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Hetero-Atom Effects on Kinetic Acidities: The Metalation of 1-Methyl-cyclohexene and its 4-Aza- and 4-Oxa-Analogs**

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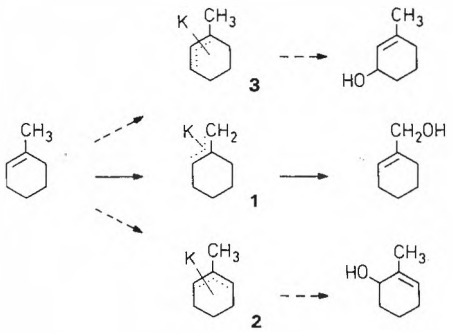
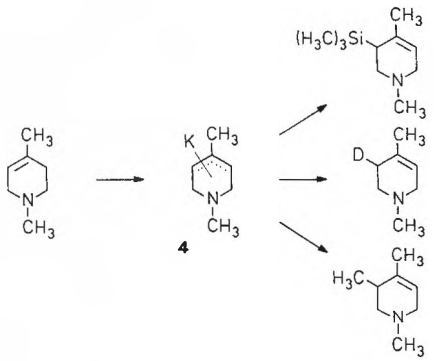
Dedicated to Professor Albert Eschenmoser on the occasion of his 60th birthday

Abstract: Hexane suspensions of trimethylsilylmethylpotassium or butyllithium/potassium *tert*-butoxide deprotonate 1-methyl-cyclohexene almost exclusively at the methyl group. In contrast 1,4-dimethyl-1,2,3,6-tetrahydropyridine and 4-methyl-5,6-dihydro-2*H*-pyran preferentially undergo hydrogen/metal-exchange at the nitrogen-distant and, respectively, oxygen-adjacent allylic methylene group. Strong amide bases convert 5,6-dihydro-2*H*-pyrans into (*Z*)-pentadienols. The latter ring-opening reaction follows a concerted and not a stepwise pathway (*E2* rather than *E1cb-irrev*, as a novel «common intermediate»-criterion reveals).

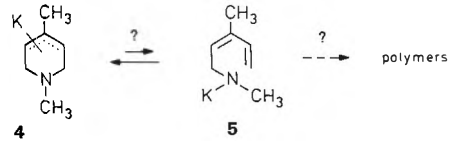
When 1-methyl-cyclohexene is treated consecutively with the butyllithium/potassium *tert*-butoxide («LICKOR») reagent[1] or trimethylsilylmethylpotassium («KQ»)[1] in hexane, fluorodimethoxyborane[2], and hydrogen peroxide, 1-cyclohexenyl-methanol is obtained as the main product (40–65%, depending on the reaction conditions). Only trace amounts of two other regioisomers, 2-methyl-2-cyclohexenol and 3-methyl-2-cyclohexenol were identified (ca. 1.0% and 0.1%, respectively)[3].



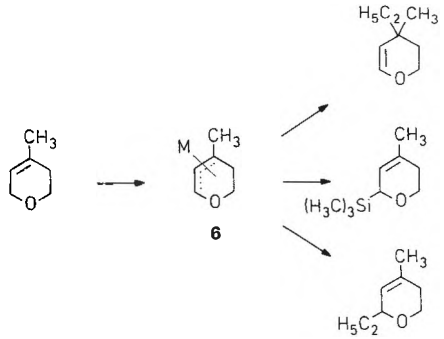
When the structurally related 1,4-dimethyl-1,2,3,6-tetrahydropyridine was submitted to KQ-metalation and the intermediate intercepted with deuterium chloride, methyl iodide or chlorotrimethylsilane, no methyl substitution product was detected. The only volatile compounds that were isolated, besides some starting material, had the electrophile incorporated into the nitrogen-distant allylic methylene group: 1,4-dimethyl-3-[^{2}H]-1,2,3,6-tetrahydropyridine (50%), 1,3,4-trimethyl-1,2,3,6-tetrahydropyridine (10%), and 1,2-dimethyl-3-trimethylsilyl-1,2,3,6-tetrahydropyridine (25%).



