Tetrahedron Vol. 43, No. 1, pp. 101 to 108, 1987
Printed in Great Britain.

0040-4020/87 $5.00+.00
Pergamon Journals Ltd.

KINETIC STUDIES OF THE ADDITION OF METHYLTITANIUM REAGENTS TO CARBONYL COMPOUNDS

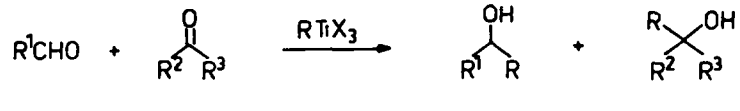
M.T. Reetz* and S. Maus
Fachbereich Chemie der Universität
Hans-Meerwein-Strasse
3550 Marburg, BRD

(*Received in Germany* 16 *September* 1986)

SUMMARY: The relative rates of the addition of $CH_3Ti(OCHMe_2)_3$ to various aldehydes and ketones have been determined at room temperature. Aldehydes react faster than ketones by a factor of ~500. Steric factors are primarily responsible. The synthetically and mechanistically important observation hat α-alkoxy and aminoketones are more reactive than the heteroatom-free analogs has been put on a quantitative basis (k_{rel} = 10-30) and interpretated on the basis of chelation. The activation parameters of the addition of $CH_3Ti(OCHMe_2)_3$ to heptanal depend profoundly on the solvent (THF or CH_2Cl_2). In all cases 2. order kinetics are observed. This also applies to the addition of the ethoxy-analog $CH_3Ti(OEt)_3$ in THF, but not to its reaction in CH_2Cl_2. Mechanistic implications are discussed.

INTRODUCTION

The titanation of such classical reagents as RLi, RMgX and a host of "carbanions" generated by deprotonation of CH-acidic compounds often increases chemo- and stereoselectivity in reactions with carbonyl compounds and alkyl halides[1]. Early examples pertain to the aldehyde-selective behavior of $RTiX_3$. In competition experiments in which a mixture of an aldehyde (one part) and a ketone (one part) were reacted with the reagent (one part), only the aldehyde adduct was detected[1,2].



> 99 : < 1

Although this type of information is sufficient for synthetic purposes, it does not reveal the exact degree of selectivity. In order to ascertain the latter, precise kinetic experiments are required. In this paper we present the results of a kinetic study of the addition of the parent reagent $CH_3Ti(OCHMe_2)_3$ to carbonyl compounds. Included are relative rates (k_{rel}-values) as well as activation parameters ($\Delta G^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$).

METHODS

In determining k_{rel}-values of a reactive species, it has become customary to use an excess of two trapping agents so that their concentrations do not change during the reaction[3]. In the present study such pseudo first order conditions caused analytical problems, e.g., peak overlapping of the excess carbonyl compounds with the products in the GC analysis[4]. We therefore used two carbonyl compounds and the titanium reagent in 1:1:1 competition experiments. In this case the following equation holds[5]:

$$k_{rel} = \frac{\log\left(1 + \frac{[P_A]}{[A]}\right)}{\log\left(1 + \frac{[P_B]}{[B]}\right)}$$

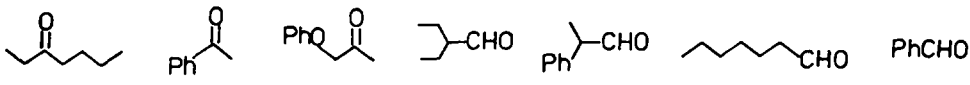
where [A] = final conc. of carbonyl compd. A
[B] = final conc. of carbonyl compd. B
$[P_A]$ = final conc. of product P_A
$[P_B]$ = final conc. of product P_B

The relative rates of the addition of $CH_3Ti(OCHMe_2)_3$ [6] to carbonyl compounds at +22°C in ether were calculated using the above equation, the parameters being obtained from a capillary GC analysis. The latter included a calibration curve for each compound[4]. In linking aldehyde with ketone reactivity, relatively fast reacting ketones and slow reacting aldehydes had to be found empirically. In each run two carbonyl compounds were chosen which do not differ in reactivity greatly to ensure maximum accuracy in the GC analysis.

