rotation transition state the predominant steric interactions between o-methyl and tert-butyl groups are not modified by the change from –OH to $-O^-Li^+$; consequently the barrier to rotation will be lowered.

Rotation is known to be provoked by organolithium compounds in certain cases: optically active 3,3′-bithinpenyls are rapidly racemized by ethyllithium via an internally bridged dimetalated compound;[34] slow metalation of ap-9-(2-methoxy-1-naphthyl)fluorene leads to the more stable sp-9-(2-methoxy-1-naphthyl)fluorenide.[35] These reactions involve, however, C-metalation and are therefore not directly related to the present case. In the organolithium-catalyzed rotation of o-tolyldi-tert-butylcarbinols the role of the n-BuLi is twofold: firstly, it serves to generate the lithium alkoxide ion pair; secondly, excess n-BuLi enhances the rotation rate, probably by increasing the effective size of the reacting species by aggregation.

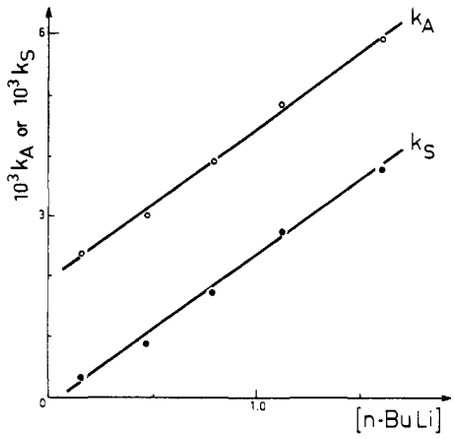


Figure 2. Rate constants for the equilibration of o-tolyldi-tert-butylcarbinols by n-butyllithium in n-hexane at 25 °C ($10^3 k$, s^{-1}).

The Transition State for the Addition of Aryllithium Compounds to Ketones. There is a small increase in the amount of the sp isomer **5** as we proceed from an electron-withdrawing substituent 5-Cl (7%) to an electron-donating substituent, 4-Me or 4-OMe (15%), but the addition process always favors formation of the less stable isomer (Table IV). We previously attributed this phenomenon to destabilization (of a product-like transition state) by steric interaction between the o-methyl and the incipient lithium alkoxide ion pair and its accompanying solvation shell.[11]

If the transition state is product-like we might expect the rotation of the ap alkoxide ion, prepared from the alcohol by treatment with an alkyllithium, to lead ultimately to a mixture with an ap/sp ratio similar to that of the addition reaction. Attempts to check this hypothesis in diethyl ether did not give satisfactory results, but treatment of either alcohol **5d or 6d** with n-butyllithium in n-hexane led to an equilibrium mixture, the apparent equilibrium constant for the reaction decreasing to 1.57 (38% of **6d** at equilibrium) for the highest concentration of n-BuLi used, 1.6 M (Table III). This is already much less than is found in the addition reaction, and extrapolation from data at higher concentrations indicates that, for equimolar n-BuLi and alcohol, the sp alkoxide is by far the most stable.[36] The alkoxide ions are therefore not valid models of the transition state for the addition of o-tolyllithium to di-tert-butyl ketone. We now propose a more satisfactory, though necessarily incomplete, interpretation.

Recent reviews on organolithium compounds[37] and on the addition of organometallic compounds to cyclic ketones[38] reveal two areas of uncertainty regarding the addition of an aryllithium to a ketone: (i) the identity of the kinetically active Li species and (ii) the geometry of the transition state.

(i) Fractional kinetic orders ($[RLi]^{1/n}$ where n is an integer) in organolithium reactions with various substrates have been interpreted in terms of polymer–monomer equilibria where the monomer is the kinetically active species,[39] but there is a growing awareness of the importance of the molecular aggregates[40] containing not only the organolithium, but also solvent molecules,[41] alkoxides,[42] and halides.[43] The ^7Li spectra of mixtures of phenyllithium and p-tolyllithium[44] indicate

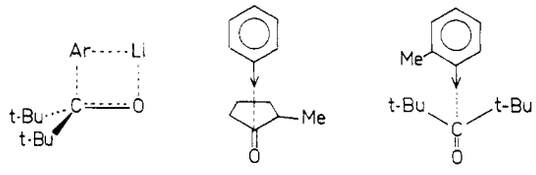
Table IV. Synthesis of *o*-Tolyldi-*tert*-butylcarbinols, 5-sp and 6-ap: Isomer Ratios and Yields

