

THE RELATIVE REACTIVITY OF CYCLIC KETONES
TOWARDS METHYLTITANIUM REAGENTS

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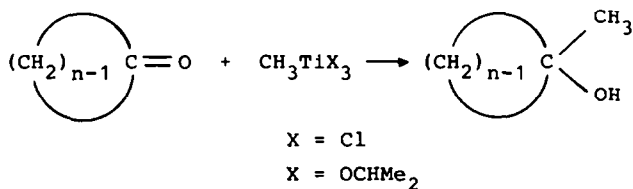
SUMMARY: The relative rates of the addition of CH_3TiCl_3 and $\text{CH}_3\text{Ti}(\text{OCHMe}_2)_3$ to various cyclic ketones of different ring size have been determined. In contrast to CH_3Li and CH_3MgCl , significant rate differences were observed. For CH_3TiCl_3 (at -18°C) the following decreasing order in rate pertains, the numbers symbolizing the ring size: $6 > 5 > 7 > 15 > 8 > 12 > 9 > 11 > 10$. For $\text{CH}_3\text{Ti}(\text{OCHMe}_2)_3$ (at $+22^\circ\text{C}$) it is slightly different: $6 > 5 > 7 > 8 > 15 > 9 > 12 > 13 > 11 > 10$. Most of the results can be explained on the basis of Brown's hypothesis of I-strain. However, the 15-membered ring cyclopentadecanone represents the major "irregularity".

INTRODUCTION

In previous studies we have reported that titanium reagents behave chemo- and stereoselectively in reactions with carbonyl compounds¹⁾. Detailed rate studies involving $\text{CH}_3\text{Ti}(\text{OCHMe}_2)_3$ show that steric factors play the dominant role, e.g., in the discrimination between aldehydes and ketones ($k_{\text{rel}} = k_{\text{ald.}}/k_{\text{ket.}} = 500-700$ at room temperature)²⁾. In the present paper we extend our rate studies to include the relative reactivity within a family of carbonyl compounds, namely cyclic ketones.

METHOD

The parent compounds $\text{CH}_3\text{Ti}(\text{OCHMe}_2)_3$ ³⁾ and CH_3TiCl_3 (prepared from CH_3Li and TiCl_4)⁴⁾ were reacted with ketone pairs at $+22^\circ\text{C}$ and -18°C , respectively, and the k_{rel} -values for a series of cyclic ketones were determined using the method and the kinetic scheme previously described²⁾. The difference in temperature has to do with the increased reactivity of CH_3TiCl_3 relative to $\text{CH}_3\text{Ti}(\text{OCHMe}_2)_3$. At room temperature the reactions of the former are too fast to be monitored conveniently.



It is important to note that titanation of CH_3Li /ether with TiCl_4 is essentially quantitative, but a mixture of methyltitanium reagents is nevertheless formed. The highly Lewis acidic reagent CH_3TiCl_3 forms mono- and bis-etherates which are in equilibrium with one another^{4,5)}. Evidence has accumulated that the bis-etherate probably does not react with carbonyl compounds. Rather, either the mono-etherate or the free CH_3TiCl_3 represent the reacting species (or both)⁴⁾.

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RESULTS

The results of the competition experiments are recorded in Table 1. The relative rates have been calculated with cyclopentanone as the reference ketone ($k_{rel} = k_5/k_n$). The numbers were brought into graphical form in which $\log k_{rel}$ was plotted against the ring size (Figures 1 and 2).

Table 1. k_{rel} -Values of the addition of CH_3TiCl_3 and $CH_3Ti(OCHMe_2)_3$ to cyclic ketones in ether

Ring Size (n)	k_{rel} at $-18^\circ C$ for CH_3TiCl_3	k_{rel} at $+22^\circ C$ for $CH_3Ti(OCHMe_2)_3$
5	1.0	1.0
6	0.07	0.05
7	1.2	1.0
8	9.4	11.6
9	17.9	33.6
10	71.1	203.1
11	39.6	121.8
12	13.2	48.7
13	--a)	52.7
15	2.6	24.4

a) Not measured.

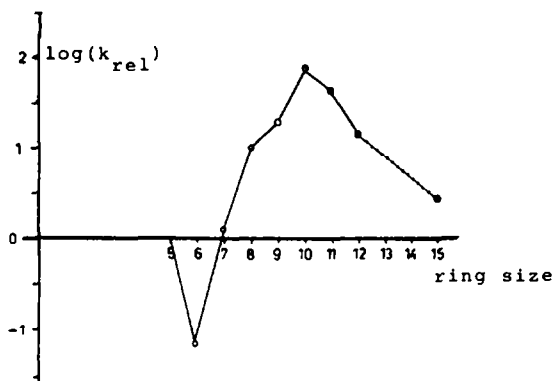
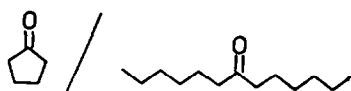