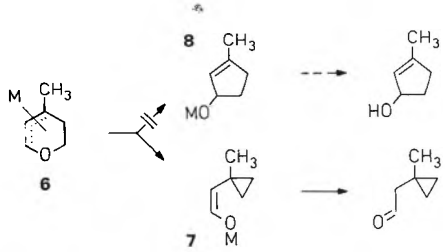
Several factors may be responsible for the poor yields. All tetrahydropyridine derivatives are labile compounds and considerable losses of material were encountered during chromatographic purification. On the other hand, we suspect the organometallic intermediate **4** to be at equilibrium with an open-chain isomer **5**[4]. Strong nucleophiles such as **4** and **5** should cause the latter to polymerize. Actually, substantial amounts of tarry residues were obtained in each case.



Finally, 3,6-dihydro-2*H*-pyran was already known to be metalated preferentially at the oxygen-adjacent allylic position[5]. Its 4-methyl analogue was now found to behave in the same way, although it reacted much more sluggishly. Strong metalating reagents such as butylpotassium[6] or *tert*-butyllithium[7] are required to generate the intermediate **6**. When trapped with chlorotrimethylsilane, **6** afforded 43% of 4-methyl-2-trimethylsilyl-5,6-dihydro-2*H*-pyran as the sole product, while ethyl iodide gave rise to a 3:1-mixture of the regioisomers 2- and 4-ethyl-4-methyl-5,6-dihydro-2*H*-pyran (total yield 45%).



At temperatures above −40°C, intermediate **6** undergoes a Wittig rearrangement to afford the enolate **7** of (1-methylcyclopropyl)acetaldehyde. Like its lower homolog[5], intermediate **6** does not produce any trace of a cyclopentenol derivative **8**. In contrast to the latter case, however, the yield of rearranged product **7** is poor (16%). In addition, starting material (22%) is recovered after hydrolysis and ring opening products (35%; see below) as well as viscous polycondensates are isolated.



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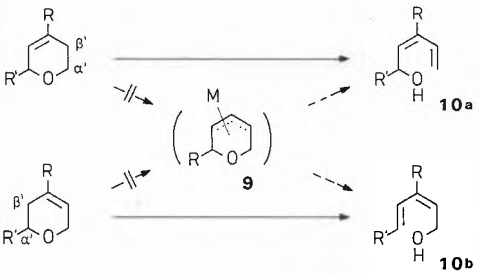
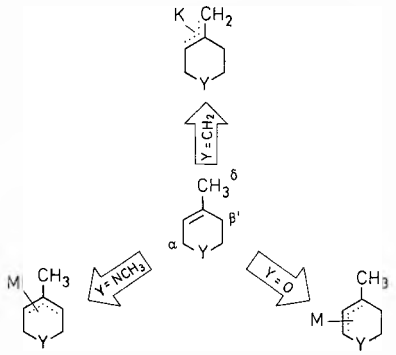
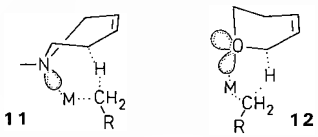
Instead of deprotonating 4-methyl-5,6-dihydro-2*H*-pyran at the allylic α-position, less polar organometallic reagents like ordinary butyllithium and notably lithium diisopropylamide in the presence of potassium *tert*-butoxide («LIDA-KOR»[8]) rather promote its ring-opening to give lithium (*Z*)-3-methyl-2,4-pentadienolate (**10**, R = CH_3, R′ = H) by *concerted* proton abstraction and CO-bond scission at the β′- and α-position, respectively. The alternative step-wise mechanism can be ruled out: 6-ethyl- and 2-ethyl-4-methyl-3,6-dihydro-2*H*-pyran lead to different products, a primary pentadienolate (**10a**) in the first, a secondary one (**10b**) in the second case (R = CH_3, R′ = C_2H_5). If the deprotonation at the β′-position did precede CO scission, both precursors would give rise to the same organometallic intermediate **9** (analogous to **4**!) and hence to the same mixture of ring-opening products.



In conclusion, each member of the investigated series of three isoperiodic analogues exhibits a different kind of reactivity towards metalating agents. The outcome of the reaction with 1-methyl-cyclohexene as substrate may be considered as typical, methyl groups beeing more readily deprotonated than methylene groups[1b]. Moreover, the allylpotassium compound **1** is thermodynamically roughly as stable as isomer **2** and significantly more stable than **3**, since the destabilizing effect of alkyl groups R attached to allyl anionoids increases in this order: $H < R_{endo} \lesssim R_{middle} < R_{exo}$[9].



