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Strained Rings to Assess the "*endo* Preference" of 2-Alkyl Branched 2-Alkenylpotassium Species

Martina Kotthaus and Manfred Schlosser *

Institut de Chimie organique de l'Université
Bâtiment de Chimie (BCh), CH-1015 Lausanne-Dorigny, Switzerland
(Fax ++41 / 21 / 692 39 51)

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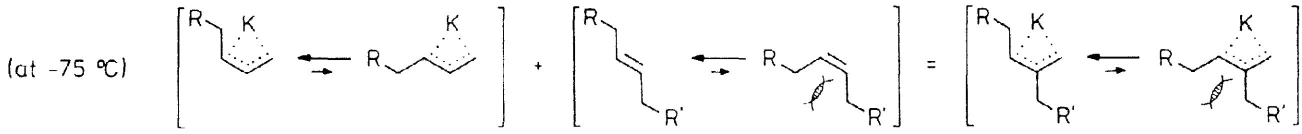
Abstract : Upon deprotonation using trimethylsilylmethylpotassium or butyllithium in the presence of potassium *tert*-butoxide, two allylic organopotassium species (**2**) are generated from the (*E*)-isomeric caryophyllene and the (*Z*)-isomeric isocaryophyllene. Torsional equilibration occurs slowly at -50 °C (in tetrahydrofuran) and rapidly at 0 °C (in hexane) to afford *endo*-**2**/*exo*-**2** mixtures of about 95 : 5 (as evidenced by the isomeric composition of the trapping products **3**). The relative thermodynamic stabilities of the two stereoisomeric organometallic intermediates can be derived by mere superposition of ring-strain differences and the "*endo* preference" of open-chain 2-alkyl-2-alkenylpotassiums.

The thermodynamic preference for the *endo* stereoisomers of allylic potassium intermediates [1, 2] (the origin of which appears to be an electronic discrimination against the *exo* isomers [3]) is reflected by (*Z/E*) product ratios of about 125 : 1 (ΔG° 1.9 kcal/mol) in the case of 2-butenylpotassium and 15 : 1 (ΔG° 1.1 kcal/mol) in the case of straight-chain 2-alkenylpotassiums [3], both in tetrahydrofuran at -75 °C. The attachment of an additional alkyl group at the 2-position, the nodal point of the allyl entity, causes little harm to the *endo* species but represents an additional disadvantage for the *exo* isomer. At first sight, the steric repulsion exerted by two neighboring alkyl groups in branched 2-alkenylpotassiums and in simple internal alkenes should not differ very much, hence average 0.8 kcal/mol. This free energy difference corresponds to a (*Z/E*) ratio of 1 : 75, if the equilibrium is established. Assuming additivity of the factors affecting the relative stabilities of allylic organopotassium isomers, one expects *endo/exo* equilibrium ratios of 10^3 and 10^2 for 2-alkyl substituted 2-butenylpotassiums and their higher homologs, respectively. The agreement with estimates based on experimental data [3], 500 and 50, is amazingly good.



R = H, R' = alkyl	125 : 1	7.5 : 1	937.5 : 1
R = R' = alkyl	15 : 1	7.5 : 1	112.5 : 1

In order to submit the additivity postulate to a further test, we have selected caryophyllene (*trans*-caryophyllene, β-caryophyllene), an ubiquitous natural sesquiterpene, and the isomeric isocaryophyllene (*cis*-caryophyllene) as model compounds. The deprotonation [4] of these olefinic substrates, in particular of the (*Z*)-isomer proceeded only sluggishly under the conditions applied. The organometallic intermediates were trapped by consecutive treatment with fluorodimethoxyborane [5] and hydrogen peroxide; the yields of (*E*)- and (*Z*)-"caryophyllen-14-ol" (11,11-dimethyl-8-methylenebicyclo[7.2.0]undec-4-ene-4-methanol) [6 - 9] and the amount of recovered starting material were determined by gas chromatography [10]. In tetrahydrofuran at

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-75 °C, the metalated (*E*)-isomer retained its configuration to a large extent. The torsional isomerization was accelerated at -50 °C and went to completion in hexane at 0 °C, despite the heterogeneous medium. The metalation of the isocaryophyllene required minimum reaction temperatures of around -50 °C. Under these circumstances, inevitably isomerization occurred giving rise to (*Z/E*) organopotassium mixtures of approximately 95 : 5 (see Table).