RESULTS AND DISCUSSION

Relative Rates

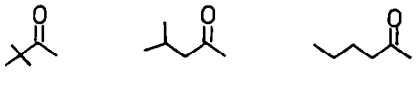
Using the procedure outlined above, the following relative rates were obtained for the addition of $CH_3Ti(OCHMe_2)_3$ at +22°C in ether.



	1		2		3		4		5		6		7
k_{rel}	1	:	2.2	:	13	:	44	:	105	:	680	:	1087

The calculated k_{rel}-value for benzaldehyde/acetophenone is 494, for heptanal/3-heptanone it is 680. These numbers are slightly different from the ones reported on the basis of preliminary rate measurements[1a] and are more precise due to the fact that they were not determined directly using a single aldehyde/ketone pair. From a synthetic viewpoint, a relative rate of 500-700 is certainly more than sufficient for chemoselective addition. Also, in synthetic applications involving aldehyde-selectivity, lower temperatures are generally used, conditions under which the k_{rel}-values are expected to be even larger. From the relative rate of 494 for the benzaldehyde/acetophenone pair obtained in the present study at room temperature, a $\Delta\Delta G^{\ddagger}$ value of 15.5 kJ/mol (=3.7 kcal/mol) can be estimated.

Both steric and electronic factors are expected to influence the relative reactivities. The present and other results point to the dominant role of steric factors[1]. For example, heptanal (6) reacts 15 times faster than 2-ethylbutanal (4). In the transition state of C-C bond formation, the ligands at titanium interact sterically with the substituents flanking the carbonyl function. Thus, the most pronounced effect occurs in going from an aldehyde to a ketone, and even significant differences within a common carbonyl family are "felt" by the reagent, as shown by the following ketone series (reagent: $CH_3Ti(OCHMe_2)_3$ at +22°C in ether):

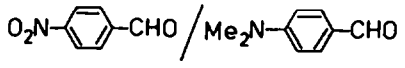


	8		9		10
k_{rel}	1	:	9	:	18

It should be noted that in case of CH_3Li or CH_3MgX, aldehyde-selectivity is small or non-existent[1,2]. These reagents are more polar and less sterically hindered. Interestingly, the zirconium analogs $CH_3Zr(OR)_3$ are not as selective as the Ti-reagents; in 1:1:1 competition experiments considerable "leakage" is observed, i.e., 5-10% of ketone adducts. We have ascribed this to the greater Zr-O bond length ($\sim$ 2.1 Å), compared to Ti-O ($\sim$ 1.7 Å), which means that the transition

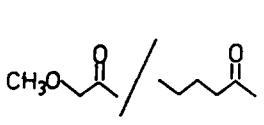
state of the former is not as compact[1,7]. In similar comparisons Kauffmann has advanced a related explanation based on relative atomic volumes[8].

The conclusion that electronic factors are not as important as steric properties is also in line with competition experiments involving p-nitrobenzaldehyde/p-dimethylaminobenzaldehyde (reagent: $CH_3Ti(OCHMe_2)_3$ in ether:



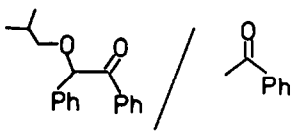
k_{rel} = 1.2 (0°C); k_{rel} = 3.5 (-40°C)

Phenoxyacetone (3) is different from the other compounds in that it has an oxygen function at the α-position which may form an initial chelate with the Ti-reagent leading to increased reactivity. We first postulated such an activating effect in the special case of o-methoxybenzaldehyde which is more reactive than sterically less shielded benzaldehyde[1a]. Similar qualitative observations have since been made in ketone systems[1,9]. In order to define the effect more closely, the following compounds were studied (k_{rel} in ether at +22°C using $CH_3Ti(OCHMe_2)_3$):