X	6/(6 + 5)[a]	% 5 (bp/mm; mp)	Registry no.	% 6[b] (mp)	Registry no.
4-OMe[f]	0.85 (0.96)	27[b,d] (–; 96)	63121-51-7	28–36 (62–63)	63121-53-9
4-Me[g]	0.85 (0.97)	60[c] (112/1.2; 58–59)	63076-53-9	50 (40–41)	63121-54-0
5-Me[g]	0.91 (0.98)	64[c] (106/0.8; 56–57)	63076-54-0	51 (40–42)	63121-55-1
H[h]	0.89 (0.98)	69[c] (116/2.0; 35)	63121-52-8	56–66 (–)	63162-57-2
5-Cl[i]	0.93 (0.99)	46[b,d] (–; 41)	63076-55-1	24 (47–48.5)	63121-56-2
3,4,5-Me_3[j]	0.84 (0.93)	44[b,e] (–; 129)	63076-56-2	52 (65–67)	63121-57-3

[a] Values in parentheses obtained when 1 mol/mol of TMEDA was added to the aryllithium. [b] By chromatography on Al_2O_3. [c] Distilled. [d] After 3 h at 112 °C. [e] After 10 h at 112 °C. [f] Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found for **5a:** C, 77.01; H, 10.63. **6a:** C, 77.35; H, 10.74. [g] Calcd for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found for **5b:** C, 81.74; H, 11.30. **6b:** C, 82.29; H, 11.04. **5c:** C, 82.18; H, 10.97. **6c:** C, 82.04; H, 11.15. [h] Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.08. Found for **5d:** C, 81.78; H, 10.96. **6d:** C, 81.79; H, 10.92. [i] Calcd for $C_{16}H_{25}OCl$: C, 71.49; H, 9.38; Cl, 13.19. Found for **5e:** C 71.92; H, 9.56; Cl, 13.37. **6e:** C, 71.12; H, 9.21; Cl, 13.29. [j] Calcd for $C_{19}H_{32}O$: C, 83.15; H, 11.02. Found for **5f:** C, 83.58; H, 11.38. **6j:** C, 83.51; H, 11.15.

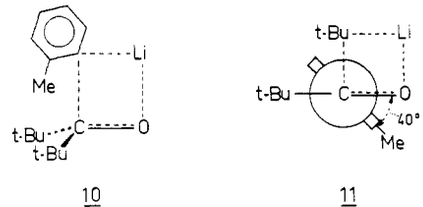
that these compounds are monomeric in ether solution, though differential vapor pressure[45] and elullioscopic measurements[46] favor dimeric species. The kinetics of phenyllithium reactions with 1,1-diphenylethylene,[47] triphenylmethane,[48] and benzonitrile[49] are consistent with a scheme involving active monomer *and* dimer species in equilibrium; the reaction of aryllithium compounds with ketones has yet to be studied kinetically.

(ii) The very existence of the ap isomer **6** resolves one problem regarding the transition state. If we consider the simplest plausible model wherein the aryllithium monomer attacks the ketone via a four-center transition state **7,** there



7 8 9

are two distinct ways in which the aryl group can be oriented: either in the plane which bisects the *t*-Bu–C–*t*-Bu angle, or orthogonal to the plane. In an attempt to explain the anomalous behavior of PhMgBr in its additions to 4-*tert*-butylcyclohexanone and 2-methylpentanone, Ashby[38] assumes that the plane of the entering phenyl group is orthogonal to that which bisects the C–CO–C angle, as in **8.** However, if this were so in the addition of *o*-tolyllithium to di-*tert*-butyl ketone, **9,** there would be no grounds for the formation of the ap alcohol **6,** since the *o*-methyl would always be situated between a *tert*-butyl group and the carbonyl oxygen and would inevitably give the sp isomer **5** only. We conclude, therefore, that the aryl group lies in the plane which contains the carbonyl group and is perpendicular to the C–CO–C system, as shown in **10.** Why then does the aryllithium attack in the observed



10 11

manner to give the less stable isomer? The perturbation of the C_1–Li bond upon approach of the C=O bond requires that the lithium atom shift toward either C_2 or C_6. Our results would appear to indicate that the shift is toward C_6 rather than upward C_2, which bears the methyl group, and, furthermore, that this shift controls the orientation of attack, i.e., that the orientation is determined at an early stage of the approach, before repulsive interactions between the *o*-methyl and the *tert*-butyl groups become dominant. Both TMEDA and an electron-withdrawing substituent reduce the amount of sp isomer formed in the addition (Table IV), possibly enhancing charge separation in the C–Li bond and thus favoring an even earlier transition state.