Fig. 1. CH_3TiCl_3 Additions



Fig. 2. $CH_3Ti(OCHMe_2)_3$ Additions

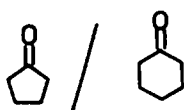
In case of CH_3TiCl_3 , the acyclic ketone 7-tridecanone was included in the competition experiments at $-18^\circ C$. Accordingly, cyclopentanone reacts faster by a factor of 6.



$$k_{rel} = 6.0 (CH_3TiCl_3)$$

Although CH_3Li and CH_3MgBr were not tested in the whole series, they were used for the purpose of comparison in the following two reactions at $-18^\circ C$ in ether. The results show that only the Grignard reagent is capable of a small degree of

discrimination, cyclohexanone reacting about four times as fast as cyclopentanone:

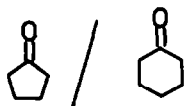


$$k_{\text{rel}} = 1.0 \text{ (CH}_3\text{Li)}$$

$$k_{\text{rel}} = 0.23 \text{ (CH}_3\text{MgBr)}$$

(both reactions at -18°C in ether)

In other cases Grignard reagents do not show any degree of selectivity, in contrast to the titanium analogs⁶⁾:



$$k_{\text{rel}} = 1.0 \text{ (CH}_2=\text{CHCH}_2\text{MgCl)}$$

$$k_{\text{rel}} = 0.1 \text{ (CH}_2=\text{CHCH}_2\text{Ti(NEt}_2)_3)$$

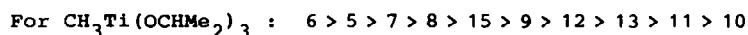
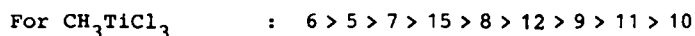
$$k_{\text{rel}} = 0.1 \text{ (CH}_2=\text{CHCH}_2\text{Ti(OCHMe}_2)_4\text{MgCl)}$$

(all reactions at -78°C in THF)

DISCUSSION

Reactivity as a function of ring size was discussed systematically more than three decades ago by Prelog⁷⁾, Brown⁸⁾ and others⁹⁾ and more recently by Rüchardt¹⁰⁾, Schneider¹¹⁾, Müller¹²⁾ and others¹³⁾. Of particular relevance to the present results is Brown's study of the NaBH_4 induced reduction of cyclic ketones⁸⁾. He observed the following sequence of decreasing reactivity (the numbers denote the ring size): $4 > 6 > 5 > 7 > 15 > 13 > 12 > 8 > 9 > 11 > 10$. This correlates well with the equilibrium constants of the dissociation of the corresponding cyanohydrins^{7,8)}. The results were interpreted on the basis of the concept of internal strain (I-strain), which is the sum of Baeyer strain (angle strain), Pitzer strain (torsional strain) and Prelog strain (transannular strain). The I-strain hypothesis has been applied successfully in other reactions of cyclic compounds which involve $\text{sp}^2 \rightleftharpoons \text{sp}^3$ changes⁷⁻¹¹⁾.

In the case of methyl addition reactions, the following sequences hold (Table 1).



This means that the order of relative reactivity is the same in case of the first three members (cyclohexanone > cyclopentanone > cycloheptanone), which also corresponds to Brown's findings in NaBH_4 reductions. According to Brown, cyclohexanone is the fastest reacting cyclic ketone (other than cyclobutanone) because the change from sp^2 to sp^3 hybridization is most favored, this being due to a somewhat reduced angle strain and the fact that only staggered interactions result as a consequence of the reaction. In case of 5- and 7-membered rings a similar change brings about considerable torsional strain. Another common feature among the three sets of data is the observation that cyclodecanone is the slowest reacting ketone. This medium sized ring is known to be an extreme case in which the change from sp^2 to sp^3 hybridization causes an increase in Prelog strain. This bond opposition force also operates in the reactions of the other medium sized rings, although to a lesser degree. Finally, the reactivity range in case of NaBH_4 reductions is larger

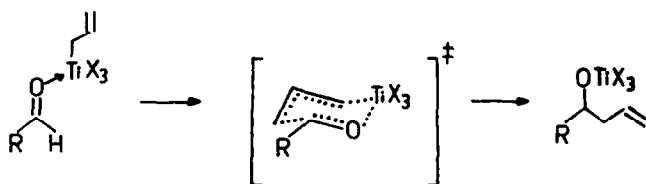
than in the CH_3TiX_3 addition reactions. The most reactive ketone (cyclohexanone) is reduced about 12000 times faster than the slowest reacting ketone (cyclo-decanone). In the addition reactions of $\text{CH}_3\text{Ti}(\text{OCHMe}_2)_3$, the factor is 4000. It is known that NaBH_4 is a very mild reducing agent, capable of distinguishing between various kinds of functionalities¹⁴⁾.

