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STUDIES ON THE STEREOCHEMISTRY OF REDUCTION REACTIONS ON 10-R SUBSTITUTED *trans* DECAL-2-ONES.

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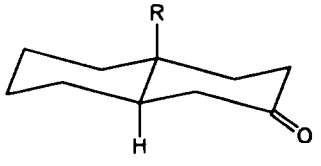
Abstract: Relative rates k_{ax} and k_{eq} of reduction reactions of title compounds (R=H, Me, CO_2Et, Cl) have been measured in three different reaction conditions ($LiAlH_4$, $LiEt_3BH$, $NaBH_4$). We found that k_{eq} decreases as the substituent electronegativity increases when lithium reactants are used and that k_{ax} increases as the substituent electronegativity increases when sodium reactant is used. The synthesis of *trans* and *cis* 10 chloro-decal-2-ones is also described.

Introduction

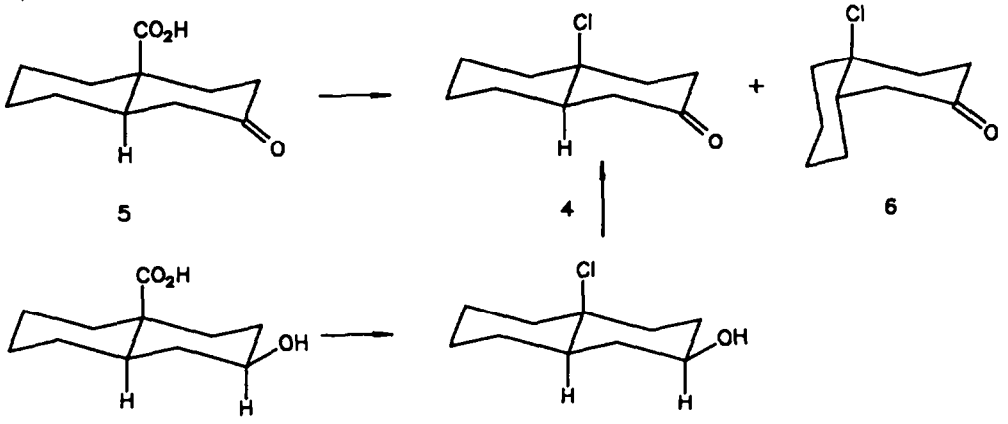
The discussion concerning factors influencing diastereoselection of addition reactions to C=O bond is very lively [1]. In particular, a matter of great interest is to focus and clarify in which way substituents transmit their influence to the reacting site. We are currently carrying on in our lab experiments whose aim is to explore the effects exerted by remote substituents on the reactivity and the stereochemistry of a carbonyl group in cyclohexane systems. In a recent work [2] on addition reactions to a carbonyl group we pointed out that it is sometimes hardly possible to infer mechanistic interpretation only using changes in the stereochemical ratio (k_{ax}/k_{eq}) obtained while varying the substituents; more precise informations can be drawn from kinetic experiments' data since they allow to distinguish what happens on the two sides of the ring. Our data showed that stereochemical product ratio changes (k_{ax}/k_{eq}) sometimes originate from uneven increase (or decrease) of both k_{ax} and k_{eq} and sometimes from their divergent change. In the latter case we concluded that the nucleophilic vs. electrophilic nature of the reaction is different for the axial and equatorial side of the molecule. We extended our researches to reduction reactions and in the present paper we describe the results obtained in reactions with: 1) $LiAlH_4$ in Et_2O; 2) $LiEt_3BH$ in THF; 3) $NaBH_4$ in i-PrOH on the following compounds: *trans* decal-2-one (**1**); *trans* 10-methyl decal-2-one (**2**); *trans* 10-carbethoxy decal-2-one (**3**); *trans* 10-chloro decal-2-one (**4**), namely on rigid substrates having their 10-R substituents in axial conformation.