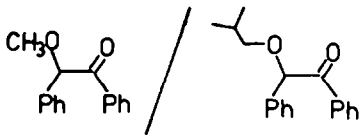
11 12

k_{rel} = 10



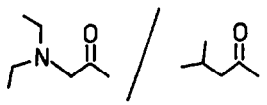
13 2

k_{rel} = 27



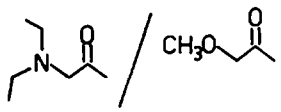
14 13

k_{rel} = 6.1



15 9

k_{rel} = 23

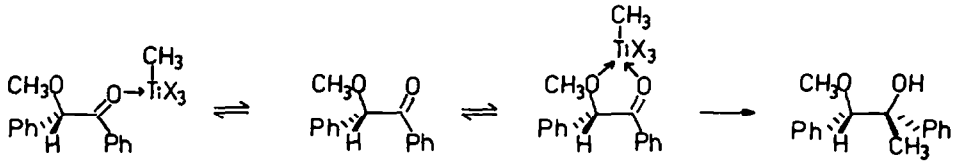


15 11

k_{rel} = 3.3

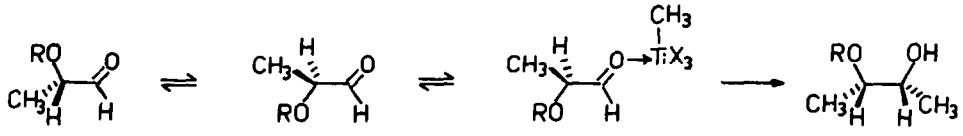
It can be seen that the alkoxy or amino derivatives are always more reactive than the ketones devoid of heteroatoms, even if the former are sterically more hindered (13 vs. 2). Sometimes ketones are more reactive than aldehydes (14 vs. 4)! These and related observations by Kauffmann[9] are of synthetic significance. The activating effect of an alkoxy or amino group can be explained on the basis of chelation, e.g., 17 vs. 16. In fact, in stereochemically relevant cases (e.g., 14), the chelation-controlled diastereomer adduct 18 is the sole product[4,10]. This also applies to 13, inspite of the fact that it reacts 6.1 times slower than 14. This difference is undoubtedly due to slightly increased steric crowding in the intermediate analogs of 17. The extremely bulky t-butyldimethylsiloxy group must

be used in order to obtain non-chelation-controlled adducts[11]. Such reactions are expected to be very slow, which is indeed the case.



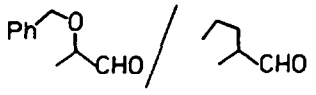
16 (X = $OCHMe_2$) 14 17 18

The above stands in complete contrast to α-alkoxyaldehydes (e.g., 19) which react with $CH_3Ti(OCHMe_2)_3$ to deliver the non-chelation-controlled adduct (e.g., 21) preferentially (92 : 8 diastereomer ratio)[10]. We believe that this is due to initial complexation anti to the alkyl group of the aldehyde function followed by C-C bond formation. The difference between 16 and 20 lies primarily in greater steric crowding of the former. This not only disfavors Lewis acid/Lewis base adduct formation thermodynamically, but also product forming C-C bond formation originating from these intermediates (e.g., 16).



19 (R = benzyl) 19 20 (X = $OCHMe_2$) 21

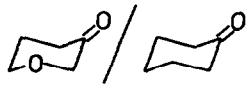
These arguments lead to the prediction that α-alkoxyaldehydes of the type 19 should not be more reactive than desoxy analogs. Indeed, the following competition experiment substantiates this (reagent: $CH_3Ti(OCHMe_2)_3$ in ether):



19 22 k_{rel} = 0.7 (at -20°C)

In addition to chelation as an explanation for increased reactivity in the ketone series, the electron-withdrawing inductive effect of the heteroatom must be considered. The above competition experiment (19/22) indicates that such an effect is not expected to be important. Furthermore, ketone 23, which cannot form chelates, was compared with 24. If the inductive effect were the sole factor in determining increased reactivity of α-alkoxy carbonyl compounds relative to the desoxy analogs, a k_{rel} value of 10-20 would be expected. The experimental value of 1.8 shows that it plays a minor role, if at all, in line with all of the previous argumentation. The small difference in reactivity of 23/24 is probably of steric origin (1,3 diaxial interactions).

$CH_3Ti(OCHMe_2)_3$ in ether at +22°C:



23 24 k_{rel} = 1.8

Activation Parameters

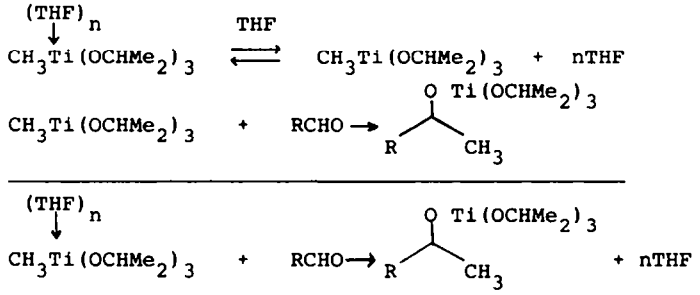
The activation parameters of the addition of $CH_3Ti(OCHMe_2)_3$ to heptanal in CH_2Cl_2 and THF are summarized in Table 1[12].

