Revisiting the Reduction of Di-*tert*-butyl Ketone with Alkali Metals

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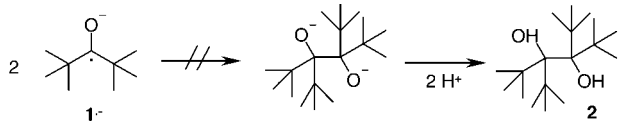
Keywords: Density functional theory / Ketone dianions / Pinacol coupling / Radical anions / Steric hindrance

The reduction of di-*tert*-butyl ketone (**1**) with alkali metals has been revisited. A novel product, 2,5,5-tri-*tert*-butyl-3-methyl-4,5-dihydrofuran (**4**), was isolated from the product mixture in very low yield. The formation of **4** requires the elimination of a methyl radical from the radical anion of **1** as key step. An alternative reaction mechanism, which involves the formation of the dianion of **1**, was ruled out on the basis of the results of DFT calculations.

Introduction

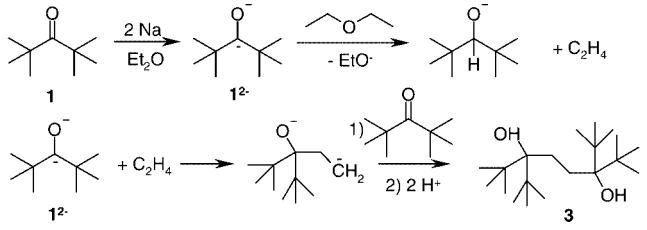
The pinacol coupling of aliphatic ketones through treatment with reactive metals (Mg, Na) is an old reaction, which generally gives good yields of the corresponding glycols. If di-*tert*-butyl ketone (**1**) is selected as starting material, however, no tetra-*tert*-butylethylene glycol (**2**) is formed (Scheme 1).[1,2] An early report[3] on the formation



Scheme 1

of this interesting compound was later shown to be wrong.

Investigations by Eberson[1] and by Bartlett and co-workers[2] revealed that the compound erroneously identified as glycol **2** could instead be characterized as tetra-*tert*-butyl-1,4-butanediol (**3**). According to Bartlett et al.,[2] diol **3** is formed by initial addition of the dianion of ketone **1** to



Scheme 2

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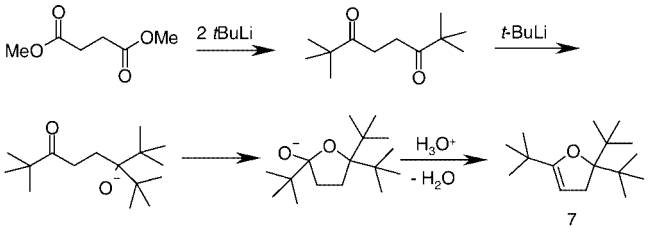
ethylene, which is in turn formed by E_2 elimination of the ethoxide anion of the diethyl ether solvent (Scheme 2).

The chemistry depicted in Scheme 1 is based on the intermediary formation of the superbasic dianion $\mathbf{1}^{2-}$. Dianions based on benzophenone derivatives have been known for some time.[4] Unlike those in these aromatic dianions, however, the two negative charges in $\mathbf{1}^{2-}$ cannot be delocalized, which forces them to reside essentially on two directly connected atoms. This produces an exceedingly basic species, but it also destabilizes the dianion to a significant degree. In particular, the comproportionation of dianion $\mathbf{1}^{2-}$ with unchanged ketone **1**, yielding 2 equiv. of ketyl $\mathbf{1}^{\cdot-}$, should be a reaction with high driving force and little barrier. At least in the absence of a significant excess of alkali metal, as in Stevens and Mowat's initial study[3] as well as in Eberson's work,[1] the formation of $\mathbf{1}^{2-}$ in significant amounts thus seems to be a questionable proposition.[5a] This study was performed in order to shed light on the possible reaction pathways. It includes product studies and DFT calculations.

Results and Discussion

Initial product studies were designed to check for the formation of glycol **2** in small or trace amounts, which may have gone unnoticed in prior studies. Glycol **2**, however, could not be found. Much to the author's surprise, an investigation of this reaction by GC/MS analysis instead revealed that a product showing a mass peak with $m/z = 252$ was present in the product mixture besides the products already identified in previous studies.[1,2][5b] The product with $m/z = 252$ could be isolated in very low yield (0.4%) by column chromatography (SiO_2; *n*-hexane). NMR spectroscopy (^1H, ^{13}C, COSY, HMBC, HMQC, ROESY) revealed that this product was not the long sought-after[6,7] tetra-*tert*-butylethylene. Instead, it could be identified as the dihydrofuran **4** (Scheme 3). A similar compound **5** had pre-



Scheme 3

viously been described by Hopf and Hänel (Scheme 3).[8] As would be expected, the spectroscopic data of **4** and **5** are very similar.