R=H (1); R=Me (2); R=CO_2Et (3); R=Cl (4)

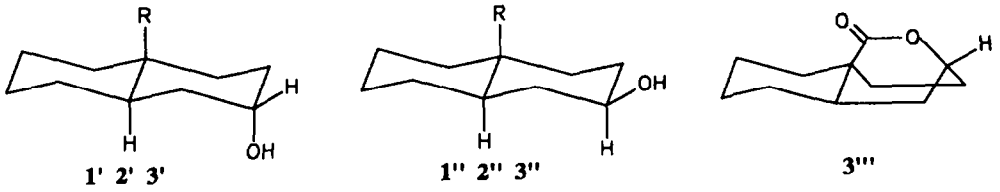
Results

Starting materials - Synthesis of compounds **1,2** and **3** was performed according to known methods [3,4]. *trans* 10-chloro decal-2-one (**4**) is not known; all our attempts to prepare it using the general method of Robinson annelation[5] gave complex reaction mixtures and very low yields of the desired product. We had better results with the halodecarboxylation reaction[6]: *trans* 10-carboxy decal-2-one (**5**) (obtained by alkaline hydrolysis of ketoester **3**) was decarboxylated in the presence of a large excess of N-chlorosuccinimide and of a radical initiator, giving a mixture of two chlorinated species[7], corresponding respectively to *trans* 10-chloro-decal-2-one (**4**) and *cis* 10-chloro-decal-2-one (**6**). The total yield was 65%; the *trans* isomer has been obtained as the main product (82%).



Structures **4** and **6** were assigned on the basis of ^1H NMR spectra[*]:
for the *trans* isomer **4**: H_{1ax}, δ =2.41, H_{1eq}, δ =2.07; $J_{1ax,1eq}$=13.8; $J_{1ax,9}$=13.2;
for the *cis* isomer **6**: H_{1ax}, δ =3.04, H_{1eq}, δ =2.03; $J_{1ax,1eq}$=14.0; $J_{1ax,9}$=5.9.

A similar synthetic procedure[8] on *trans* 10-carboxy-decal-2-ol (**7**), gave only *trans* 10-chloro-decal-2-ol (**8**) in good yield (77%). **8** was converted to **4** by Jones oxidation. In this case we accomplished the preparation of **4** with a two-step procedure, but with higher yield and without any lack of the stereochemical features of the starting bicyclic compound (see experimental for details).



* See a forthcoming paper for complete NMR analysis of **4** and **6**.

Reaction products - In all the above mentioned reaction conditions we obtained alcohols **1'** and **1"**, already known [9,10], from ketone **1**; alcohols **2'** and **2"**, already known [10,11], from ketone **2**; alcohols **3'** and **3"** and lactone **3'"** from ketoester **3**; chloroalcohol **8** from chloroketone **4**.

We assigned structure **3'** to the alcohol with a HO-C-H proton signal appearing at lower field as a single broad band as expected for an equatorial proton. The same signal in compound **3"** is at higher field as a well defined multiplet in agreement with this proton being in axial conformation. Accordingly the ^{13}C NMR spectra of **3'** shows the C(2) signals at higher field with respect to the same signal in compound **3"**. The chloroalcohol derived from the reduction of chloroketone **4** is identical with that obtained from the hydroxyacid **7** by chlorodecarboxylation reaction, that is **8**.

Reaction orders. Relative axial and equatorial reactivities - In all the above mentioned reaction conditions we determined whether compounds **1**, **2**, **3** and **4** have the same reaction order. We performed three competitive reaction sets on equimolecular mixtures of compounds **1**, **2**, and **3** and of compounds **1** and **4**. Because of peaks overlapping in the GLC analysis it was not possible to perform competition experiments in which all the four compounds **1**, **2**, **3** and **4** were present at the same time .Each reaction set differed from one another in the concentration of the added reducing agent which was respectively 0.1, 0.02 and 0.01 N. The relative reaction rates k_1, k_2, k_3 and k_4 have been obtained by GLC determination of the reaction yields (see after). They were computed in the hypothesis that all reactions are first order in ketone and same order in reducing agent. The variations of the ratios $k_1/k_2/k_3/k_4$ varying the concentrations of the added reactant were not significative as shown in Table 1. They show that the reaction order is always the same for compounds **1**, **2**,**3** and **4**.

