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STUDIES ON THE STEREOCHEMISTRY OF ADDITION REACTIONS ON CYCLOHEXANONES VII. THE EFFECT OF THE AXIAL ESTER GROUP ON THE REACTIVITY OF trans 2-DECALONES.

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Abstract - Relative rates k_{ax} and k_{eq} of addition reactions to title compounds have been measured in eight different reaction conditions. The effect of changing the axial substituent in the position 3 and 4 to the carbonyl group from -H to -Me and $-CO_2R$ is described. Data show that stereochemical product ratios (k_{ax}/k_{eq}) changes originate sometimes from uneven increase (or decrease) of both k_{ax} and k_{eq} and sometimes from their divergent change. This last case points to a different nucleophylic vs. electrophylic character of the axial and equatorial attack.

Inspite of the large experimentation devoted to the effects of substituents on reactivity much remains to be understood about their behaviour in the cyclohexane system and about the way they transmit their influence to the reacting site[§]. In fact most of the results that appeared in the literature deal with the ax/eq attack ratio changes with changing the substituent.

Few kinetic data allow to distinguish the effects a substituent change produces on the axial and on the equatorial side of the ring. And, what is more, the flexibility of the system seldom gives firm grounds about the equatorial or the axial conformation of the substituent itself in the reaction transition state; the choice of the particular reaction condition can be crucial with this respect, mainly so when the substituent is a polar one. Examples of this kind relative to $NaBH_4$ reduction[2] and addition reactions[3] on cyclohexanones are known.

In the present paper we describe the results we obtained for reactions of:
1) MeMgI in Et_2O and 2) in C_6H_6; 3) Me_3Al in C_6H_6 in the ratio 1:1 to the ketone and 4) in the ratio 3:1 to the ketone; 5) MeLi in Et_2O at 20°C and 6) at -78°C; 7) $Me_2CuLi/MeLi$ in Et_2O; 8) $Me_2Zn/2MgI_2$ in Et_2O, with:
i) trans decalone-2 (1); ii) trans 10-methyl decalone-2 (2); iii) trans 10-carbethoxy decalone-2 (3) and iiii) trans 10-carbomethoxy decalone-3 (4).

RESULTS

Reaction products

The products of the addition reactions are invariably:
from ketone 1, alcohols 1' and 1" already known[4]; from ketone 2 alcohols 2' and 2" already known[5], from ketoester 3, alcohols 3' and 3" and lactone 5 (see experimental for their identification and spectral characteristics); from ketoester 4, lactone 6 (see experimental for its identification

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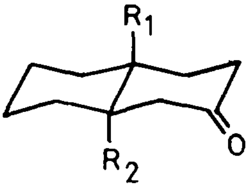
§ A discussion, based on orbital control, of the effects a substituent in the 4 position exerts on the reactivity of a cyclohexanone can be found in a recent paper by Cieplak[1].

and spectral characteristics).



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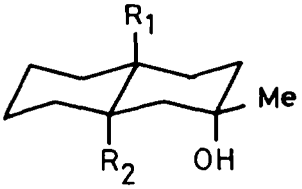

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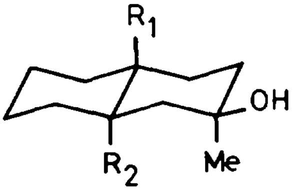

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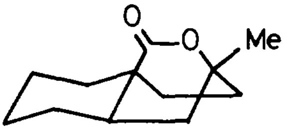

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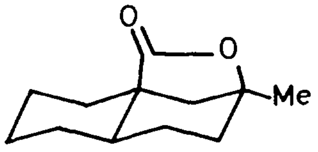

