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STUDIES ON THE STEREOCHEMISTRY OF ADDITION REACTIONS OF CYCLOHEXANONES. A DICHOTOMY IN SUBSTITUENT EFFECT DEPENDING ON REACTION CONDITIONS.

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Abstract - The stereochemistry of addition reactions of 4-t-Bu, 4-OMe and 4-Cl cyclohexanones, determined under seven different reaction conditions is described. A dichotomy in the substituent influence on stereochemistry is outlined and discussed suggesting that it parallels the changes in reaction mechanism.

Two of us recently described some steric and kinetic effects of changing solvent and reactant in Grignard reactions on some 4-substituted cyclohexanones[1]. Those results indicated that the remote substituent not only influences the reaction at the ketonic group through its field effect (as measured by the Taft's σ's), but it can also cause its axial conformation in the transition state to be more stable than the equatorial one. Also the remote substituent can increase the reaction order by complexing a molecule of the Grignard reactant in an early reversible step of the reaction sequence.

Additionally it appeared that the choice of the reaction solvent could determine the occurrence of the above described complicating phenomena. Thus both reaction stereochemistries and rates turned out to be the result of a number of parameters in addition to the substituent electronegativity.

We have now extended our stereochemical investigation to different alkylation agents and in this paper we described the results we obtained for reactions of:

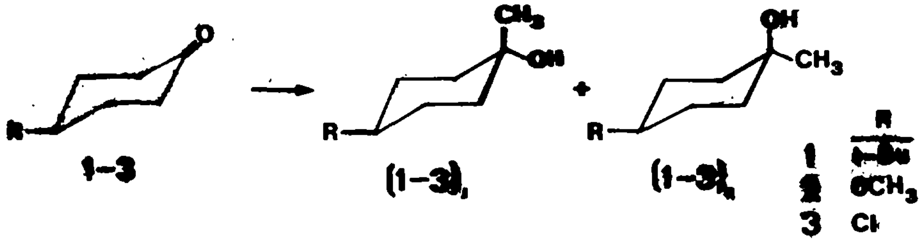
1) $Me_2Zn+2MgI_2$ in Et_2O; 2) MeLi in Et_2O; 3) Me_3Al in C_6H_6 in the ratio 3:1 to the ketone;
4) MeMgI in Et_2O; 5) Me_3Al in C_6H_6 in the ratio 1:1 to the ketone
with:
i) 4-t-Bu (1); ii)4-OMe (2) and iii) 4-Cl (3) cyclohexanones.

We also established that compounds 1,2 and 3 have the same reaction order in reactant for reactions with $Me_2Zn/2MgI_2$, MeLi and Me_3Al (1:1).

RESULTS

Stereochemistry of the addition reactions

The products from the addition reactions are invariably the alcohols $(1\text{-}3)_I$ and $(1\text{-}3)_{II}$ (Scheme 1) which have been already described[1].



Scheme 1

We have measured the percentages of $(\underline{1}-\underline{3})_{I}$ and $(\underline{1}-\underline{3})_{II}$ by GLC examination as already described[1]. Table 1 collects our results together with those obtained for reactions with MeMgI in C_6H_6 and with MeMgCl in THF we previously discussed[1].

Table 1. Isomer percentages in addition reactions on cyclohexanones ($\underline{1}-\underline{3}$).

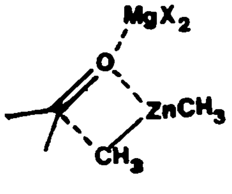
Row	Reaction conditions	R	$\underline{1}$ = -t-Bu		$\underline{2}$ = -OMe		$\underline{3}$ = -Cl		
		σ_I	+0.016		+0.25		+0.47		
			$\underline{1}_{II}$	$\underline{1}_{I}$	$\underline{2}_{II}$	$\underline{2}_{I}$	$\underline{3}_{II}$	$\underline{3}_{I}$	
A	$Me_2Zn+2MgI_2/Et_2O$		44	56	51	49	56	44	set $\underline{a}$
B	$MeLi/Et_2O$		63	37	67	33	74	26	
C	Me_3Al (3:1)[a]/C_6H_6		15	85	47	53	67	33	
D	$MeMgI/C_6H_6$		60	40	52	48	61	39	set $\underline{b}$
E	$MeMgI/Et_2O$		65	35	47	53	56	44	
F	Me_3Al (1:1)[a]/C_6H_6		69	31	33	67	44	56	
G	MeMgCl/THF		72	28	46	54	50	50	

a) Ratio Me_3Al to ketone

The figures of Table 1 can be grouped in two distinct sets ($\underline{a}$ and $\underline{b}$) whose main difference consists in that set $\underline{a}$ exhibits an increase of the $(\underline{1}-\underline{3})_{II}$ percentage in passing from R=-t-Bu to R=-OMe and R=-Cl, while all reactions of set $\underline{b}$ show a more or less deep minimum for R=-OMe.