Although the condensation of the aryllithium with di-*tert*-butyl ketone is generally the easier method, aryldi-*tert*-butylcarbinols have been prepared by reaction of *tert*-butyllithium with the aryl *tert*-butyl ketone.[2] We find that the addition of *tert*-butyllithium to *o*-tolyl *tert*-butyl ketone in diethyl ether at −40 °C gives no trace of the ap isomer **6d;** the only tertiary alcohol formed has the sp conformation. Spectral evidence[52] indicates that the dihedral angle between the carbonyl group and the aryl group is about 40° and that the carbonyl oxygen is close to the *o*-methyl group. The ketone molecule is therefore set up in a conformation which lends itself to preferential formation of the sp alcohol **5d** upon attack by *tert*-butyllithium via a four-center transition state depicted in **11.**

Experimental Section

The IR spectra were determined on a Perkin Elmer 225 grating instrument using 1-cm silica cells containing a 10^{-2} M solution of the alcohol in CCl_4. The NMR spectra were recorded on a Jeol HF60 instrument at 60 MHz with internal Me_4Si as reference. Melting points are uncorrected.

The "low temperature–low retention time" GLC technique previously[11] described was slightly modified. A 40-cm column of 1% SE30 on HMDS-washed Chromosorb 80/100 was used at temperatures between 100 and 115 °C with an inlet pressure of 1 atm; the injector temperature was 160 °C. Under these conditions the retention times ranged from 65 (**5d** at 100 °C) to 230 s (**6f** at 115 °C) and the extent of isomerization was in no case greater than 7% (**6a** at 115 °C).

Synthetic Procedures. Aryl bromides were obtained either commercially or by molecular bromination of substituted benzenes in methylene dichloride. In the case of 4-chlorotoluene this gave rise to a mixture of isomers (70/30) which were separated by GLC on Carbowax 20M; the most abundant isomer was identified as the required 2-bromo-4-chlorotoluene. Aryllithium compounds were prepared either directly by reaction of aryl bromide with lithium metal or indirectly by exchange between *n*-butyllithium and the aryl bromide. After addition of di-*tert*-butyl ketone the alcohols were isolated as described previously[11] for **5d** and **6d.** For small-scale preparations (**5e**) or when the product was involatile (**5a,f**) the sp alcohols were isolated by column chromatography after ap → sp isomerization at 112 °C for a suitable time; alcohol **5** was obtained in yields of 27–69% (Table IV, 3rd column).

Standard Procedure for the Determination of the 6/5 Isomer Ratio. *n*-Butyllithium in *n*-hexane (1.6 M, 2 mL, 0.0032 mol) was diluted with diethyl ether (10 mL). Under argon and at room temperature (20–22 °C) the aryl bromide (0.003 mol) was syringed in dropwise. After 15 min stirring, di-*tert*-butyl ketone (0.48 g, 0.0032 mol) was introduced in the same way. After a further 15 min the reaction was stopped by pouring the mixture into water; the organic phase was washed to neutrality and dried (Na_2SO_4). A sample of the crude product after removal of the solvent was taken for determination of the isomer ratio and the remainder was chromatographed on alumina (activity II–III) in light petroleum (35–60 °C) followed by

ether/light petroleum mixtures to isolate **6** in yields of 24–66% (Table IV, 5th column).