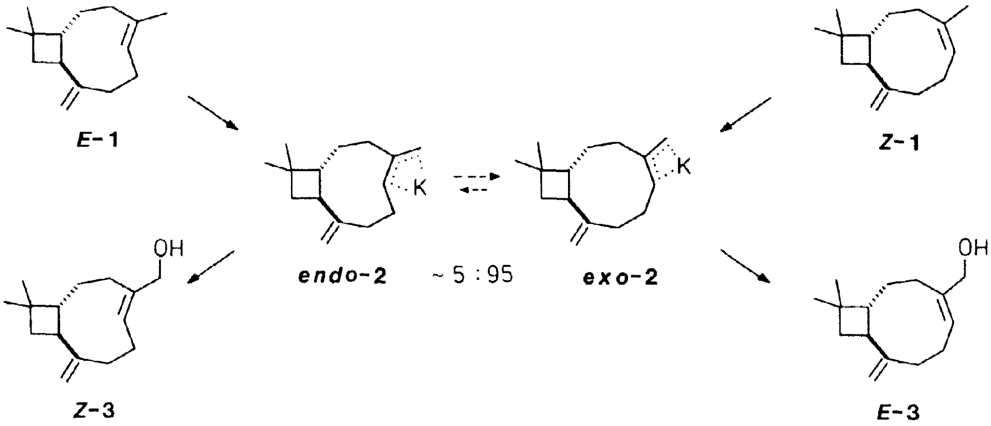

Table. Metalation of caryophyllene and isocaryophyllene followed by borylation and oxidation : yields and (*Z/E*) ratios of the caryophyllenols formed depending on the reaction conditions.

sub-strate	reagent [a]	reagent conc	solvent [b], time, temp.	yield of **3**	*Z*-**3**/*E*-**3**
Z-**1**	$KCH_2Si(CH_3)_3$	(1.0 M)	THF, 20 h -75 °C	0%	-
Z-**1**	$KCH_2Si(CH_3)_3$	(1.0 M)	THF, 6 h -50 °C	15%	5 : 95
Z-**1**	$KCH_2Si(CH_3)_3$	(0.4 M)	THF, 20 h -60 °C	30%	5 : 95
Z-**1**	LIC-KOR	(0.5 M)	HEX, 20 h 0 °C	< 2%	-
Z-**1**	LIC-KOR	(0.8 M)	HEX, 60 h +25 °C	10%	2 : 98
E-**1**	$KCH_2Si(CH_3)_3$	(0.4 M)	THF, 20 h -50 °C	49%	8 : 92
E-**1**	$KCH_2Si(CH_3)_3$	(0.5 M) [c]	THF, 6 h -50 °C	49%	60 : 40
E-**1**	LIC-KOR	(0.3 M)	THF, 2 h -75 °C	10%	98 : 2
E-**1**	LIC-KOR	(1.0 M)	HEX, 2 h 0 °C	43%	18 : 82
E-**1**	LIC-KOR	(1.0 M)	HEX, 20 h 0 °C [d]	56%	6 : 94

a) LIC-KOR means a 1 : 1 mixture of butyllithium ("LIC") and potassium *tert*-butoxide ("KOR"); trimethylsilylmethylpotassium was prepared from the mercury compound [11, 12]. The reagents were employed in equimolar quantities relative to the substrate, unless stated otherwise. The concentration indicated refers to the metalation reagent. b) THF = tetrahydrofuran; HEX = hexane fraction petroleum ether. c) The metalation reagent was employed in a two-fold excess. d) The reaction mixture was diluted with twice the volume of precooled THF before, after 1 h at -75 °C, the electrophile was added. - When repeating the reaction twice, yields of 57% and 62% (*Z/E* ratios 7 : 93 and 5 : 95) were found. However, the yield dropped to 34% (*Z/E* 5 : 95) when the metalation time was shortened to 4 h at 0 °C.

