Ring Tension, Hydrocarbon Acidity, and New «Super-Bases»**

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Abstract: Addition of disodium pinacolate or, particularly, potassium *tert*-butoxide considerably increases the transmetalating power of pentylsodium. A hexane slurry of such «NACNAOR» or «NACKOR» reagent mixtures readily and selectively converts 3,3-dimenthyl-1-butene, camphene, bicyclo[2.2.2]oct-2-ene, and spiro[4.4]nona-1,3-diene into sodio derivatives. The metalation of cyclopropanes such as nortricyclane, norcarane or bicyclo[2.1.0]pentane («housane») proved to be possible too, although the yields were less satisfactory. On the other hand, cyclobutanes were found to be virtually inert towards alcoholate-activated pentylsodium.

As a first approximation[1] one can distinguish between «geometrically» and «electronically» activated hydrocarbon acids[2, 3]. We have already described «super-basic» reagents such as butyllithium in the presence of potassium *tert*-butoxide («LICKOR-reagent») or trimethylsilylmethylpotassium which are powerful enough to metalate practically all hydrocarbons that belong to the latter group[4]. On the other hand, it remained still to be explored what would be a minimum structural requirement to make a geometrically activated substrate undergo a hydrogen/metal exchange reaction and what type of reagent would be most suitable for this purpose. The present communication tries to answer this question.

Although butyllithium metalates acetylenes (p$K \approx 30$) instantaneously it reacts with benzene (p$K \approx 50$) only to a negligeable extent[5] unless activated by *N,N,N′,N′*-tetramethylethylenediamine (TMEDA)[6]. On the other hand, ethylsodium, butylsodium, and pentylsodium («amylsodium») were reported to be sufficiently basic to promote exchange of aromatic[7], olefinic[8], and cyclopropanic[9] hydrogen atoms with sodium. A closer examination of the experimental conditions, however, reveals some shortcomings of this method: very long reaction times and poor yields despite the large excess of hydrocarbon substrates commonly em-

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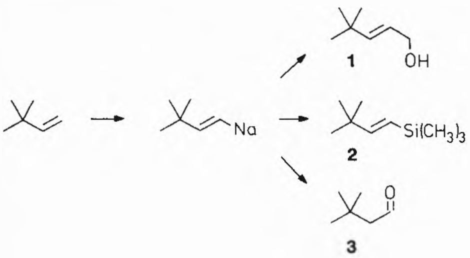
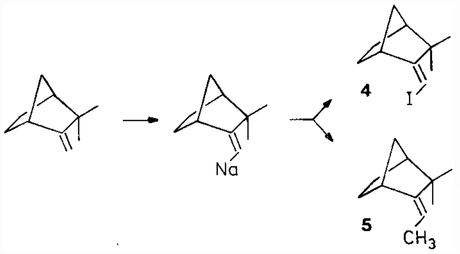
ployed. We wondered whether it would be possible to activate pentylsodium by adding potassium *tert*-butoxide or other alcoholates and thus improve the results. This indeed turned out to be the case.

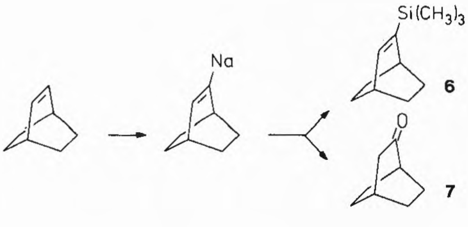
It required 200 h of shaking a solution of 3,3-dimethyl-1-butene in hexane with pentylsodium[8a, 10] and subsequent treatment with monomeric[11] formaldehyde in tetrahydrofuran to give 11% of 4,4-dimethyl-2-penten-1-ol (**1**). In the presence of potassium *tert*-butoxide (1 equiv.), however, 40% **1** (*Z*/*E* = 6 : 94) was obtained already after 20 h of metalation and 88% **1** (*Z*/*E* < 0.5 : 99.5) after 50 h of metalation in the presence of disodium pinacolate[12] (again 1 equiv.). With chlorotrimethylsilane as the electrophile 66% of (*E*)-(3,3-dimethyl-1-butenyl)trimethylsilane (**2**)[13] was formed, whereas the dimethoxyborylation-oxidation sequence[14] afforded 3,3-dimethylbutanal (**3**) in 37% yield[15, 16].