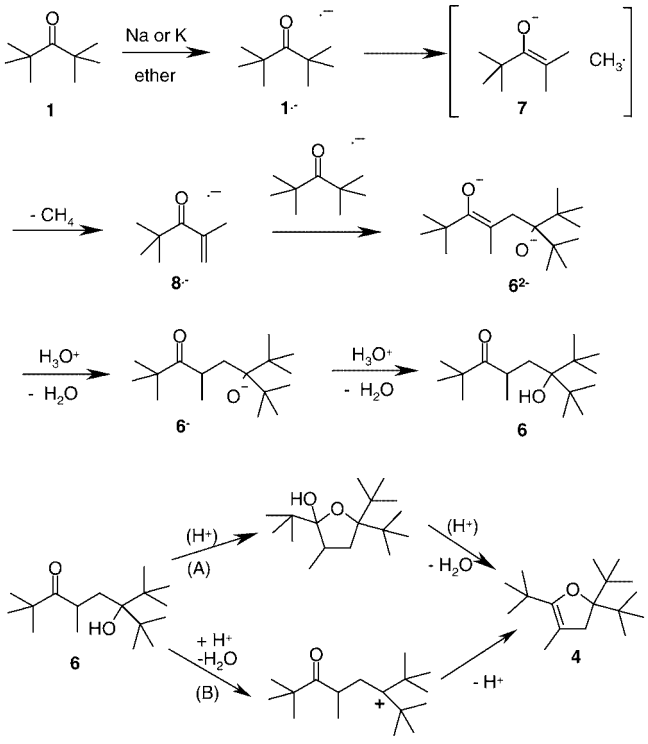
The mechanism for the formation of **5** has been discussed by Hopf and Hänel[8] (see Scheme 3). Unlike this reaction, the cyclization reaction of **6** is unlikely to occur via the monoanion $\mathbf{6}^-$. In the course of the reaction and workup, **6** will either be present as a dianion $\mathbf{6}^{2-}$ (reaction) or as a neutral species **6** (during acidic workup and column chromatography). Dianion $\mathbf{6}^{2-}$ would not be expected to cyclize. It therefore appears likely that cyclization to **4** occurs under acidic conditions, possibly during column chromatography. This reaction could involve intramolecular nucleophilic attack of the alcohol functionality present in **6** on the carbonyl moiety, activated by *O*-protonation (Scheme 4, mechanism A). Alternatively, protonation of the hydroxy group in **6** might yield a tertiary carbenium ion, which would be quenched intramolecularly by nucleophilic attack by the carbonyl oxygen atom, followed by loss of a proton (Scheme 4, mechanism B). Given the relative ease of solvolysis of tertiary alcohols under acidic conditions, mechanism B appears much more likely than mechanism A, which would involve attack of a sterically highly hindered alcohol at a sterically hindered carbonyl functionality.

The formation of **6** from two molecules of ketone **1** necessitates the removal of a methyl group. The two following reaction mechanisms are suggested:

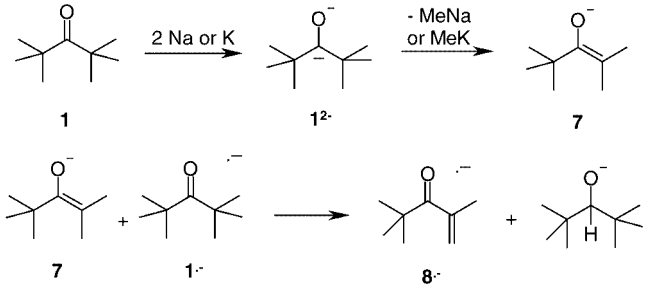
Cleavage of a $C-C_{Methyl}$ bond in $\mathbf{1}^{\cdot-}$ affords the enolate of *tert*-butyl isopropyl ketone (**7**). Abstraction of a further hydrogen atom from **7**, either in the solvent cage by the methyl radical, or by $\mathbf{1}^{\cdot-}$, gives the radical anion of *tert*-butyl isopropenyl ketone ($\mathbf{8}^{\cdot-}$), which reacts with $\mathbf{1}^{\cdot-}$, yielding the dianion of **6**. Protonation and cyclization followed by dehydration finally results in the formation of **4** (Scheme 4). Alternatively, the reaction could initially proceed from dianion $\mathbf{1}^{2-}$, which could eliminate methylsodium (or methylpotassium) to yield the enolate **7**. Enolate **7** would then have to react with $\mathbf{1}^{\cdot-}$ to yield $\mathbf{8}^{\cdot-}$, which would again react with $\mathbf{1}^{\cdot-}$ (Scheme 5).