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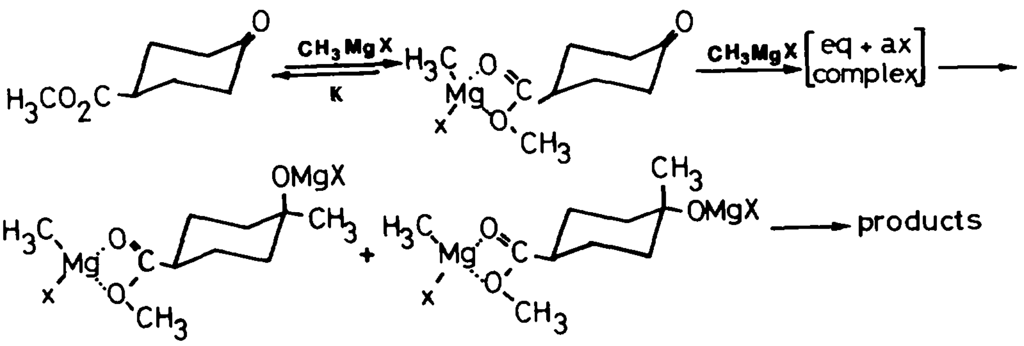
1,1',1"; (R_1=R_2=H); 2,2',2"; (R_1=Me; R_2=H); 3,3',3"; (R_1=CO_2Et; R_2=H); 4; (R_1=H; R_2=CO_2Me)

Reaction orders

In all the above mentioned reaction conditions (except Me_3Al 3:1§) we determined whether compounds 1 and 3 have the same reaction order. Their relative reactivities have been determined at 20°C in competitive reactions on equimolecular amounts of them (total ketonic concentration .2 M) using thre different concentrations of the added reactant. For reactions with Grignard reactant the concentrations were .3; .03 and .006 M. The results have been obtained by GLC determination of the reaction yields (vide infra). The relative reaction rates k_1/k_3, computed hypothesizing that reactions are first order in ketone both for 1 and 3 were .9; 1.0; 1.3 for reactions in Et_2O and .9, 1.1 and 2.7 for reactions in C_6H_6. Similar experiments with aluminium and lithium reactants showed no significan changes in the k_1/k_3 ratios. This behaviour is analogous to that of 4-carbomethoxy cyclohexanone and means that reactions with ketoester 3 can proceed (mainly in C_6H_6) with an higher order in reactant than reactions of simple ketones. Since for reactions with MeMgI the stereochemical product ratios (3"+5)/3' does not change (see Table 1 for the actual values) with varying the concentration of the added reactant one must conclude that both the axial and the equatorial attack reactions on 3 have the same reaction order. As in the already mentioned case of 4-carbomethoxy cyclohexanone we propose that (in C_6H_6) a Grignard reagent molecule is complexed by the ester group in an unproductive fas equilibrium having a large K and preceeding the reaction at the ketonic group as depicted in the following equation (pertinent to the 4-carbomethoxy cyclohexanone):



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§ For a discussion about the feasibility of competition experiments with Me_3Al see[6].

The above results indicate that the 4-carbomethoxy group, even when forced in the axial conformation is not able to accompany the complexed Grignard reactant to the ketonic group as it does in the case of open chain, more flexible δ-ketoesters[7]. For these last ones we proposed[7] (reactions in C_6H_6) a cyclic transition state containing a single Grignard molecule which works as alkylating agent too. This is not the case for compound 3 whose alkylation, both in the axial and equatorial side, necessitates of another molecule of Grignard reactant thus making it impossible to change reaction stereochemistry by varying the added reactant concentration.

Relative axial and equatorial reactivities

a) In the above mentioned reaction conditions (1-7) we performed competitive reactions on equimolecular amounts of 1, 2 and 3. Reaction mixtures were examined by GLC measuring the areas of the peaks corresponding to compounds 1, 1', 1"; 2, 2', 2"; 3, 3', 3" and 5. Each area was divided by the corresponding molecular weight and the obtained values were used for calculating the yields of each competing reaction. Reaction yields varied from run to run and only data from reactions with yields ranging from 20 to 80% were used to compute relative rates. These were calculated assuming that reactions are first order in ketone for all ketones[§].

b) Analogous competitive experiments were performed on equimolecular amounts of 1 and 4. Areas of peaks corresponding to compounds 1, 1', 1"; 4 and 6 were measured this time. Data were handled as above[§].