Table 1: Relative rates of reduction reactions on decal-2-ones (**1-4**)

Reaction conditions	Run *)	$k_1/k_2/k_3/k_4$
	a	1/0.96/1.1/0.9
$LiAlH_4/Et_2O$	b	1/0.89/1.1/0.98
	c	1/0.92/1.1/1
	a	1/0.82/0.85/0.6
$LiEt_3BH/THF$	b	1/0.84/0.79/0.76
	c	1/0.76/0.79/0.76
	a	1/0.86/2.2/5.0
$NaBH_4$/i-PrOH	b	1/0.88/2.4/5.2
	c	1/0.84/2.4/5.2

*) Concentration of the added reactant: run a 0.1 N, run b 0.02 N, run c 0.01 N.

The calculations were performed using GLC examination of the reaction mixtures. We measured the areas of starting materials and products; each area was divided (*) by the corresponding molecular weight and the obtained values were used for calculating the yields of each competing reaction. Although yields varied from run to run, the material balance (i.e. the sum of starting and final products) was always greater than 90% of the starting material. We used only data from reactions with yields ranging from 15 to 85% to compute relative rates.

The experimental data are collected in Table 2 as a mean of at least five separate experiments. Relative rates k_{ax} and k_{eq} were computed taking as one k_{ax} of compound **1**.

Although we have too few points to attempt any LFER, we put columns in Table 2 in order of increasing electronegativity (σ_I) of substituents, that is: H=0, Me=0.03, CO_2Et=0.30, Cl=0.47 (**).

Table 2 : Stereochemical product ratios and axial and equatorial relative rates of reduction reaction of decal-2-ones (**1-4**).

Columns	1	2	3	4	5	6	7	8	9	10	11	12	13
Reactant	Stereochemical product ratios (k_{ax}/k_{eq})				Overall rates ratios	Relative rates k_{eq}				Relative rates k_{ax}			
	1''/1'	2''/2'	(3''+3''')/3'	8	$k_1/k_2/k_3/k_4$	1	2	3	4	1	2	3	4
$LiAlH_4/Et_2O$	6.2	8.9	19	∞	1/0.95/1.10/1.0	0.16	0.11	0.06	0	1	0.98	1.14	1.2
$LiEt_3BH/THF$	2.4	4.7	28.3	∞	1/0.81/0.85/0.71	0.42	0.20	0.04	0	1	0.94	1.16	1.0
$NaBH_4$/i-PrOH	7.4	9.1	15	∞	1/0.86/2.24/5.2	0.13	0.096	0.15	0	1	0.87	2.37	6.0

Discussion

We can draw some observations from data of Table 2.

Ratios k_{ax}/k_{eq} increase with the electronegativity of the substituent in all reaction conditions. These changes although homogeneous hide different phenomena for lines 1 and 2 on one side and line 3 on the other as it will be clear in examining values from columns 6 to 13. Changes from column 6 to column 7, although of

(*)Preliminary experiments showed that GLC responses of compounds (**1-4**) on one hand and the products of their reduction reactions on the other, were very close to each other. Thus no correction was introduced at this point

(**) Kwart, H.; Takeshita,T. *J. Am. Chem. Soc.* **1962**, *84*,, 2833 and references therein.

different size, are homogeneous for all reaction conditions. Steric crowding by the axial substituent at the ring junction can operate only on the equatorial side of the π_{co} bond. This effect, if any, can be observed only for the methyl substituent (changes from column 6 to column 7). For the CO_2Et substituent, steric and electronic effects cannot be separated from one another. Owing to the smaller conformational energy of the ester group with respect to the methyl group, one can argue that the further decrease from column 7 to column 8 is electronic in origin.

With lithium reactants,indipendently of the used solvent, (lines 1 and 2, columns 6, 7, 8 and 9) k_{eq} values decrease systematically as the substituent's electronegativity increases. This is peculiar for an electrophilic reaction and can be explained by an O...Li bond more developed in the transition state than the C...H bond. Relative rates k_{ax}, deriving from attack on the other face of the molecule (lines 1 and 2, columns 10, 11, 12 and 13) don't show sharp variations, suggesting a less polar, more "square" transition state. The axial attack transition state turns out again to have polar character in the last reaction condition (line 3, columns 10, 11, 12 and 13). This time k_{ax} increases when substituent's electronegativity increases in keeping with a reaction nucleophilic in nature and with the O...Na bond less developed in the transition state than the C...H bond.