In the case of 4-t-Bu cyclohexanone it has been shown that reactions of set $\underline{b}$ are first order in reactant[1,2-5], whereas reactions of set $\underline{a}$ belong to those for which evidences for transition states containing one mole of ketone and two moles of metal-containing species have been found. More explicitly structures $\underline{4}$[6,7,9], $\underline{5}$[8,9] and $\underline{6}$[4c] have been suggested for the addition of respectively Me_2Zn in ethereal solution, for the addition of MeLi to ketones in Et_2O in the presence of lithium salts and excess of Me_3Al to ketones in benzene solutions.

Transition states $\underline{4}$, $\underline{5}$ and $\underline{6}$ are substantially more crowded than those of first order reactions, and the large differences in the stereochemical outcome of the addition reactions of 4-t-Bu cyclohexanone have been accounted for in terms of changes in steric compression in the transition states.



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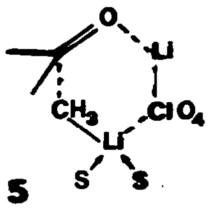

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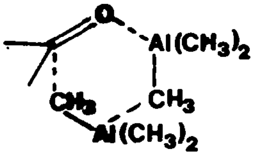

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Furthermore in the case of Grignard reactions we showed[1] that compounds 1, 2 and 3 have the same order in alkylating agent: in order to throw some light on the origin of the difference between reactions of set a and b the question whether reactions of 1, 2 and 3 have the same order must be answered also for reactions with other reactants. At this aim the following kinetic measurements were carried out.

Competitive addition reactions

In analogy with reactions of rows D and G[1], three competitive reaction runs on equimolecular amounts of compound 1 with compounds 2 or 3 respectively in reaction conditions A and B have been performed. The three runs differed from one another in the concentration of the added reactant which decreased in going from run a to run c (see Table 2).

Table 2. Relative rates of addition reactions on cyclohexanones (1-3).

Row	Reaction conditions	Run[a)]	k_1/k_2	k_1/k_3
A	Me_2Zn+$2MgI_2/Et_2O$	a	0.84	0.37
		b	0.84	0.36
		c	0.84	0.35
B	$MeLi/Et_2O$	a	0.90	0.70
		b	0.89	0.68
		c	0.88	0.69
F	Me_3Al (1:1)/C_6H_6	b	1.31	1.15
		c	1.24	1.26

a) Concentration of the added reactant: run a .3N; run b .03N; run c .006N

Reaction mixtures were examined by GLC measuring the areas of the peaks corresponding to compounds 1, 1_I, 1_{II} on one hand and 2, 2_I, 2_{II} (or 3, 3_I, 3_{II} depending on the chosen partner for that particular experiment) on the other. Each area was divided by the corresponding molecular weight[§] and the values obtained were used for calculating the yields of each competing reaction. Although reaction yields varied from run to run, the material balance (i.e. the sum of starting product and final products) was always greater than 90% of the starting material. The relative reaction rates were calculated assuming that reactions are first order in ketone for all ketones.

[§] Preliminary experiments showed that GLC responses of each of compounds (1-3) on one hand and the reaction products $(1\text{-}3)_I$, $(1\text{-}3)_{II}$ on the other were very close to each other. Thus no correction was introduced at this point.

Only data from reactions with yields of final products ranging from 20 to 80% were used to compute relative rates. Each figure of Table 2 represents the mean value of at least three separate experiments.

Analogous competitive experiments were done for reaction conditions C and F. The trouble in doing such experiments with Me_3Al consists in that reactions of the first and second order in alkylating reactant can proceed contemporaneously depending on the concentration of the added reactant. Thus when Me_3Al was used in 3:1 ratio and added as diluted solution, reactions occurred also via first order kinetics as evidenced by the higher (72%) $\underline{1}_{II}$ percentage. This is true also when the reverse procedure is adopted, i.e. when the mixtures of the two ketones is added to the diluted solution of Me_3Al (ratio 3:1). Another major problem in the 3:1 competition experiments is the difficulty of stopping the reactions well before than one of the two competitors is completely consumed. Neverthless, owing to the similarity in the stereochemical trend of reactions of set a we believe it reasonable to consider that also for condition C the order is the same for compounds $\underline{1}$, $\underline{2}$ and $\underline{3}$.