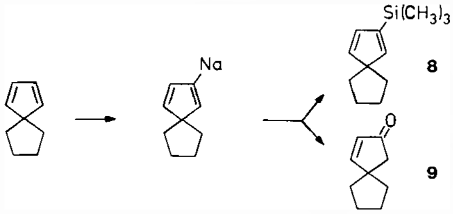
Camphene contains in its bicyclic skeleton the partial structure of 3,3-dimethyl-1-butene. Pentylsodium in hexane suspension produced, during 1 h of high-speed stirring and 25 h of occasional shaking, a sodio derivative which reacted with methyl iodide to afford a 1:1 mixture of (*E*)-3-iodomethylene-2,2-dimethyl-norbornane (**4**) and (*E*)-3-ethylidene-2,2-dimethylnorbornane (**5**). The combined yield of 33% was raised to 60% when the same reaction sequence was repeated in the presence of a small excess of potassium *tert*-butoxide[17].



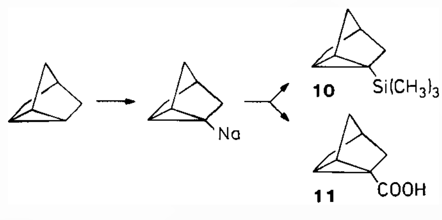
Bicyclo[2.2.2]octene has an internal rather than a terminal double-bond and thus was expected to undergo metalation more sluggishly. Actually, 170 h (!) of stirring with pentylsodium were necessary to generate an organometallic intermediate which upon subsequent treatment with chlorotrimethylsilane or fluorodimethoxyborane[14] and alkaline hydrogen peroxide was converted into 2-trimethylsilyl-bicyclo[2.2.2]oct-2-ene (**6**; 60%)[18] and bicyclo[2.2.2]octanone (**7**; 65%)[19], respectively. When the exposure to metalating agent was shortened to 10 h and still no activating alcoholate was added the yields dropped below 10%, while in the presence of equimolar quantities of disodium pinacolate or potassium *tert*-butoxide they increased to approximately 40% and 70%, respectively, after the same period of time.



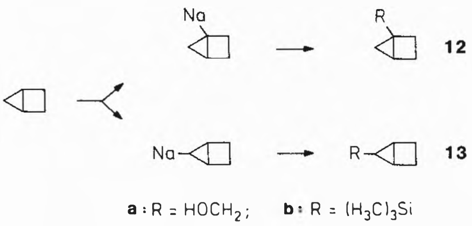
We are not aware of any example of diene metalation at an olefinic position[20]. The spiro[4.4]nona-1,3-diene seemed to us to be an attractive candidate. After 100 h of stirring with pentylsodium in pentane and subsequent addition of chlorotrimethylsilane or fluorodimethoxyborane and alkaline hydrogen peroxide, indeed 66% of 2-trimethylsilyl-spiro[4.4]nona-1,3-diene (**8**)[18] and 45% of spiro[4.4]non-3-en-2-one (**9**)[18, 21] were isolated. Without doubt the steric hindrance around the quaternary center explains best why the 2-position is attacked exclusively even if an additional «polarization effect»[22] may operate in the same sense. Again alcoholate complexands are capable of accelerating the metalation step although this time the yields diminish to some extent. Possibly a considerable quantity of starting material was lost due to polymerization.