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

Table 1: Stereochemical product ratios and axial and equatorial relative rates of addition reactions to decalones (1 - 4)

Columns		1	2	3	4	5	6	7	8	9	10	11	12
Lines	Reactant	Stereochemical product ratios (k_{ax}/k_{eq})			Overall rates ratios		Relative rates k_{eq}				k_{ax}		
		1"/1'	2"/2'	(3"+5)/3'	$k_1/k_2/k_3$	k_1/k_4	1	2	3	4	1	2	3
1	MeMgI	.44	.56	1.0	1/.73/1.10	1/1.03	2.3	1.5	1.8	3.4	1	.9	1.8
2	MeMgI	.40	.51	.97	1/.70/1.14	1/2.5	2.5	1.6	2.0	8.7	1	.8	2.0
3	$Me_3Al(1)^a$	.27	.33	.33	1/.38/.56	1/.44	3.7	1.3	2.0	2.1	1	.4	.7
4	$Me_3Al(3)^a$	2.60	4.40	2.60	1/.84/1.04	1/.24	.4	.2	.4	.3	1	.9	1.05
5	$MeLi^b$	.44	.57	2.56	1/.94/.98	1/.78	2.3	1.9	.9	2.6	1	1.1	2.3
6	$MeLi^c$	.30	.36	2.43	1/.97/1.03	1/.85	3.3	3.1	1.3	3.6	1	1.2	3.2
7	Me_2CuLi	.12	.16	.68	1/.68/.67	1/.58	8.3	5.4	3.7	5.4	1	.9	2.5
8	Me_2Zn	.97				1/3.55	1			7.2	1		

Reactions of lines 1, 5, 6, 7 and 8 were performed in Et_2O; reactions of lines 2, 3 and 4 in C_6H_6

a) Ratio Me_3Al to ketone

b) Reactions performed at 20°C

c) Reactions performed at -78°C

[§] Preliminary single ketone experiments conducted in presence of GLC standards showed that material balance (i.e. the sum of starting products and final products) was always greater than 90% of the starting material with the exception of ketoester 3 in reaction condition 8. For this reason Table 1 lacks values of columns 2, 3, 4, 7, 8, 11 and 12, line 8.

DISCUSSION

A number of observations can be done about data of Table 1:

a) Changes in the stereochemical product ratios among columns 1, 2 and 3 may have different causes. Sometimes they originate from uneven increases (or decreases) of both k_{eq} and k_{ax}, and sometimes from divergent changes of them. For instance, increases in lines 1 and 2 between columns 2 and 3 are due to uneven (mostly axial) increases of k_{eq} and k_{ax} (compare changes between columns 7 and 8 to those between columns 11 and 12, lines 1 and 2). On the other hand the increase 2.60 ⟶ 4.40 between columns 1 and 2, line 4, is mostly due to a decrease in k_{eq} for compound 2. On the contrary, one can easily see that increases from column 2 to column 3, lines 5 (and 6) is due to divergent changes in k_{ax} (increase) and k_{eq} (decrease) (compare changes between columns 7 and 8 to those between columns 11 and 12), and that an analogous divergence causes the increase from column 1 to column 3, line 7 (decrease in k_{eq}, increase in k_{ax}). We shall discuss later these divergences in more detail. Other similar examples can be easily found in Table 1. On the whole they suggest that some care must be used in handling stereochemical product ratios in mechanistic discussion and that whenever possible k_{eq} and k_{ax} should be separately measured.