Table 1. Activation parameters[a] of the addition of $CH_3Ti(OCHMe_2)_3$ to heptanal

Solvent	$\Delta G^{\ddagger}$ (kJ/mol)	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta S^{\ddagger}$ ($J \cdot K^{-1} \cdot mol^{-1}$)
CH_2Cl_2	70.7 ± 5	51.2 ± 5	-83.6 ± 16
THF	69.0 ± 5	85.8 ± 5	+72.3 ± 16

a) Calculated for mean temp. = -40°C

The negative value of $\Delta S^{\ddagger}$ in case of CH_2Cl_2 as the solvent can be viewed as being "normal" for the present 2. order reaction. However, in case of THF it is positive, while the $\Delta G^{\ddagger}$ value remains essentially constant due to compensation by the larger $\Delta H^{\ddagger}$ term. Thus, THF must play an intimate role in the overall reaction. The results do not necessarily prove the following scheme, but they are certainly in line with it. The reagent is solvated via THF-adduct formation and must first kick off the THF to form free $CH_3Ti(OCHMe_2)_3$ before reacting with the aldehyde. This is reflected in the high $\Delta H^{\ddagger}$ value and in the positive $\Delta S^{\ddagger}$.



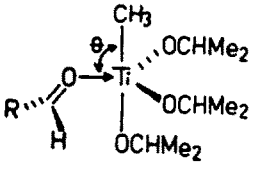
If CH_2Cl_2 is used as the solvent, donor complexes are not involved, i.e., CH_2Cl_2 solvates the reagent but does not form σ-bonds with it. Thus, free $CH_3Ti(OCHMe_2)_3$ is present and reacts directly with the aldehydes. These schemes neglect the possible role of dimeric forms of the reagent which have been shown to be in rapid equilibrium with the monomer in CD_2Cl_2[1b,4]. However, if the dimers were to play an essential role, 2. order kinetics would not be observed[4].

Another aspect concerns the amount of THF used. If the kinetics are performed in CH_2Cl_2 as the solvent and in the presence of two equivalents of THF, the same activation parameters as in the absence of THF are obtained[4]. Thus, the above equilibrium involving THF-complexation lies on the left only if an excess of THF is used.

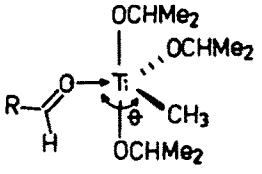
Do the present results provide a basis for additional mechanistic conclusions? The literature contains little data concerning activation parameters of Grignard-type reactions, although a great deal of mechanistic work has been reported[13]. Holm has determined activation parameters for the reactions of several Grignard compounds with ketones, but the alkyllithium reagents react too fast to allow measurements by his thermographic method[14]. For example, CH_3MgBr adds to benzophenone in ether with $\Delta H^{\ddagger}$ = 13.7 kcal/mol and $\Delta S^{\ddagger}$ = -12.2 e.u., while the more reactive t-BuMgBr leads to a lower $\Delta H^{\ddagger}$ (4.5 kcal/mol) and an unfavorable $\Delta S^{\ddagger}$ (-33.3 e.u.). Besides

the normal 1,2 adducts, attack at the aromatic ring was also observed. These and other results were interpreted on the basis of an electron transfer mechanism[14].

In our study, $CH_3Ti(OCHMe_2)_3$ reacted with benzophenone extremely sluggishly. The half-life of the addition at room temperature in the absence of solvent is about five days, and only the 1,2 adduct was formed[4]. We tentatively assume that $CH_3Ti(OCHMe_2)_3$ does not add via electron transfer. Two extreme mechanisms then need to be discussed, a concerted four-center process and the already mentioned two-step mode in which C-C bond formation is preceded by the intermediacy of a Lewis acid/Lewis base adduct. Other Lewis acids have been shown to add to the oxygen function of aldehydes RCHO anti to the R group, which lowers the LUMO (π^*)[15]. Assuming this in the present case, two penta-coordinate bipyramides 25 (methyl axial) and 26 (methyl equatorial) are relevant, each shown in the conformation in which the methyl group is closest to the carbonyl C-atom. Stereoelectronically, 26 is less favorable for an intramolecular 1,3 shift because the methyl group is "tilted" away from the carbonyl group. If such complexes are involved, the kinetics suggest intramolecular transfer of methyl groups. Alternative mechanisms in which $CH_3Ti(OCHMe_2)_3$ attacks 25/26, or 25/26 add to non-complexed aldehyde in the rate determining step would not be in line with the observed clean 2. order kinetics[4]. Related complexes as intermediates on the way to the products have been postulated (and sometimes discarded) in other Grignard-type additions[8,13-16].