On the equatorial side of the molecule (line 3, columns 6, 7, 8 and 9) the sensitivity to substituent's effects is scarce and not systematic. We suggest that, in analogy with lithium reactants, the O...Na bond becomes shorter on this side of the molecule; the transition state is again more "square" and less polar. The common feature of all reactions is the vanishing of the equatorial reactivity when the substituent is chlorine (column 4)(*). Chlorine is a too small substituent to exert any steric crowding from a so large distance to the equatorial attack reaction. Our data therefore suggest that the MO phase amplitude of the π_{co} is highly distorted toward the axial side under the effect of the axial chlorine atom on the other side of the molecule. On the other hand values of the columns 10 (11), 12 and 13 (line 3) suggest that also π^*_{co} should increase in phase amplitude on the axial side as the substituent electronegativity increases.

Experimental

IR spectra were recorded on a Perkin Elmer 457 apparatus. ^1H and ^{13}C NMR were recorded on a Varian XL 300 apparatus. MS spectra were recorded on a MS-HR Kratos MS-80 (R.P.=15000) for exact mass determination and on GC-MS HP 59970 Chemstation Mass Selective Detector connected with a HP 800 gaschromatograph. The relative intensities of the peaks (in parentheses) are referred to the most intense one taken as 100%. HPLC separations were carried out on a Violet apparatus using a Microporasil 30 cm, 7.9 mm i.d. Waters column. GLC analyses were carried out on a Carlo Erba HRGC Mega Series 5300 apparatus using a 25m, 0.4 mm i.d. fused silica capillary column (stationary phase Carbowax 20 M), H_2 flow= 0.5 ml/

(*) Of course figures "zero" in column 9 simple mean "impossible to measure" with the employed method (GLC).

min. We report, in sequence, the elution order of compounds from each mixture and the most suitable temperature conditions (in parentheses T_{oven}, $T_{inj} = T_{det}$) of respectively: **1, 1', 1"** (85, 220°); **2, 2',2"** (85, 220°); **3, 3', 3"** and **3'"**(110, 220°); **4, 8** (180, 220°).

Starting materials

Compound **1** was synthesized according to described methods [3]. Compound **2** was synthesized according to the method of Dreiding and coworkers [4] and to Monson [3]. Compound **3** was synthesized according to the method of Dreiding and coworkers [4]. The purity of each compound was checked by GLC. Compound **5** was obtained by alkaline hydrolysis of the corresponding ethyl ester **3**[4].Compound **7** was also obtained by alkaline hydrolysis of the corresponding ethyl ester [4].

Synthesis, isolation and characterization of compounds 4, 6 and 8

Compounds **4** and **6** were synthesized by chlorodecarboxylation of **5** according to the method of Grob and coworkers [7]. The reaction mixture (65%) was separated by HPLC chromatography, using hexane/ethyl acetate=9/1 as eluant (ϕ= 3.5 ml/min); we obtained, in the order, compound **6** (40 mg, 18%) and compound **4** (180 mg, 82%), whose purities were checked by GLC analyses.

For compound **4**: m.p. 30-31°C; MS m/e: 41(88%), 42(24), 43(10), 51(24), 52(15), 53(56), 54(17), 55(52), 65(29), 66(14), 67(80), 68(21), 77(40), 78(15), 79(87), 80(29), 81(88), 82(11), 91(30), 93(62), 94(22), 95(57), 96(96), 107(23), 108(100), 109(30), 122(25), 150(16), 151(67), 186(44), 187(5, M+1), 188(15, M+2). HRMS M^+: 186.0811 (theoretical for $C_{10}H_{15}ClO$ 186.0809). IR spectra showed ν_{max}(CCl_4) cm^{-1}: 2940s, 2857m, 1714s, 1443m, 1358w, 1349w, 1273w, 1256w,1169m, 1147w, 1130w, 1031w, 835m,548w.