b) Changes of values from columns 6 to columns 7 and 8 represent the effects produced by a -H -Me ⟶ $-CO_2R$ (all axial) change in the ring position 4 to the ketonic group on k_{eq}, that is on the reactivity of the molecule on the same side of the substituent. Figures show that always the bulkier axial methyl group decreases k_{eq} with respect to the hydrogen substituent. The more electronegative ester group increases again k_{eq} values with the noticeable exception of reactions with lithiated reactants which show a further decrease of k_{eq} (lines 5, 6 and 7). Ab initio calculations[8] showed that O-Li bond is well developed in the TS of MeLi addition to CH_2O whereas the same is not true for the new C-C bond. This suggested that MeLi addition to carbonyl group is an electrophylic attack in nature. This is in agreement with the lower k_{eq} for 3 in lines 5, 6 and 7 but is contrasted by the increase in reactivity on the other face of the molecule (see changes from column 11 to column 12, lines 5, 6 and 7), which suggests, on the contrary, a nucleophylic attack to the carbonyl group. This means that, inspite of the higher steric hindrance of the axial attack, the new C-C bond is more developed in the TS on the axial side than the O-Li one. Actually it is already known that k_{eq} and k_{ax} may have very different ρ values in free energy relationships[2,3]. The present could be the first case in which equatorial and axial reactivity have different electrophylic vs. nucleophylic character.

c) k_{ax} always increase with the change -Me ⟶ $-CO_2R$ on the other face of the molecule (columns 11 ⟶ 12) as one would expect for a nucleophylic attack to the carbonyl group. Smaller and seemingly random changes of k_{ax} are produced by the changes -H ⟶ -Me (columns 10 ⟶ 11). One exception is found for reactions with Me_3Al 1:1 (line 3) for which k_{ax} for compound 3 is smaller than for compound 1 (columns 1 ⟶ 3). This is the only reaction condition in Table 1 whose rate determining step is the dissociation, inside the solvent cage, of the adduct ketone - Me_3Al. In all the other reaction conditions the slow step is represented by an attack of the reactant either to the ketone molecule or to the ketone-reactant complex.

d) The substitution $-H_{ax}$ ⟶ $-CO_2Me_{ax}$ in position 3 to the ketonic group has most random effects resulting sometimes in an increased k_{eq} (compare columns 6 and 9 in lines 1, 2, 5 and 6) and sometimes in a decrease of k_{eq} (compare lines 3 and 8 with respect to the reference rate, k_{ax} of compound 1). The rate change is the maximum observed in the present paper ranging from .3 to 8.7 that is a factor 29.

EXPERIMENTAL

Mps were taken on a Kofler apparatus and are uncorrected. IR spectra were recorded using a Perkin Elmer 457 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a WP-80-SY Bruker spectrometer. MS were recorded on a MS-HR Kratos MS-80 spectrometer. The relative intensities of the peaks (in parenthesis) are referred to the most intense one taken as 100%. GLC analyses were carried out on a Carlo Erba HGRC Mega Series 5300 apparatus using a 25m, .40 mm i.d. fused silica capillary column (stationary phase Carbowax 20 M); H_2 flow: .5 ml/min. We report, in sequence, the elution order of compounds and the most suitable temperature conditions (in parenthesis T_{oven}, $T_{inj}=T_{det}$ respectively): 1, 1', 1" (85, 220°C); 2, 2', 2" (85, 220°C); 3, 3', 5, 3" (130, 220°C); 6, 4 (130, 220°C). The following program was used for GLC examination of competition reactions between 1, 2 and 3 and 1 and 4: $T_{initial\ oven}$= 85°C for 5 min.; $T_{final\ oven}$= 130°C (heating rate 25°C/min.). HPLC separations were carried out on a Violet apparatus equipped with a RI Jobin Yvon iota detector using a 30 cm, 7.9 mm i.d. μ Porasil column.

Starting materials

Compound 1 was synthesized according to described methods[9]. Compound 2 was synthesized according to the methods of Dreiding and coworkers[10] and to Monson[9]. Compound 3 was synthesized according to the methods of Dreiding and coworkers[10]. Compound 4 was synthesized according to the methods of Stork and coworkers[11] and to Haworth[12]. The purity of each compound was checked by GLC.