25 ($\theta \cong 90^\circ$)



26 ($\theta > 90^\circ$)

Finally, the kinetics of addition reactions of $CH_3Ti(OEt)_3$, which is known to be primarily dimeric in benzene[17], were studied. Since this reagent is less reactive than $CH_3Ti(OCHMe_2)_3$[1,2], the temperature range of 0°C to -50°C was chosen for the determination of the activation parameters of the addition to heptanal. In THF second order kinetics (1. order in aldehyde and 1. order in monomeric $CH_3Ti(OEt)_3$) were observed. As shown in Table 2, $\Delta G^{\ddagger}$ (THF) is slightly higher than in case of $CH_3Ti(OCHMe_2)_3$ (THF), while $\Delta H^{\ddagger}$ is lower, and $\Delta S^{\ddagger}$ is negative (-40.4 $J \cdot K^{-1} mol^{-1}$). The latter value is different from the large negative $\Delta S^{\ddagger}$ value obtained for $CH_3Ti(OCHMe_2)_3$ in CH_2Cl_2 (Table 2). Although the results are difficult to interpret, monomeric $CH_3Ti(OEt)_3$ seems to be the reactive species, and perhaps at least one THF molecule at the reagent is retained throughout the addition process.

Table 2. Activation parameters[a] of the addition of $CH_3Ti(OEt)_3$ to heptanal in THF

$\Delta G^{\ddagger}$ (kJ/mol)	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta S^{\ddagger}$ ($J \cdot K^{-1} \cdot mol^{-1}$)
78.4	68.0	-40.4

a) Calculated for mean temp. = -25°C

In sharp contrast, the reactions in CH_2Cl_2 do not adhere to 2. order kinetics over the whole range of conversion. Evaluation according to 3. order kinetics also fails to provide a reasonably good fit[4]. The rate seems to decrease significantly after about one half of the active methyl groups has reacted[4]. These results show that in this case the mechanistic picture is even more complex. Perhaps the postulate that the dimer (having two active methyl groups) reacts initially, followed by a somewhat slower reaction of a sterically more hindered monomethyl dimer is not overly simplified[4].

EXPERIMENTAL SECTION

Reagents

Methyltriisopropoxytitanium was synthesized from $ClTi(OCHMe_2)_3$ and methyllithium and distilled according to a known procedure[6]. Methyltriethoxytitanium was prepared according to a literature procedure[17] using $ClTi(OEt)_3$ and methyllithium. Distillation in this case was not possible. However, LiCl was separated from the ethereal solution of $CH_3Ti(OEt)_3$ using a frit under an atmosphere of nitrogen. The ether was removed, pentane added and the rest of the LiCl removed as above. Removal of the solvent afforded a clear red oil which was used in the kinetics without further purification.

Competition Experiments

All kinetic experiments were performed in dry reaction vessels using dry solvents under an atmosphere of nitrogen. Typically, a 100 ml flask equipped with a serum cap and a magnetic stirred was charged with 40 ml of solvent and immersed in a water bath to maintain room temperature (22°C). Two carbonyl compounds (each 10.0 mmol) were then added. To such a stirred solution the titanium reagent $CH_3Ti(OCHMe_2)_3$ (10.0 mmol) was added via a syringe. The solution was stirred until conversion to the carbinols was >95%. This can be checked by taking a small sample, hydrolyzing with 0.1 M HCl, working up in the usual way[6] and inspecting the crude product by capillary gas chromatography. Typically, reaction times of 5-40 h were required for aldehydes, and up to 4 days for ketones. The solution was then treated with 0.1 M HCl, extracted three times with ether, and the ether phase washed with H_2O and saturated $NaHCO_3$. After drying over $MgSO_4$, most of the solvent was carefully evaporated and the residue examined by capillary gas chromatography. Peak area ratios were corrected by using standard solutions of the compounds involved, which were synthesized separately[4]. The k_{rel}-values were then calculated using the formula described above (METHODS).