For compound **6**: m.p. 33-35°C; MS m/e: 41(73%), 42(21), 51(20), 52(14), 53(49), 54(13), 55(41), 65(24), 66(12), 67(69), 68(19), 77(37), 78(15), 79(73), 80(25), 81(72), 82(11), 91(28), 93(67), 94(22), 95(54), 96(79), 107(27), 108(100), 109(23), 122(24), 150(31), 151(73), 186(50), 187(7, M+1), 188(16, M+2). HRMS M^+: 186.0812 (theoretical for $C_{10}H_{15}ClO$ 186.0809). IR spectra showed ν_{max} (CCl_4) cm^{-1}: 2940s, 2860s, 1705s, 1145m, 1385m, 1350w, 1260m, 1175w, 950w, 930w, 865m.

Compound **8** was obtained by chlorodecarboxylation in CH_3CN of **7**, according to the method of Kochi [8]; the reaction mixture was purified by HPLC (hexane/AcOEt=6/4, ϕ=3.5 ml/min), affording compound **8** in 77% yield.

For compound **8**: m.p. 75-77°C; MS m/e: 41(100%), 42(139), 43(34), 44(24), 51(20), 52(12), 53(479, 54(16), 55(50), 57(25), 65(28), 66(13), 67(91), 68(16), 69(11), 70(12), 77(42), 78(18), 79(81), 80(28), 81(54), 82(11), 83(21), 91(55), 92(37), 93(67), 94(33), 95(89), 96(40), 97(14), 105(20), 106(16), 107(17), 108(49), 109(34), 110(22), 119(30), 123(149),130(13), 134(49), 135(82), 152(61), 153(14), 188(4), 190(2, M+2).HRMS M^+188.0968 (theoretical for $C_{10}H_{17}ClO$ 188.0967).IR spectra showed ν_{max} (CCl_4) cm^{-1} : 3620m, 3400-3300 broad, 2940s, 2865s, 1450m, 1370w, 1260m, 1140w, 1100m, 1085m, 1050s, 1030s, 965w, 935w, 870w, 840w, 615 w. ^1H NMR showed the following peaks δ ($CDCl_3$) 3.6 m (1 H), 2.1-0.8 m (14 H). ^{13}C NMR δ ppm from TMS: 21,62, 25.39, 28.56, 31.04, 37.95, 40.08, 40.84, 44.22, 70.08, 76.61.

Preparation of reagents

Solns. of $NaBH_4$/i-PrOH were prepared adding 0.388 gr. of $NaBH_4$ to 1 l of i-PrOH; just before use, this soln. was titrated by sampling the supernatant clear soln.. Solns. of $LiAlH_4$ were prepared adding 0.76 gr. of $LiAlH_4$ to 200 cc. of anhydrous ether in a dry container under N_2 flow. This soln. was also titrated before use[12]. $Li(Et)_3BH$ (Janssen) (1 M) in THF was used as such.

Reactions

Reactions with $NaBH_4$/i-PrOH were carried out in a 25 ml flask equipped with a magnetic stirrer and a dropping funnel, adding the reducing agent (0.1 M) to a soln. 0.1 M of each substrate. Reactions with $LiAlH_4/Et_2O$ and $Li(Et)_3BH$/THF were carried out as described below in a two necked flask equipped with gas-inlet, dropping funnel and a magnetic stirrer. The apparatus was carefully dried by flaming it under N_2 flow.

The reaction mixtures were hydrolised after 10 min. with NaCl s.s., extracted three times with Et_2O and two times with benzene. The combined extracts were washed with NaCl s.s., dried over Na_2SO_4, filtered and evaporated. Analyses of reaction mixtures by GLC were carried out as described, using n-hexadecane as GLC standard for compound **1**, n-heptadecane for compound **2**, and n-eicosane for compounds **3** and **4**.