Preparation of reagents

Solns. of Grignard reagents were prepared by known methods[13], then diluted to the desired conc. and kept under dry N_2. Just before use they were titrated[14] by sampling the supernatant clear soln. through a rubber septum. The trimethylaluminium (Fluka) was used without further purification. The conc. of the Me_3Al solns. (in C_6H_6) was determined by titration[14]. Methyllithium in Et_2O (Aldrich) was employed as received after titration[15]. Dimethylzinc in Et_2O was prepared according to Jones and coworkers[16], kept under dry N_2 and titrated before use[14].

Reactions

All the reactions were carried out under a pure dry nitrogen atmosphere and the glassware was carefully flamed and flushed with dry nitrogen before use. Tipically: a 2.3 ml of standard benzene soln. of Me_3Al (.596 M, 1.37 mmoles) was added via a syringe into a flask containing either 68 mg (.447 mmoles) of compound 1 in 4 ml of anhydrous benzene, or the equimolecular amounts of compounds 2, 3 or 4 (with n-eicosane as GLC standard). Reactions lasted 1 hour. After this time, the reaction mixtures were cooled (ice bath), slowly hydrolized with NH_4Cl s.s. and extracted five times with Et_2O. The ethereal solns., washed with water were combined, dried over Na_2SO_4, filtered and evaporated. Analyses of reaction mixtures by GLC were carried out as described. The same procedure was adopted for reactions of Me_3Al (1:1) in C_6H_6. Reactions lasted 1 hour also in this case. Reactions with MeLi and methylmagnesium compounds were carried out in a similar fashion and lasted 10 min., whereas reactions with dimethylzinc lasted 3 hours. The yields in isomeric alcohols are invariably very high for reactions with Me_3Al (3:1), and varied from run to run in other cases.

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 a nitrogen flow. each flask contained an equimolecular mixture of 1, 2 and 3 (.3 mmoles in all) dissolved in 3 ml of anhydrous solvent (C_6H_6 or Et_2O). The graduated burette was filled via a syringe with the suitable, conveniently diluted reactant, and the stoichiometric amount of it was added, under vigorous stirring to the substrates mixture. Reaction mixtures were then hydrolized and worked up as described, and finally examined by GLC in order to measure the relative areas of products and starting materials. In the case of competitive experiments performed on compounds 1 and 4 we used the same procedure.

Isolation and characterization of compounds 3', 3" and 5

A reaction was performed using standard procedure adding the alkylating agent (i.e. MeMgI in Et_2O) to compound 3 (400 mg) until almost complete disappearence of the starting compound (revealed by GLC). After working up, the mixture of reaction products was chromatographed by HPLC using Hexane/EtOAc 70/30 as eluant (φ=7.0 ml/min.). We obtained, in the order, the residual portion of starting material together with lactone 5 (70 mg), 180 mg of 3' and 90 mg of 3". The purity of 3'and 3" was tested by GLC. Lactone 5 was subsequently separated from compound 3 by HPLC using Hexane/EtOAc 85/15 as eluant, obtaining 20 mg of 5. Also the purity of 5 was tested by GLC.

For compound 3: m.p. 37-38°C; MS m/e: 53(19%), 55(23), 67(33), 77(18), 79(34), 81(36), 91(25), 93 (23), 95(18), 105(17), 107(19), 108(16), 109(18), 148(37), 149(100), 150(16),151(44), 155(26), 166 (13), 170(20), 194(12), 225(21), 240(21), 241(4). IR spectra showed ν_{max}^{CCl4} cm^{-1}: 3500-3300br, 2940s, 2860s, 1730s, 1715sh, 1460sh, 1455s, 1375m, 1320m, 1260w, 1195s, 1175w, 1150w, 1125w, 1075w, 1050m, 1025m, 990w, 970m, 950w, 940w, 920w, 905m. ^{1}H NMR showed the following peaks $\partial(CCl_4)$: 1.23 s, 3H; 4.14 q, 2H (J=4.37 Hz). ^{13}C NMR in $CDCl_3$ ∂ ppm from TMS: 14.5, 23.6, 26.6, 28.9, 31.8 (equatorial Me 33.6, 36.1, 38.0, 40.1 (-CH), 42.5, 47.9, 59.6, 70.1 (ester Me group), 175.4.