Activation Parameters

The same precautions regarding the handling of air sensitive reagents were followed as above. A thermostat (Ultra-Kryomat K-120 W, Messgeräte Lauda) equipped with a precision thermometer (Firma Normag) was used to maintain a constant temperature (±0.2°C). A 100 ml flask containing 70 ml of solvent and 20 mmol of heptanal was cooled to the desired temperature (e.g., -20.7°C, -30.1°C, -41.3°C, -45.6°C, -50.5°C, -61.0°C) and the cooled reagent added. At various time intervals samples were taken, worked up as usual and examined by capillary gas chromatography, until >95% conversion was observed. Evaluation of the GC data allowed the calculation of rate constants. This was done three times in parallel separate runs, from which average values were computed. The values were used to calculate the activation parameters (Table 1)[4]. No significant difference was observed if the aldehyde was injected into the solution of the reagent. Clean second order kinetics were observed in all cases using $CH_3Ti(OCHMe_2)_3$. In case of $CH_3Ti(OEt)_3$ a temperature range of 0°C to -50°C was chosen (Table 2).

ACKNOWLEDGEMENT: We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for support of this work.

LITERATURE AND NOTES

1) a) M.T. Reetz, Top. Curr. Chem. 106, 1 (1982); b) M.T. Reetz, "Organotitanium Reagents in Organic Synthesis", Springer-Verlag, Berlin 1986.

2) B. Weidmann and D. Seebach, Angew. Chem. 95, 12 (1983); Angew. Chem., Int. Ed. Engl. 22, 31 (1983).

3) See for example R. Huisgen, Angew. Chem. 82, 783 (1970); Angew. Chem., Int. Ed. Engl. 9, 751 (1970).

4) S. Maus, Dissertation, Universität Marburg, 1986.

5) This equation is a special case (1:1:1 ratios used) of the more general equation derived by Ingold: C.K. Ingold and F.R. Shaw, J. Chem. Soc. 575 (1949).

6) For details of the preparation, see M.T. Reetz, J. Westermann, R. Steinbach, B. Wenderoth, R. Peter, R. Ostarek and S. Maus, Chem. Ber. 118, 1421 (1985).

7) M.T. Reetz, Pure Appl. Chem. 57, 1781 (1985).

8) T. Kauffmann, C. Pahde and D. Wingbermühle, Tetrahedron Lett. 26, 4059 (1985).

9) T. Kauffmann, T. Möller, H. Rennefeld, S. Welke and R. Wieschollek, Angew. Chem. 97, 351 (1985); Angew. Chem. Int. Ed. Engl. 24, 348 (1985).

10) For a review of chelation and non-chelation-controlled additions, see M.T. Reetz, Angew. Chem. 96, 542 (1984); Angew. Chem., Int. Ed. Engl. 23, 556 (1984).

11) M.T. Reetz and M. Hüllmann, J. Chem. Soc., Chem. Commun., in press.

12) The numbers are the average of several runs and thus differ minutely from the initial results published tentatively in our review [1b].

13) a) E.C. Ashby, Pure Appl. Chem. 52, 545 (1980); b) T. Holm, Acta. Chem. Scand. B 30, 985 (1976).

14) a) T. Holm, Acta. Chem. Scand. B 37, 567 (1983); b) personal communication.

15) M.T. Reetz, M. Hüllmann, W. Massa, S. Berger, P. Rademacher and P. Heymanns, J. Am. Chem. Soc. 108, 2405 (1986).

16) a) J.D. Wilkins, J. Organomet. Chem. 80, 357 (1974); b) G. Kreisel and W. Seidel, J. Organomet. Chem. 260, 301 (1984); c) D. Lozach, G. Molle, P. Bauer and J.E. Dubois, Tetrahedron Lett. 24, 4213 (1984); d) E. Kaufmann, P.v.R. Schleyer, K.N. Houk and Y.D. Wu, J. Am. Chem. Soc. 107, 5560 (1985).

17) K. Kühlein and K. Clauss, Makromol. Chem. 155, 145 (1972).