For the following reasons, the mechanism shown in Scheme 4 (thermal methyl radical elimination) is believed to operate:

(1) The reaction is not photochemical. Performing the pinacol coupling of **1** in the dark also yields dihydrofuran **4** in 0.4% yield. The absence of light does not prolong the lifetime of $\mathbf{1}^{\cdot-}$.



Scheme 4



Scheme 5

(2) Radical anion $\mathbf{8}^{\cdot-}$ does indeed react with $\mathbf{1}^{\cdot-}$. Addition of 1 equiv. of *tert*-butyl isopropenyl ketone (**8**)[9] to 1 equiv. of $\mathbf{1}^{\cdot-}$ and 1 equiv. of potassium in diethyl ether results in the formation of **4** in significantly improved yield (6.2%).

(3) Performing the reduction of **1** with a twofold excess of potassium metal does not result in an increased yield of **4**.

(4) The barrier for the $C-C_{Methyl}$ cleavage in $\mathbf{1}^{\cdot-}$ was calculated by density functional theory[10] [UB3LYP/6-31+G(d)] as $\Delta H^{\neq} = 22.2$ kcal/mol. The C−C distance in the TS is calculated as 244.8 pm, which fits well for a late transition structure. The barrier calculated for the back reaction is significantly lower (1.3 kcal/mol). Accordingly, the elimination of a methyl radical from $\mathbf{1}^{\cdot-}$ is endothermic by 17.7 kcal/mol. A barrier of 22.2 kcal/mol would correspond to an estimated first-order rate constant for the decay of $\mathbf{1}^{\cdot-}$ of $k = 8.5 \times 10^{-5}\ s^{-1}$ ($\tau \approx$

195 min, log A taken as 12). If compared both with the literature value[11] ($\tau \approx 30$ min corresponding to $k \approx 5.5 \times 10^{-4}$ s^{-1}) and with observations made in this study (the lifetime of an ethereal solution of $\mathbf{1}^{\cdot-}$ with Na^+ or K^+ as counterion is of the order of several days), this value for k_{decay} of $\mathbf{1}^{\cdot-}$ appears to be of the right order of magnitude. In any case, the calculations indicate that a thermal cleavage of $\mathbf{1}^{\cdot-}$ into a methyl radical and enolate **7** should be feasible even under mild conditions (ambient temperature).

(5) According to the calculations [UB3LYP/6-31G+(d)], the barrier for abstraction of a hydrogen atom from the enolate **7** by the methyl radical is very small. The transition structure for the formation of *s-cis*-$\mathbf{8}^{\cdot-}$ lies 0.4 kcal/mol below the sum of the energies of **7** and the methyl radical. Even if one takes complex formation between **7** and CH_3 into account, the actual barrier should hardly be larger than 1 kcal/mol. A barrier of this size corresponds to a lifetime of the (**7** + CH_3) complex in the picosecond regime ($k \approx 2 \times 10^{11}$ s^{-1} for $E_a = 1$ kcal/mol and log $A = 12$). Hence, a hydrogen abstraction from enolate **7** by the methyl radical within the solvent cage appears likely. The total reaction $\mathbf{1}^{\cdot-} \rightarrow \mathbf{8}^{\cdot-} + CH_4$ is exothermic by 13.9 kcal/mol (*s-trans*-$\mathbf{8}^{\cdot-}$) or 8.8 kcal/mol (*s-cis*-$\mathbf{8}^{\cdot-}$) according to UB3LYP/6-31G(d). Figure 1 shows the transition structures for the elimination of CH_3 from $\mathbf{1}^{\cdot-}$ and for the abstraction of a hydrogen atom from enolate **7** by CH_3. In the TS, the C−H distance of the bond to be broken is 121 pm, and the C_{methyl}−H distance is calculated as 172 pm.