Other aspects of the results are more difficult to understand. The three sequences of relative reactivities involving NaBH_4 , CH_3TiCl_3 and $\text{CH}_3\text{Ti}(\text{OCHMe}_2)_3$ are qualitatively not identical, and switches in the reactivity order are observed even in the reactions of the two organotitanium reagents. For example, in case of CH_3TiCl_3 cyclooctanone reacts faster than cyclopentadecanone (factor of 3.6), whereas with $\text{CH}_3\text{Ti}(\text{OCHMe}_2)_3$ the opposite is observed (factor of 2.1). Of course, it is clear that relative to the whole span of reactivity in the series, these differences are small.

Perhaps the most dramatic observation is the relative position of the 15-membered cyclic ketone in the set of reactions involving $\text{CH}_3\text{Ti}(\text{OCHMe}_2)_3$. A ketone of such a large ring size is not expected to react so slowly. The effect is not as pronounced in case of CH_3TiCl_3 . The breakdown in the free-energy relationship between the k_{rel} -values of the two series indicates unusual steric interactions in the reactions of the bulky $\text{CH}_3\text{Ti}(\text{OCHMe}_2)_3$ with cyclopentadecanone. Other types of "irregularities" have been noted in certain solvolytic reactions of cyclic derivatives^{8,11,12)}.

It is important to note that the direction of attack (equatorial or axial) in case of cyclohexanone is different in the three series. Hydride attack on conformationally locked 4-t-butylcyclohexanone in the system NaBH_4 /isopropanol occurs preferentially from the axial direction (87:13 product ratio)¹⁵⁾. In contrast, CH_3TiCl_3 and $\text{CH}_3\text{Ti}(\text{OCHMe}_2)_3$ add mainly from the equatorial direction (82-93% of the axial alcohol), the latter reagent showing the slightly higher degree of diastereoselectivity¹⁶⁾. Thus, not only the nature of the nucleophile is different (H vs. CH_3), but also the metal, solvent and temperature as well as the direction of attack. In case of the larger ring ketones, the problem of diastereoselective Grignard-type additions to appropriately substituted derivatives has not been studied systematically¹⁷⁾.

The observation that allylmagnesium and allyltitanium reagents are much more reactive towards carbonyl compounds than the saturated n-alkyl analogs is no exception in organometallic chemistry^{1,18,19)}. We believe that this is due to stereoelectronic factors. For example, assuming Ti-O complexation prior to C-C bond formation as postulated for additions of CH_3TiX_3 ²⁾, it becomes clear that the end of the allyl groups can "reach" the carbonyl C-atom much more easily than a methyl group. Indeed, substituted allyl groups react with allylic inversion via a six-membered cyclic transition state^{1,19)}. This argument also holds if the transition state is reached directly without prior Lewis acid/Lewis base adduct formation. Such increased reactivity leads to a decrease in chemoselectivity, as shown in the competition experiments involving cyclopentanone and cyclohexanone.



In summary, most of the features of the addition of CH_3TiX_3 to cyclic ketones are in line with the concept of internal strain. The 15-membered ring is an important exception. CH_3TiCl_3 and $\text{CH}_3\text{Ti}(\text{OCHMe}_2)_3$ are considerably more selective than CH_3Li or CH_3MgBr . Allylmagnesium chloride shows no degree of chemoselectivity in the case tested (cyclopentanone/cyclohexanone) even at low temperatures (-78°C). This is due to the fact that it is much more reactive than the saturated analogs such as CH_3MgX , which in turn is a consequence of stereoelectronic factors. However, titaniation of allylmagnesium chloride with $\text{ClTi}(\text{NET}_2)_3$ or $\text{Ti}(\text{OCHMe}_2)_4$ results in the species $\text{CH}_2=\text{CHCH}_2\text{Ti}(\text{NET}_2)_3$ and $\text{CH}_2=\text{CHCH}_2\text{Ti}(\text{OCHMe}_2)_4\text{MgCl}$, respectively, which show a fair degree of chemoselectivity³⁾. In case of titanium reagents in general, the type of ligand (Cl vs. OCHMe_2) at the metal is important in determining the degree of chemoselectivity.

EXPERIMENTAL SECTION

The same techniques as in the previous report²⁾ were used in determining the relative rates in case of $\text{CH}_3\text{Ti}(\text{OCHMe}_2)_3$ at $+22^\circ\text{C}$. This includes calibration curves of the compounds examined in the capillary gas chromatographic analyses. In reaction involving the more reactive CH_3TiCl_3 , -18°C was chosen, the techniques being the same. The reagent was prepared by quantitative titaniation of methyl-lithium with TiCl_4 ^{4,18)}: 1.9 g (10 mmol) of TiCl_4 was added via a syringe to about 50 ml of cooled ether (-78°C) under an atmosphere of nitrogen, resulting in a yellow suspension of the TiCl_4 -bis-etherate. An ethereal solution of methyl-lithium (10 mmol) was slowly added. The solution was allowed to reach -18°C , at which the competition experiments were performed. The mixture is homogenous under these conditions. Evaluation of the data was carried out as previously delineated²⁾.

ACKNOWLEDGEMENT

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