Under conditions of full equilibration, the *Z*-**3**/*E*-**3** ratios, which correlate with *endo*-**2**/*exo*-**2** ratios, reproducibly approximate 95 : 5. At -50 °C, this corresponds to a free energy difference of 1.3 kcal/mol. The free energy difference between caryophyllene (*E*-**1**) and isocaryophyllene (*Z*-**1**) should amount to some 3.5 kcal/mol, *i.e.*, typically [13] a bit less than the enthalpy difference which has been calculated to be 3.6 - 3.8 kcal/mol [14, 15]. When 1.9 kcal/mol (= 1.1 + 0.8 kcal/mol; see above) are deducted from this number to account for the *endo* preference of a long-chain 2-alkyl-2-alkenylpotassium species, one obtains a free energy difference of 1.6 kcal/mol which corresponds to an *endo*-**2**/*exo*-**2** ratio of 36 : 1 at -50 °C. Again the agreement with the experimentally determined *endo*/*exo* ratios (19 : 1; ΔG° 1.3 kcal/mol; see above) is quite satisfactory. Apparently, the structural deformation imposed by the CCC angle widening upon deprotonation of allylic units [16] does not significantly alter the relative stabilities of the two isomeric caryophyllene skeletons.

Although the accuracy of the presently collected data should not be overvalued, a quantitative parametrization of substituent effects on the thermodynamic stability (*i.e.*, basicity) of allylmetal species begins to emerge. This approach makes predictions both more meaningful and more challenging.

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8. Physical properties and elementary analysis of (*E*)-11,11-dimethyl-8-methylenebicyclo[7.2.0]undec-4-ene-4-methanol (*E*-**3**) : Treibs, W.; Lossner, G.; *Liebigs Ann. Chem.* **1960**, *634*, 124 - 131. - ^{1}H-NMR ($CDCl_3$, 400 MHz) [7] : δ 5.53 (1 H, t, *J* 7.8), 4.84 (1 H, d, *J* 1.8), 4.75 (1 H, m), 4.03 (2 H, s), 2.51 (1 H, q, *J* 9.1), 2.2 (6 H, m), 1.82 (1 H, ddd, *J* 11.4, 9.1, 3.9), 1.73 (1 H, dd, *J* 10.8, 8.7), 1.5 (4 H, m), 1.00 (3 H, s), 0.96 (3 H, s).
9. (*Z*)-11,11-Dimethyl-8-methylenebicyclo[7.2.0]undec-4-ene-4-methanol (*Z*-**3**) : n_D^{20} 1.5130. - ^{1}H-NMR : ($CDCl_3$, 400 MHz) [7] : δ 5.45 (0.4 × 1 H, dd, *J* 11.1, 5.5), 5.34 (0.6 × 1 H, symm. m), 5.06 (0.6 × 1 H, s), 4.93, (0.4 × 1 H, s), 4.88 (0.4 × 1 H, s), 4.74 (0.6 × 1 H, s), 4.16 (0.4 × 1 H, d, *J* 12.2), 4.11 (0.6 × 1 H, d, *J* 11.8), 3.93 (0.4 × 1 H, d, *J* 12.2), 3.67 (0.6 × 1 H, d, *J* 11.8), 2.4 (3 H, m), 2.1 (3 H, m), 1.4 (7 H, m), 0.97 (3 H, s), 0.96 (0.4 × 3 H, s), 0.95 (0.6 × 3 H, s). - Analysis : calc. for $C_{15}H_{24}O$ (220.35) calc. C 81.76, H 10.98; found C 81.65, H 10.99%. - Like the alcohol *Z*-**3**, β-caryophyllene (*E*-**2**) exists as two atropisomeric conformers, although in the ratio of 3 : 1 rather than 3 : 2 as in the former case. The "ansa-flip" of *E*-**2** requires an activation energy of 16 (± 1) kcal/mol as evidenced by the coalescence of the olefinic signals in the temperature range between + 45 and + 55 °C. - ^{1}H-NMR (D_3C-C_6D_5, 400 MHz) of *E*-**2** : δ 5.40 (0.75 × 1 H, dd, *J* 10.2, 5.2), 5.26 (0.25 × 1 H, d, *J* 11.0), 5.08 (1 H, d, *J* 0.8), 4.95 (0.25 × 1 H, s), 4.92 (0.75 × 1 H, s), 2.2 (7 H, m), 1.78 (3 H, symm. m), 1.67 (0.25 × 3 H, s), 1.64 (0.75 × 3 H, s), 1.5 (2 H, m), 1.09 (0.75 × 3 H, s), 1.07 (0.25 × 3 H, s), 1.03 (3 H, s).
10. Conditions : 30 m capillary, silicon rubber DB-1701, 80 °C [10 min, then 10 °C increase/min] → 200 °C [10 min]; 2 m packed glass column, 8% Carbowax 20M, 80 °C [10 min, then 10 °C increase/min] → 180 °C [10 min]; internal standard : undecane.
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