The **6/5** isomer ratio of the crude reaction product was determined by selective dehydration. Since the ap alcohol **6** is dehydrated some 10^4 times faster than the sp isomer **5**, a brief treatment with dilute H_2SO_4 destroys completely the former while the latter is untouched. Procedure was as follows: a solution of crude product (50–60 mg) with a suitable hydrocarbon standard (20 mg) in acetic acid (10 mL) was treated with 10 mL of a 2% v/v solution of H_2SO_4 in acetic acid at 25 °C. When the alcohol mixture is chromatographed on a standard column (SE30 10%, 5 ft × ⅛ in.) with a high injector (250 °C) and oven (200–220 °C) temperature the two alcohols emerge as a single peak. A sample taken at zero time gives the ratio of total alcohol to standard, while a sample taken after 10–15 half-lives of the ap alcohol gives the ratio of unreactive sp alcohol to standard, whence the **6/5** isomer ratio (Table IV).

Synthesis of 2-Methylpivalophenone. Alcohol **5d** (4 g) upon heating under reflux for 3 h at 240–260 °C decomposed to give, after purification on SE30 15% at 190 °C, the required ketone (2.36 g, 78% yield): IR (CCl_4) 1684 cm^{-1}; NMR (CCl_4), singlet (δ 1.19), 9 H of *tert*-butyl; singlet (δ 2.17), 3 H of 2-methyl; multiplet (δ 7.10), 4 aromatic H.

Addition of *tert*-Butyllithium to 2-Methylpivalophenone. *tert*-Butyllithium[53] was prepared by slow addition (1 h) of *tert*-butyl chloride (2.5 g, 0.03 mol) in diethyl ether (40 mL) to vigorously stirred finely chopped lithium (0.5 g, 0.07 g atom) in ether (30 mL) at −40 °C. At the same temperature, 2-methylpivalophenone (1.8 g, 0.01 mol) in ether (30 mL) was added during 30 min. The mixture was allowed to warm to room temperature overnight and was then worked up as usual. GLC analysis of the crude produce revealed only the secondary alcohol, *o*-tolyl-*tert*-butylcarbinol, and the sp isomer, **5d**. Chromatography on alumina in light petroleum followed by ether gave secondary alcohol (1.44 g, 63%) and **5d** (0.55 g, 23%).

Kinetic Procedures. The method used for the determination of alcohol rotation rates in dodecane was as described previously.[11]

Equilibration of Alcohols 5d and 6d Catalyzed by *n*-Butyllithium in *n*-Hexane. A thermostated 5-mL flask was fitted with a rubber septum cap pierced with two syringe needles so that it could be continuously flushed with argon. Into 5 mL of an *n*-butyllithium solution in *n*-hexane, stirred magnetically, was injected 15 μL of a solution of alcohol **5d** in the same solvent (150 mg in 100 μL; final alcohol concentration ca. 0.01 M). Samples (0.25 mL) were withdrawn by means of a syringe at approximately 5-min intervals and injected into ice-cooled water. Low-temperature GLC analysis of the organic phase revealed that the **5d/6d** ratio rose to a constant value after 5–10 min and did not vary significantly thereafter. Approximately the same ratio was found when the sp isomer **5d** was replaced by the ap isomer **6d**. The sum of the apparent forward and reverse rate constants, k_A and k_S, was obtained by following the rotation of alcohol **6d** during 3–4 reaction half-lives and plotting $\log([ap]_t - [ap]_{eq})$ against elapsed time. The standard deviation on $k_A + k_S$ is within ±5%; the equilibrium percentage of either isomer is reproducible to ±2%. Probable errors on k_S are greater than those on k_A and increase as k_S approaches zero.

Acknowledgments. We are indebted to Professor K. Mislow for access to the STRAIN program, to Dr. E. Hough for communication of crystallographic data prior to publication, and to P. Fellman for helpful discussions.

Supplementary Material Available. Calculated Cartesian coordinates for structures **5**-Me, **5**-H, **6**-Me, and **6**-H (4 pages). Ordering information is given on any current masthead page.

Registry No.—2-Methylpivalophenone, 2041-37-4; *tert*-butyllithium, 594-19-4.