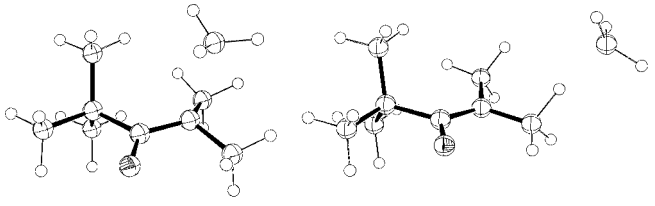
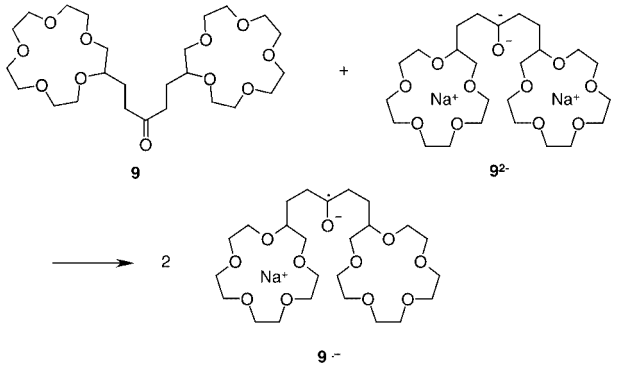


Figure 1. ORTEP drawings of the transition structure connecting $\mathbf{1}^{\cdot-}$ and **7** + CH_3 (left) and of the transition structure connecting **7** + CH_3 and *s-cis* $\mathbf{8}^{\cdot-}$ + CH_4, calculated at the UB3LYP/6-31+G(d) level of theory

(6) All attempts to localize a transition structure for a concerted *syn* elimination of methane from $\mathbf{1}^{\cdot-}$ failed. Instead, the optimizations led to the transition structure for H abstraction from **7** by the methyl radical.

(7) The barrier for the demethylation of the radical anion of butanone was calculated [UB3LYP/6-31G(d)] to be 16.6 kcal/mol, which is below even the value obtained for $\mathbf{1}^{\cdot-}$ (19.0 kcal/mol). The sterically demanding substitution in $\mathbf{1}^{\cdot-}$ therefore does not result in a reduced barrier for demethylation. Addition of diffuse functions [optimization at UB3LYP/6-31+G(d)] gives a somewhat larger predicted barrier (19.6 kcal/mol).

(8) As far as the mechanism shown in Scheme 5 is concerned, it appears unlikely since comproportionation of $\mathbf{1}^{2-}$ and **1**, yielding 2 equiv. of $\mathbf{1}^{\cdot-}$,would be expected to be an exothermic reaction. The fact that a twofold excess of potassium does not improve the yield of **4** [see (3) above] further argues against the intermediacy of a dianion. Attempts to optimize (semiempirical or DFT methods) the geometry of $\mathbf{1}^{2-}$ without a counter-ion resulted in a fragmentation of the molecule ("coulomb explosion"). In order to account for the strong solvation of the alkali metal cations by the ether solvent, the comproportionation reaction was studied [(U)B3LYP/6-31G(d)] for 1,5-bis(15-crown-5)-substituted 3-pentanone **9**, its dianion and radical anion as a model system, where solvation of the Na^+ counter-ions is provided by the crown ether moieties (Scheme 6).



Scheme 6

Without diffuse functions, the comproportionation of **9** and $\mathbf{9}^{2-}/2Na^+$ to 2 equiv. $\mathbf{9}^{\cdot-}/Na^+$ was predicted to be exothermic by 7.7 kcal/mol. With inclusion of diffuse functions [(U)B3LYP/6-31++G(d,p)//(U)B3LYP/6-31G(d); ZPE calculated with (U)B3LYP/6-31G(d)], the reaction was calculated to be slightly more exothermic (−9.8 kcal/mol). The equilibrium constant for the comproportionation of **9** and $\mathbf{9}^{2-}$ can thus be estimated to be of the order of $k = 2 \times 10^7$. Under the assumption that the equilibrium parameters are similar for $\mathbf{1}/\mathbf{1}^{\cdot-}/\mathbf{1}^{2-}$, one can conclude that the concentration of $\mathbf{1}^{2-}$ present in the absence of an excess of sodium or potassium metal should be small. This does not strictly exclude that **4** could be formed via $\mathbf{1}^{2-}$. In this case, however, the barrier for elimination of MeK or MeNa from $\mathbf{1}^{2-}$ would have to be significantly smaller than the barrier for methyl radical elimination from $\mathbf{1}^{\cdot-}$ in order to be able to compete. Hence, both the calculations and the absence of an effect of excess potassium metal on the yield of **6** indicate that $\mathbf{1}^{2-}$ probably does not play an important role in the formation of **4**. As far as the formation of **3** is concerned, it appears likely that this species is indeed formed as depicted in Scheme 1, if an excess of alkali metal is used in combination with conditions that remove the dianion from the equilibrium.[2,5a,12]