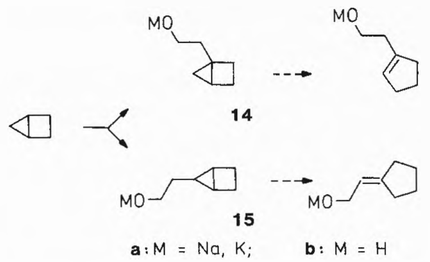
Alcoholate-activation proved to be particularly efficient when applied to the metalation of cyclopropanes. After consecutive exposure to the «NACKOR»-mixture during 24 h at 25 °C in pentane and to chlorotrimethylsilane, tricyclo[2.2.1.$0^{2,6}$]heptane («nortricyclane») gave a 60% yield of the corresponding silane **10**[17], while with pentylsodium alone even after 500 h (!) of stirring and subsequent carboxylation, not more than 5% of the acid **11** was formed[23].



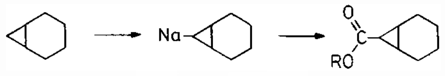
The increased ring-strain of bicyclo[2.1.0]pentane («housane») should facilitate its metalation. According to a report by *Gassman* et al.[24] reaction times with pentylsodium of 200 h were nevertheless required before organosodium intermediates could be trapped by carboxylation, esterification, and reduction, affording the primary alcohols **12a** (20%) and *exo*-**13a** (18%). In the presence of potassium *tert*-butoxide most of the hydrocarbon substrate was consumed after 20 h, and in the presence of disodium pinacolate after 40 h. After addition of chlorotrimethylsilane we were able to collect 7% of the silane **12b** together with 20% of the isomer *exo*-**13b**[18]. With disodium pinacolate instead of potassium *tert*-butoxide, 7% of **12b** was obtained as the sole isolable product.



We suspect all bicyclo[2.1.0]pentane derivatives to be structurally labile, notably when carrying a metal[25] or a substituent at one of the bridgehead positions. How alcoholates and other strong bases can play a detrimental role under such circumstances was demonstrated when oxirane served as the electrophile to intercept the metalated intermediates. Besides the primary reaction products 2-(1-bicyclo[2.1.0]pentyl)ethanol (**14b**; 2.2%) and 2-(*exo*-5-bicyclo[2.1.0]pentyl)-ethanol (**15b**; 0.5%) two typical ring-opened products, 2-(1-cyclopentenyl)-ethanol (6.9%) and 2-cyclopentylidene-ethanol (2.3%) were isolated and characterized[18].



The unstrained six-membered ring of norcarane (bicyclo[4.1.0]heptane) should act as a pair of alkyl groups and, due to steric and electronic effects, impede the proton abstraction from the cyclopropane sites to which it is attached. Consequently norcarane was expected to undergo metalation exclusively at the 7-position, if at all. Indeed, 100 h shaking with a pentylsodium suspension in hexane followed by carboxylation, neutralization, and esterification with diazomethane afforded just 3.1% of methyl *exo*-7-norcarancarboxylate (**16**; R = CH_3). While disodium pinacolate proved to be inefficient, addition of potassium *tert*-butoxide increased the yield to 30%.



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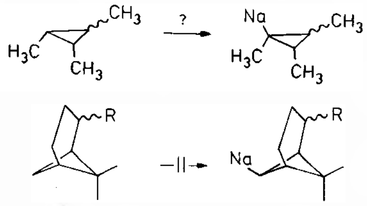
Presumably norcarane is the least acidic hydrocarbon which has been metalated in a stoichiometric reaction. Attempts to promote the hydrogen/metal-exchange with a *cis/trans*-mixture of 1,2,3-trimethylcyclopropane (**17**) as the substrate failed completely or gave only trace amounts of products. Cyclobutane, *cis*-pinane (**18**), and *trans*-myrtanol (**19**) were recognized to be completely inert towards «NACNAOR»-and «NACKOR»-type reagents.



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18: R = *cis*-CH_3

19: R = *trans*-CH_2OH

Alcoholate-activated organometallics are particularly powerful reagents for the metalation of weakly acidic hydrocarbons. Cyclopropanes as substrates (see Fig. 1), however, appear to be a limiting case. Presently no preparatively useful method exists for the direct replacement of a hydrogen by a metal atom in either an open-chain paraffinic hydrocarbon or in cyclobutane and larger cycloalkanes[26].