Analogously, when Me_3Al is used in the molar ratio 1:1 (reaction condition F) and added as concentrate solution to the cyclohexanones mixture, reactions of the second order in Me_3Al took also place as suggested by the much lower (44%) $\underline{1}_{II}$ and the higher (56%) $\underline{3}_{II}$ percentage we obtained. In these cases relative rates are not reproducible even for the same concentration of the added reactant[§]. For these reasons row F in Table 2 lacks the values relative to run a conditions.

DISCUSSION

On the whole, data of Table 2 exclude a difference in order among the various substrates within each of the examined conditions and suggest that the difference in the reaction order in the reactant between the two sets can be responsible of their different stereochemical trends.

In the case of reactions of row D and G we suggested[1] that the transition states have the R=-OMe and R=-Cl groups largely in their axial conformation[§§]. Independent kinetic measurements[1] gave consistent results and strengthened this suggestion. The present paper's data hold the same conclusions for all reactions in set b. No explanation of this kind is needed to give account of the trend of reactions of set a whose transition states must be considered as having the -OMe and -Cl groups mostly in their equatorial conformation.

This obviously means that for set a ratios $(\underline{1}\text{-}\underline{3})_{II}/(\underline{1}\text{-}\underline{3})_{I}$ represent to a good approximation also k_{eq}/k_{ax}. In Fig. 1 we plotted those values in the form $1+\log k_{eq}/k_{ax}$ vs. σ_I.

In order to have an analogous representation for the values of set b one could try to use the reciprocals of the values of $(\underline{1}\text{-}\underline{3})_{II}/(\underline{1}\text{-}\underline{3})_{I}$ ratios. When the above operation produces a good alignement (reaction condition D and E) it is possible to conclude that the reaction proceeds to a large extent through a transition state having the -OMe and -Cl groups in the axial conformation.

In the case of reaction condition F and G heavily broken lines were obtained. This means that reaction products are also formed, in a non negligible amount, through -OMe/-Cl equatorial transition states.

§ Local concentration, stirring speed play perhaps a crucial role in these limit experiments.

§§ Shortly after our work[1], Allinger communicated his results[10] showing that 4-OMe and 4-Cl cyclohexanones have the 4-R groups in the axial conformation in benzene solutions. No wonder that the same could happen in a reaction transition state which involves more energetic interactions than the solution - solvent ones.

Figures 1 and 2 display, as a whole, two opposite slopes in their lines which brings to the conclusion that:

- electron attracting groups in an equatorial conformation produce increased equatorial attack (set a).
- electron attracting groups in an axial conformation cause less equatorial attack (set b)[§].

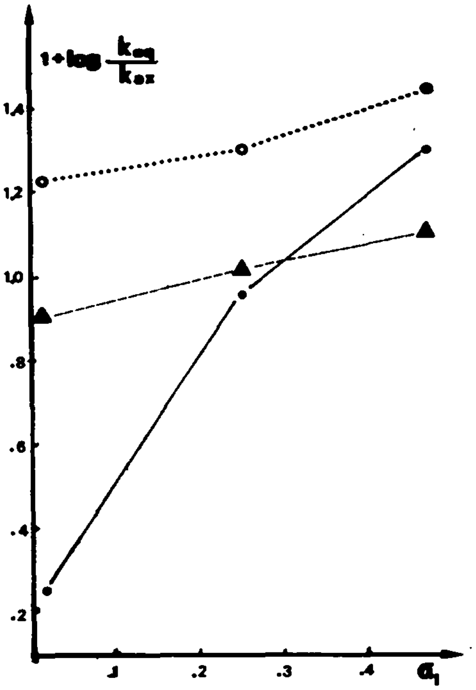

Fig. 1. Plot of 1+log k_{eq}/k_{ax} vs. σ_I for respectively reaction conditions A(▲), B(○) and C(●).

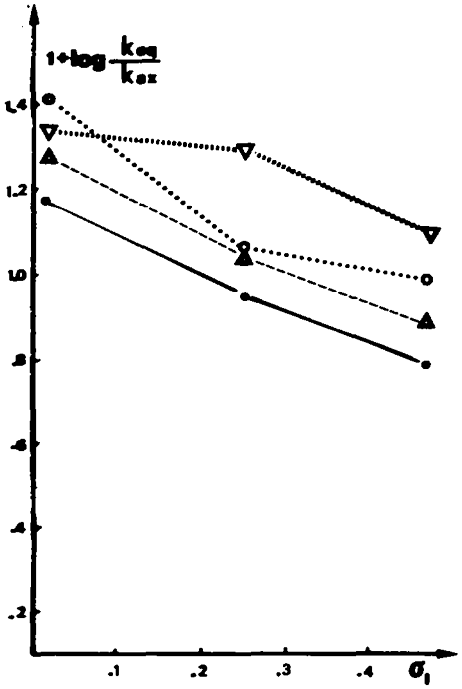

Fig. 2. Plot of 1+log k_{eq}/k_{ax} vs. σ_I for respectively reaction conditions D(●), E(▲), F(▽) and G(○).