These results indicate that the fragmentation of ketone radical anions to enolate anions plus alkyl radicals may rep-

resent a viable reaction pathway if the competing dimerization is hindered due to steric constraints. If the leaving alkyl radical is stabilized electronically (as the benzyl radical, for example), this reaction pathway would be anticipated to gain additional weight. The calculations presented suggest that the elimination of CH_3 from $\mathbf{1}^{\cdot-}$ is followed by a very facile hydrogen abstraction reaction within the solvent cage, which yields methane plus the radical anion of *tert*-butyl isopropenyl ketone (**7**). The observation, that **4** is formed in significantly enhanced yield if a mixture of **1** and **8** is reduced by potassium metal might open a valuable synthetic route towards the preparation of further sterically hindered dihydrofuran derivatives and other oxygen heterocycles.

Experimental Section

Pinacol Coupling of 1: Mineral-oil-free sodium (0.8 g), or potassium (1.4 g), was placed under dry ether (20 mL) in a 100-mL, two-necked flask equipped with a magnetic stirrer and an Ar inlet. Di-*tert*-butyl ketone (**1**,[13] 5 g, 0.035 mol) was added slowly at ambient temperature. The mixture soon took on a dark brown color. As soon as the brown color had disappeared (2−4 d) the mixture was poured onto ice (200 mL) and acetic acid (50%, 30 mL). The organic phase was separated and washed twice with saturated $NaHCO_3$ and once with water. The extract was dried with Na_2SO_4 and concentrated in a rotary evaporator. Volatile constituents of the product mixture were then distilled off in a Kugelrohr apparatus at 15 Torr pressure. The crystalline residue was worked up by column chromatography (SiO_2; *n*-hexane), yielding the colorless 2,5,5-tri-*tert*-butyl-3-methyl-4,5*H*-dihydrofuran (**4**) (40 mg, 0.15 mmol, 0.4%). A change in the eluent to 1% *tert*-butyl methyl ether in *n*-hexane allowed ca. 2% of diol **3** to be isolated.

Pinacol Coupling of 1 in the Presence of *tert*-Butyl Isopropenyl Ketone: Di-*tert*-butyl ketone (**1**, 2.0 g, 0.014 mol) was added to mineral-oil-free potassium (1.12 g, 0.028 mol) in dry ether (10 mL). The mixture was stirred at ambient temperature for 5 h, and *tert*-butyl isopropenyl ketone (**8**,[9] 1.76 g, 0.014 mol) was then added dropwise. Stirring at room temperature was continued until the brown color had disappeared (2 d). The mixture was then worked up as described above. Yield 220 mg (0.87 mmol, 6.2%) of dihydrofuran **4**, colorless crystals, m.p. 180−185 °C (from ether). The compound crystallizes only in the absence of higher alkanes.

2,2,5-Tri-*tert*-butyl-4-methyl-2,3-Dihydrofuran (4): ^{1}H NMR (400 MHz, C_6D_6, TMS): δ = 1.11 (s, 18 H), 1.29 (s, 9 H), 2.39 (s, 4 H), 2.63 (s, 6 H) ppm. ^{13}C NMR (100 MHz, C_6D_6, TMS): δ = 27.43, 28.51, 29.31, 34.12, 41.61, 41.91, 91.29, 105.31, 155.83 ppm. IR (KBr): $\tilde{\nu}$ = 692, 960, 1001, 1051, 1126, 1152, 1205, 1235, 1265, 1368, 1389, 1481, 1677, 2918, 2956 cm^{-1}. MS: *m*/*z* (%) = 252 [M^+], 195, 139, 123, 97, 85, 71, 57 (100). $C_{17}H_{32}O$ (252.44): calcd. C 80.9, H 12.8; found C 80.4, H 12.6.

Computational Methods: The DFT calculations were performed with the aid of the Gaussian 98[14] suite of programs. All stationary points were characterized as minima or transition structures by calculation of the vibrational spectra. The energies and barriers given include a zero-point energy correction and refer to a temperature of 0 K.

Supporting Information: See also footnote on the first page of this article. Calculated geometries of $\mathbf{1}^{\cdot-}$, **7**, $\mathbf{8}^{\cdot-}$, and the transition structures linking $\mathbf{1}^{\cdot-}$ and (**7** + CH_3) as well as (**7** + CH_3) and $\mathbf{8}^{\cdot-}$. Calculated geometries of **9**, $Na^+\mathbf{9}^{\cdot-}$, and $2Na^+\mathbf{9}^{2-}$.

Acknowledgments

The author thanks M. Feigel for helpful discussions.

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Received October 21, 2002