Competition experiments

Three flasks (10, 50 and 100 ml) were equipped with magnetic stirrer and connected by means of a three-point star-rotating receiver to a graduated burette, gas inlet and $CaCl_2$ tube. The apparatus was carefully dried by flaming it under N_2 flow (except for reactions carried out with $NaBH_4$/i-PrOH). Each flask contained an equimolecular mixture of **1**, **2** and **3** or of **1** and **4** (0.3 mmoles in all) dissolved in three ml of the suitable solvent. The graduated burette was filled with the suitable, conveniently diluted reactant and the stoichiometric amount of it was added under vigorous stirring to the substrates' mixture. The reaction mixtures were then hydrolised and worked up as described and finally examined by GLC in order to measure the relative areas of products and starting materials.

Isolation and characterization of compounds 3', 3'' and 3'''.

A reaction was performed using standard procedure adding the reducing agent (i.e. $NaBH_4$ in i-PrOH) to compound **3** (500 mg) until complete disappearence of the starting compound (revealed by GLC). After working up, the mixture of reaction products was chromatographed by HPLC using Hexane/EtOAc 80/20 as eluant (ϕ= 5.5 ml/min). We obtained, in the order, lactone **3'''** (100 mg), alcohol **3'** (35 mg) and alcohol **3''** (190 mg). The purity of **3'**, **3''** and **3'''** was tested by GLC.

For compound **3'**: b.p. 134-136°C/5 mm Hg; MS m/e: 67(39%), 79(26), 93(25), 134(36), 135(100), 208(10), 226(1.8).HRMS M^+ :226,1564 (theoretical for $C_{13}H_{22}O_3$ 226,1568). IR spectra showed ν_{max} (film) cm^{-1}: 3450-3340s, 2960s, 2870s, 1735s, 1715sh, 1460m, 1380m, 1260w, 1195m, 1145m, 1115m, 1050m, 970m, 930w, 850w. ^1H NMR showed the following peaks $\delta(CDCl_3)$: 4.1q, broad, (3H ,$OCOCH_2CH_3$; HO-C-H); 1.2t, (3H ,$OCOCH_2CH_3$); 2.2-1.4m, (16H).^{13}C NMR in $CDCl_3$ δ ppm from TMS :14.28, 23.52, 26.60, 28.85, 30.15, 31.76, 36.50, 38.23, 48.36, 59.59, 63.94, 66.66 (H-C-OH_{ax}), 175.47.

For compound 3'': b.p. 110-112°C/5 mm Hg; MS m/e: 55(24%), 67(48), 79(33), 81(20), 91(20), 93(31), 134(58), 135(100), 208(4), 226(17). HRMS M^+: 226.1559 (theoretical for $C_{13}H_{22}O_3$ 226.1568). IR spectra showed ν_{max} (film) cm^{-1}: 3440-3320s, 2960s, 2870s, 1735s, 1720sh, 1460m, 1375m, 1330m, 1150m, 1110m, 1030m, 995w, 970w, 910w, 845w. ^1H NMR showed the following peaks δ ($CDCl_3$): 4.1q,(2H ,$OCOCH_2CH_3$); 3.6m, (1H ,HO-C-H); 1.2t, (3H ,$OCOCH_2CH_3$); 2.1-1m, (16H). ^{13}C NMR δ ppm from TMS: 14.26, 23.36, 26.32, 29.03, 32.80, 36.43, 37.91, 38.87, 43.31, 47.50, 59.72, 70.95 (H-C-OH_{eq}), 175.13.

For compound 3''': b.p. 133-134°C/5 mm Hg; MS m/e: 53(30%), 55(30), 67(70), 77(31), 79(82), 80(34), 81(28), 91(33), 93(55), 94(79), 95(100), 107(45), 108(24), 121(50), 136(71), 180(50), 181(6). HRMS M^+:180.1146 (theoretical for $C_{11}H_{16}O_2$ 180.1150). IR spectra showed ν_{max}(film) cm^{-1} :2950s, 2880s, 1760sh, 1750s, 1470sh, 1455m, 1380w, 1225m, 1150m, 1115m, 1100m, 1080m, 1025m, 990m, 970m, 905w, 860w. ^1H NMR showed the following peaks δ ($CDCl_3$): 4.58s, (1H ,OC-O-H); 2.1-0.9m, (15H). ^{13}C NMR δ ppm from TMS: 22.41, 25.55, 25.65, 31.69, 31.81, 33.93, 34.09, 38.58, 42.03, 74.77, 177.06.

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