References and Notes

(1) Leading references are: (a) G. J. Karabatsos and D. J. Fenoglio, *Top. Stereochem.*, **5**, 167 (1970); (b) B. Nilsson, P. Martinson, K. Olsson, and R. E. Carter, *J. Am. Chem. Soc.*, **96**, 3190 (1974); (c) J. M. A. Baas, J. M. van der Toorn, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **93**, 133 (1974); (d) J. E. Anderson, C. W. Doeke, and D. I. Rawson, *Tetrahedron Lett.*, 3531 (1975).
(2) R. E. Gall, D. Landman, G. P. Newsoroff, and S. Sternhell, *Aust. J. Chem.*, **25**, 109 (1972).
(3) P. D. Bartlett and T. T. Tidwell, *J. Am. Chem. Soc.*, **90**, 4421 (1968).
(4) Reviewed by: M. Oki, *Angew. Chem., Int. Ed. Engl.*, **15**, 87 (1976).
(5) W. T. Ford, T. B. Thompson, K. A. J. Snoble, and J. M. Timko, *J. Am. Chem. Soc.*, **97**, 95 (1975).
(6) E. A. Chandross and C. F. Sheley, *J. Am. Chem. Soc.*, **90**, 4345 (1968).
(7) T. H. Siddall and W. E. Stewart, *J. Org. Chem.*, **34**, 233 (1969).
(8) See also: M. Nakamura and M. Oki, *Tetrahedron Lett.*, 505 (1974).
(9) Triptycene rotamers have also been isolated: M. Oki and G. Yamamoto, *Chem. Lett.*, 45 (1972); G. Yamamoto and M. Oki, *J. Chem. Soc., Chem. Commun.*, 713 (1974).
(10) P. Finocchiaro, D. Gust, and K. Mislow, *J. Am. Chem. Soc.*, **96**, 3198 (1974).
(11) J. S. Lomas and J. E. Dubois, *J. Org. Chem.*, **41**, 3033 (1976).
(12) H. Tanida and H. Matsumura, *J. Am. Chem. Soc.*, **95**, 1586 (1973).
(13) E. Hough, *Acta Crystallogr.*, submitted for publication.
(14) "IUPAC Tentative Rules for the Nomenclature of Organic Chemistry, Section E. Fundamental Stereochemistry", *J. Org. Chem.*, **35**, 2849 (1970); R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966).
(15) (a) R. J. Ouellette, D. L. Marks, and D. Miller, *J. Am. Chem. Soc.*, **89**, 913 (1967); (b) F. H. Hon, H. Matsumura, H. Tanida, and T. T. Tidwell, *J. Org. Chem.*, **37**, 1778 (1972).
(16) P. D. Bartlett, T. R. Steadman, T. T. Tidwell, and W. P. Weber, *Tetrahedron Lett.*, 2915 (1970).
(17) (a) N. L. Allinger, *Adv. Phys. Org. Chem.*, **13**, 1 (1976); (b) O. Ermer, *Struct. Bonding (Berlin)*, **27**, 161 (1976); (c) E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 8005 (1973).
(18) (a) M. A. Robb, W. J. Haines, and I. G. Csizmadia, *J. Am. Chem. Soc.*, **95**, 42 (1973); (b) N. L. Allinger and D. Y. Chung, *ibid.*, **98**, 6798 (1976).
(19) P. Müller and J. C. Perlberger, *J. Am. Chem. Soc.*, **97**, 6862 (1975).
(20) See, for example: D. Lenoir, D. J. Raber, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **96**, 2149 (1974).
(21) J. L. Fry, E. M. Engler, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **94**, 4628 (1972).
(22) J. D. Andose and K. Mislow, *J. Am. Chem. Soc.*, **96**, 2168 (1974); calculations were performed on an IBM 370 computer of the Centre National de la Recherche Scientifique.
(23) D. F. DeTar and C. J. Tenpas, *J. Am. Chem. Soc.*, **98**, 4567 (1976).
(24) S. Fitzwater and L. S. Bartell, *J. Am. Chem. Soc.*, **98**, 5107 (1976).
(25) We formerly attributed the lower reactivity of the sp isomer in part to steric hindrance to protonation of the hydroxyl group,[11] due to the proximity of the *o*-methyl group. In fact, we now find that the calculated difference in the steric energies of the alcohols is very nearly the same as that of the activation energies for dehydration, 5.6 kcal/mol. This means that if the transition states for dehydration of the isomeric alcohols are similar in energy, both being close to the common intermediate carbonium ion, then the difference in reactivity is completely explained by that of the ground-state energies of the two alcohols in question, without any other supplementary cause needing to be invoked. This point will be developed in a forthcoming article.