We think that the more crowded transition state of reactions of set a could explain both the postulated equatorial/axial difference between transition states of the two sets and, as a consequence, the observed opposite sensitivity to substituent electronegativity.

A final comment should be made on the reactions of rows A and C: the low equatorial vs. axial attack of 4-t-Bu cyclohexanone has been interpreted in terms of compression effect[12]. As it is evident from the figures relative to 4-OMe and 4-Cl cyclohexanones in rows A and C, substituents of higher elecronegativity than t-Bu can decrease the role of compression effect or even dominate it.

EXPERIMENTAL

Mps were taken on a Kofler apparatus and are uncorrected. GLC analyses were carried out on a Carlo Erba HGRC Mega Series 5300 apparatus using a 1.5 m, 1.5 mm i.d., glass column packed with 2% PEG on a Carbopack C; N_2 flow=30 ml/min. We report, in sequence, the elution order of compounds from each mixture and the most suitable temperature conditions (in parenthesis T_{oven}, $T_{inj.}=T_{det.}$ respectively): 1, 1_{II}, 1_I (125°, 180°); 2, 2_I, 2_{II} (130°, 180°); 3, 3_I, 3_{II} (180°, 220°).

Starting materials

4-t-Bu cyclohexanone (Merck) had m.p. 48-49° (lit.[13] 49-50°). Compound 2 was synthesized using the method of Carlson and Zey[14]. Compound 3 was synthesized using the method of Owen and Robins[15] and Grewe[16].

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§ Theoretical considerations[11] have suggested that for nucleophilic addition to cyclohexanones the predominance of axial approach should be observed for both axial and equatorial C_4 substituents.

Preparation of reagents

The $Me_2Zn+2\ MgI_2$ in Et_2O reactant was prepared using the in situ technique according to Jones et al.[7].

Methyllithium in Et_2O (Merck) was employed as received, titrated[17] and diluted to the desired concentration just before use.

The trimethylaluminium (Fluka) was used without further purification. The concentration of the Me_3Al solns. (in benzene) was determined by titration[17].

Ethereal solns. of MeMgI were prepared as described[18], then diluted to the desired concentration and kept under dry N_2. Just before use they were titrated[17] by sampling the supernatant clear soln. through a rubber septum.

Reactions

All the reaction were carried out under a pure nitrogen atmosphere and the glassware was flamed and flushed with nitrogen before use. Tipically: a 2.3 ml of standard benzene soln. of Me_3Al (0.596 M, 1.37 mmol) was added via a syringe into a flask containing either 70 mg (0.454 mmol) of compound 1 in 4 ml of anhydrous benzene, or the equimolecular amounts of compounds 2 and 3 (with respectively n-undecan and n-dodecan as internal standard) at 25°. Reactions lasted 1 hour. After this time, the reaction mixtures were cooled in an ice bath, then slowly hydrolized with 2 ml of saturated ammonium chloride soln. and extracted[§] with diethyl ether; solns. washed with water were combined, dried over Na_2SO_4, filtered and evaporated. Analyses of reaction mixtures were carried out by GLC as described.

The same procedure was adopted for reactions of Me_3Al in benzene (1:1). Reactions lasted 1 hour also in this case.

Reactions of dimethylzinc, methyllitium and methylmagnesium compounds were carried out in a similar fashion. Reactions with dimethylzinc lasted 3 hours, whereas reactions with methyllitium and methylmagnesium compounds lasted 10 min.

The yields in isomeric alcohols are invariably very high for reactions with Me_3Al (3:1). They varied from run to run in other reaction conditions. The minimum corresponds to reactions with Me_3Al (1:1) (=20%), but this is partly due to the short reaction times we adopted in this work.

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 and 2 (or 1 and 3 depending on the chosen partner for that particular experiment) (0.4 mmol in all) dissolved in 4 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 to the substrates mixtures under vigorous stirring. Reaction mixtures were then hydrolized and worked up as described. The ethereal extracts were examined by GLC and the areas of products (1-3), $(1\text{-}3)_{I}$ and $(1\text{-}3)_{II}$ were measured.

§ For compound 3 the extraction was carried out in continuo during 12 hours for reaction conditions A, C and F. That was the case also for competition experiments.

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