With 1,4-dimethyl-1,2,3,6-tetrahydropyridine and 4-methyl-3,6-dihydro-2*H*-pyran as substrates hetero-atom effects become dominant. Although it is difficult to evaluate how nitrogen and oxygen atoms may affect the excess electron-density at neighboring *carbon* atoms[10], we assume this interaction to be less important than the complexation of the *metal* M (K or Li) by the nitrogen or the (particularly powerful) oxygen lone pairs. In our view, it is this anchimeric assistance that directs the attack of the metalating reagent to the β′-position (transition state **11**) and, respectively, α-position (transition state **12**).



Typical working procedure: A solution of 11.1 g (10.0 mmol) of 1,4-dimethyl-1,2,3,6-tetrahydropyridine[11] and 10 mmol trimethylsilylmethylpotassium[12] in 20 mL tetrahydrofuran was kept at −75 °C for 25 h before 1.30 g (12.0 mmol) of chlorotrimethylsilane were added. When the mixture had reached room temperature, the solvent was evaporated at 0 °C and the residue thoroughly extracted with pentane. After purification by rapid chromatography under inert gas on alumina and bulb-to-bulb («Kugelrohr») distillation, 0.46 g (25%) of 1,4-dimethyl-3-trimethylsilyl-1,2,3,6-tetrahydropyridine were obtained; *b.p.* 71–73 °C/12 mmHg (giving correct elemental analyses and 360 MHz ^{1}H-NMR spectrum).

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[1] a) M. Schlosser, S. Strunk, *Tetrahedron Lett. 25* (1984) 741, and references therein; b) M. Schlosser, *Angew. Chem. 86* (1974) 751; *Angew. Chem. Int. Ed. Engl. 13* (1974) 701.
[2] G. Rauchschwalbe, M. Schlosser, *Helv. Chim. Acta 58* (1975) 1094.
[3] In addition, the reaction mixture contained 2–11% of benzyl alcohol, apparently arising from double metalation of the hydrocarbon and subsequent elimination of metal hydride followed by a new metalation and again hydride elimination (see also: D. Wilhelm, T. Clark, T. Friedl, P.v.R. Schleyer, *Chem. Ber. 116* (1983) 751). With 1,4,4-trimethyl-cyclohexene as a substrate, of course, no such aromatization is possible. But when we submitted this hydrocarbon to LICKOR- or KQ-metalation in tetrahydrofuran at −50 °C, we found, after borylation and oxidation, besides poor yields (5–7%) of hydroxylated derivatives considerable amounts (3–7%) of 5-(4,4-dimethyl-cyclohexenyl)-1-pentanol, an adduct of the organometallic intermediate to a solvent molecule.
[4] For the reverse reaction, the ring-closure of *N*-metal-ω-alkenyl-amides to give 2-lithio-pyrrolidines or 3-lithio-piperidines, see: M. Newcomb, W.G. Williams, R.A. Reeder, *Tetrahedron Lett. 23* (1982) 4863; M. Newcomb, M.T. Burchill, *ibid. 23* (1982) 4867.
[5] V. Rautenstrauch, *Helv. Chim. Acta 55* (1972) 3064.
[6] See also: R. Lehmann, M. Schlosser, *Tetrahedron Lett. 25* (1984) 745.
[7] See also: F.T. Oakes, R.W. Saylor, J.F. Sebastian, *Synth. Commun. 12* (1982) 607.
[8] C. Margot, M. Schlosser, *Tetrahedron Lett. 26* (1985) 1035.
[9] The allyl moiety is in **1** connected with one R_{middle} and one R_{exo}, in **2** with one R_{middle} and two R_{endo}, and in **3** with one R_{exo} and two R_{endo} substituents.
[10] T. Clark, P.v.R. Schleyer, K.N. Houk, N.G. Rondan, *J. Chem. Soc. Chem. Commun.* (1981) 579; P.v.R. Schleyer, J. Chandrasekhar, A.J. Kos, T. Clark, G.W. Spitznagel, *ibid.* (1981) 882; P.v.R. Schleyer, T. Clark, A.J. Kos, G.W. Spitznagel, C. Rohde, D. Arad, K.N. Houk, N.G. Rondan, *J. Am. Chem. Soc. 106* (1984) 6467.
[11] M. Saunders, E.H. Gold, *J. Am. Chem. Soc. 88* (1966) 3376.
[12] J. Hartmann, M. Schlosser, *Synthesis* (1975) 329; *Helv. Chim. Acta 59* (1976) 453.