(26) Cartesian coordinates for these structures are given in the Supplementary Material.
(27) H. van Koningsveld, *Cryst. Struct. Commun.*, **3**, 491 (1973).
(28) H. B. Burgi and L. S. Bartell, *J. Am. Chem. Soc.*, **94** 5236 (1972); G. Lepicard, J. Berthou, J. Delettré, A. Laurent, and J. P. Mornon, *C. R. Acad. Sci., Ser. C*, **276**, 575 (1973).
(29) As in 1,2,4,5-tetra-*tert*-butylbenzene, for example: A. van Bruijnsvoort, L. Eilermann, H. van der Meer, and C. H. Stam, *Tetrahedron Lett.*, 2527 (1968).
(30) J. S. Lomas and J. E. Dubois, *Tetrahedron Lett.*, 407 (1976).
(31) Analogous to the decomposition of tri-*tert*-butylcarbinol: J. E. Lomas and J. E. Dubois, *J. Org. Chem.*, **39**, 1776 (1974).
(32) J. S. Lomas and J. E. Dubois, unpublished data.
(33) A. Rieker and H. Kessler, *Tetrahedron Lett.*, 1227 (1969).
(34) R. Haakansson, *Chem. Scr.*, **2**, 109 (1972).
(35) M. Nakamura and M. Oki, *Chem. Lett.*, 671 (1975).
(36) Extrapolation of the linear least-squares correlation of the k_S data gives, in fact, $10^3 k_S = -0.13 \pm 0.20$ for a 90% confidence interval at [*n*-BuLi] = 0.01 M, the alcohol concentration. The upper limit gives a value of 30 for *K*, but the true value is probably higher.
(37) B. J. Wakefield, "The Chemistry of Organolithium Compounds", Pergamon Press, Elmsford, N.Y., 1974, pp 3–15.
(38) E. C. Ashby and J. T. Laemmie, *Chem. Rev.*, **75**, 521 (1975).
(39) For a complete discussion see ref 37, pp 14, 92, and ref 40–43.
(40) T. L. Brown, *J. Organomet. Chem.*, **5**, 191 (1966).
(41) P. D. Bartlett, C. V. Goebel, and W. P. Weber, *J. Am. Chem. Soc.*, **91**, 7425 (1969).
(42) L. F. Charbonneau and S. G. Smith, *J. Org. Chem.*, **41**, 808 (1976).
(43) D. P. Novak and T. L. Brown, *J. Am. Chem. Soc.*, **94**, 3793 (1972).
(44) J. A. Ladd and J. Parker, *J. Organomet. Chem.*, **28**, 1 (1971).
(45) P. West and R. Waack, *J. Am. Chem. Soc.*, **89**, 4395 (1967).
(46) G. Wittig, F. J. Meyer, and G. Lange, *Justus Liebigs Ann. Chem.*, **571**, 167 (1951); T. V. Talalaeva, A. N. Rodionov, and K. A. Kocheshkov, *Proc. Acad. Sci. USSR, Chem. Sect.*, **154**, 47 (1964); A. N. Rodionov, D. N. Shigorin, T. L. Talalaeva, G. V. Tsareva, and K. A. Kocheshkov, *Zh. Fiz. Khim.*, **40**, 2265 (1966).
(47) R. Waack and M. A. Doran, *J. Organomet. Chem.*, **29**, 329 (1971); *J. Am. Chem. Soc.*, **91**, 2456 (1969).
(48) P. West, R. Waack, and J. I. Purmort, *J. Am. Chem. Soc.*, **92**, 840 (1970).
(49) T. Holm, *Acta Chem. Scand.*, **23**, 833 (1971).
(50) NMR spectra of phenyllithium compounds[51] appear to show that all substituents other than CF_3 decrease the ionic character of the C–Li bond. The ordering of the substituents depends, however, upon which nucleus, ^7Li or ^1H, is considered and in neither case follows familiar σ or σ^+ values.
(51) J. A. Ladd and J. Parker, *J. Chem. Soc., Dalton Trans.*, 930 (1972).
(52) E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955); K. S. Dhami and J. B. Stothers, *Can. J. Chem.*, **43**, 498 (1965).
(53) P. D. Bartlett and E. B. Lefferts, *J. Am. Chem. Soc.*, **77**, 2804 (1955).