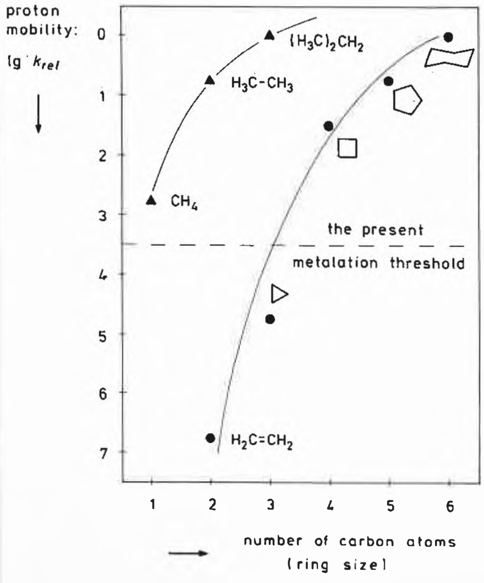

Fig. 1. Relative rates of base-catalyzed isotope exchange in representative open-chain and cyclic hydrocarbons: methane[27]*, ethane*[27]*, propane (at the methylene group)*[28]*, ethylene*[29]*, cyclopropane*[30]*, cyclobutane*[30]*, cyclopentane*[30]*, and cyclohexane*[30].

Typical working procedure: To a slurry of 25 mmol pentylsodium in 10 mL pentane, 2.7 g (25 mmol) bicyclo[2.2.2]oct-2-ene were added at room temperature. After 170 h of vigorous stirring the mixture was treated with 3.3 g (30 mmol) chlorotrimethylsilane. Upon distillation 2.7 g (60%) of the silane **6** were collected in the boiling range 69–71 °C/10 mmHg. If the metalation was carried out in the presence of potassium *tert*-butoxide (25 mmol), the time could be reduced to 10 h without affecting the yield.

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[2] The term «geometrical activation» may be replaced by «activation due to angle-strain» provided one is willing to consider ethylene as a «cycloethane» and acetylene as a «bicyclo[0.0.0]ethane». «Electronic activation» means essentially the stabilization of a carbanion by delocalization of the negative charge.

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[12] Prepared in situ by treatment of the diol with two additional equivalents of pentylsodium.

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[14] G. Rauchschwalbe, M. Schlosser, *Helv. Chim. Acta 58* (1975) 1094.

[15] If the oxidation of the boronate with alkaline hydrogen peroxide solution is not interrupted at a very early stage, practically all aldehyde is lost due to autocondensation.

[16] Recently the successful metalation of 3,3-dimethyl-1-butene (applied in a five-fold excess) with butyllithium in the presence of potassium *tert*-butoxide and TMEDA was reported; the organometallic intermediate was converted into approximately 20% 1-(ethylthio)-3,3-dimethyl-1-butene by treatment with diethyl disulfide [L. Brandsma, H.D. Verkruijsse, C. Schade, P. von R. Schleyer, *J. Chem. Soc. Chem. Commun.* (1968) 260].

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[18] Combustion analyses and spectral data confirm the identity and purity of all new compounds.

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[26] Some paraffinic substrates do undergo a hydrogen/metal-exchange with butylpotassium [R.A. Finnegan, *Tetrahedron Lett. 4* (1963) 429; H. Megard, F. Korte, *Monatsh. Chem.* 98 (1967) 763; furthermore we are grateful to Dr. G.C. Robinson, Baton Rouge, for communicating detailed unpublished information on this subject]. Such reactions, however, lack practical synthetic value: they are restricted to low-molecular weight, straight-chain alkanes, requiring the substrate to be employed in large excess (mostly even as the solvent) and nevertheless giving only poor yields (< 30%).

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