For compound 3": b.p. 114-116°C/5 mm Hg; MS m/e: 53(28%), 55(33), 67(54), 77(24), 79(54), 81(50), 91(32), 93(40), 94(32), 95(40), 105(20), 107(28), 108(36), 109(33), 127(17), 135(42), 148(81), 149 (100), 150(50), 151(46), 155(44), 166(16), 170(64), 194(27), 195(18), 222(12), 225(10), 240(15), 241(4). IR spectra showed $\nu_{max}^{CCl_4}$ cm^{-1}: 3500-3300br, 2940s, 2860m, 1730s, 1720sh, 1460sh, 1450m, 1370m, 1310m, 1195s, 1180w, 1150w, 1125s, 1080w, 1050w, 1040m, 1025m, 1000w, 985w, 960m, 940m, 905m. ^1H NMR spectra showed the following peaks δ (CCl_4): 1.25 s, 3H; 4.15 q, 2H (J=4.37 Hz).
^{13}C NMR spectra in $CDCl_3$ (and in C_6D_6) δ ppm from TMS: 14.3(14.4), 23.4(24.0), 26.4(26.8) (axial Me), 26.4(26.9), 29.1(29.6), 36.0(36.5), 38.0(38.4, 38.5), 43.0(43.4)(-CH), 44.2(44.7), 48.2(48.5), 59.7 (59.7), 71.2(70.7) (ester Me group), 175.1(174.6). The ^{13}C assignements were made with the help of Dept techniques for both compounds 3' and 3".
For compound 5: b.p. 67-69°C/5 mm Hg; MS m/e: 53(21%), 55(26), 67(36), 71(21), 79(34), 81(27), 91 (23), 93(34), 94(44), 95(54), 107(23), 108(36), 109(18), 135(100), 150(91), 194(18), 195(3.5). IR spectra showed $\nu_{max}^{CCl_4}$ cm^{-1}: 2970sh, 2920s, 2860w, 1750s, 1740sh, 1450sh, 1440m, 1380m, 1360w, 1330w, 1240m, 1210w, 1140w, 1100s, 1090m, 1060m, 1040w, 950w, 920w. ^1H NMR in $CDCl_3$ showed a peak at δ 1.38 s, 3H.

Isolation and characterization of compound 6

We performed a reaction on compound 4 (100 mg) using Me_3Al (3:1) until complete disappearence of starting material. After usual working up we obtained 80 mg of compound 6 whose purity was checked by GLC.
For compound 6: m.p. 60-61°C; MS m/e: 53(18%), 55(31), 57(45), 58(39), 67(29), 77(18), 78(31), 81 (29), 91(25), 93(35), 94(27), 95(33), 107(23), 108(35), 109(18), 135(69), 137(58), 149(21), 150(100) 151(82), 194(10), 195(3). IR spectra showed $\nu_{max}^{CCl_4}$ cm^{-1}: 2945s, 2860sh, 1780sh, 1770s, 1730sh, 1455s, 1450sh, 1385s, 1360w, 1350w, 1295m, 1280w, 1260m, 1245w, 1230m, 1200m, 1175w, 1155m, 1140s, 1130sh, 1120s, 1090s, 1050m, 1035m, 990m, 975w, 960s, 940m, 920s. ^1H NMR in $CDCl_3$ showed a peak at δ 1.43 s, 3H.

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