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Solvent effects in the Grignard reaction with alkynes

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ABSTRACT: Kinetic studies were carried out on the reaction of phenylmagnesium bromide with hex-1-yne in diethyl ether, and in binary mixtures of diethyl ether with toluene, chlorobenzene and dichloromethane. The reaction was accelerated by addition of non-donating solvents. The replacement of a coordinated solvent molecule by the alkyne is necessary for the reaction to proceed, according to density functional theory (DFT) calculations with B3LYP/6–31 + G* method. The non-donating solvents accelerate the reaction by shifting the replacement equilibrium in favour of the complex formation. An analysis in terms of the Koppel–Palm equation revealed a rate decrease with increase in solvent polarity and polarizability. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: Grignard compounds; Grignard reaction; alkynes; kinetics; solvent effects; DFT calculations

INTRODUCTION

Recently, we carried out a kinetic investigation of the Grignard reaction with acetylene.[1,2] In a solution to new details of the reaction mechanism, we observed large solvation effects which depend strongly on the steric requirements of both the Grignard reagent and the donors. However, the non-specific solvation effects were not investigated in that work.

In addition to a general interest, the effects of non-specific solvation can be informative concerning the reaction mechanism. In an earlier series of studies we were able to show quantitatively that in the Grignard addition reaction to ketones the transition states are of lower polarity than the reagents and, therefore probably have a cyclic structure.[3–6] A change in the polarity of the medium was achieved by addition of *n*-heptane or dichloromethane to the Grignard reagent prepared in a donor solvent. Linear plots of log *k* vs Kirkwood function were obtained for the reactions of pinacolone with ethylmagnesium and *n*-propylmagnesium bromides,[4] dipropylmagnesium[3,5] and diphenylmagnesium.[6] The susceptibility of the reactions to the polarity of the medium was remarkably dependent on the donating ability of donors (ethers, amines).[6,7]

In this work, we attempted to apply the same method to the Grignard reaction of alkynes with the goal of obtaining an insight into the solvation phenomena. The reaction of hex-1-yne with phenylmagnesium bromide was selected as a model process.

RESULTS AND DISCUSSION

The kinetics of the slow but sufficiently exothermic reaction were followed thermographically by means of the initial rates method in the same way as in our previous work[8] (for details, see Experimental). Phenylmagnesium bromide was prepared in diethyl ether and the required reagent solutions were obtained by addition of appropriate amounts of toluene, chlorobenzene or dichloromethane to the initial reagent. The previously used *n*-heptane[3–6] was not suitable since it caused precipitation of the reagents. Reaction media of different polarity/polarizability were generated in this way, while the specific solvation of the reagents presumably remained unchanged. The addition of toluene decreased the polarity and increased the polarizability of the solution, as can be seen in Table 1, whereas admixtures of chlorobenzene and dichloromethane caused increases in both the polarity and polarizability.

The results of the kinetic measurements are presented in Table 2. The rate constants are mean values for 3–4 parallel runs. The reproducibility of the data is within ±5%. The rate constant for the reaction in pure diethyl ether, $5 \times 10^{-5}\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ at 20 °C, is in reasonable agreement with $k_{\mathrm{II}} = 2 \times 10^{-4}\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ at 31.5 °C determined by Dessy and Salinger.[10] It can be seen from Table 2 that all the added non-donating solvents increase the reaction rate regardless of their possible polarity/polarizability contribution.

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Table 1. Polarity and polarizability parameters of the solvents investigated[9]

Solvent	Dielectric constant, ε	Refractive index, n
Diethyl ether	4.267	1.353
Toluene	2.38	1.496
Chlorobenzene	5.69	1.524
Dichloromethane	8.93	1.424

The solvent polarizability effect was excluded for the Grignard reaction with ketones on the basis that the experimental points for both *n*-heptane and dichloromethane additions fit the same log *k* vs Kirkwood function correlation.[4] For the reaction with alkynes, both medium effects can be involved. The rate constants were accordingly analyzed with the Koppel–Palm equation[11,12] [Eqn. (1)] where the terms for constant specific solvation were omitted:

$$\log k = \log k_0 + yY + pP \qquad (1)$$

According to Ref. 11, the polarity, *Y*, and polarizability, *P*, were calculated as

$$Y = (\varepsilon - 1)/(2\varepsilon + 1) \qquad (2)$$

$$P = (n^2 - 1)/(n^2 + 1) \qquad (3)$$

The dielectric constants (ε) and refractive indexes (n) for the solvent mixtures were calculated assuming additivity of the properties (by volume fractions). The Grignard reagents were considered as solvated with two ether molecules on average, so in the calculations 2 mol of ether per mole of reagent were not included in the solvent composition.

From the data in Table 2, we obtained the following equation for phenylmagnesium bromide solvated with diethyl ether:

$$\log k_{\mathrm{II}} = -5.65(\pm 0.36) - (1.02 \pm 0.61)Y + (9.4 \pm 1.4)P \qquad (4)$$

$$R = 0.925, \quad SE = 0.068, \quad n = 12$$

Although the overall correlation is satisfactory, the polarity and polarizability terms are statistically significant at the 95% confidence level. The absolute value of the susceptibility factor in the polarity term is considerably smaller than those for the reactions with ketones.[4–6] However, the negative sign of the constant indicates a smaller polarity of the transition state in comparison with the reactants. This seems to be consistent with the four-centre mechanism postulated by Dessy *et al.*[13] for this reaction and subsequently supported by evidence of nucleophilic assistance in the reaction (see, e.g., Refs 1, 14 and 15). In contrast, the preponderant solvent polarizability term, suggesting a charge separation during the activation process, is less readily understood in this context. Therefore, a significant contribution of solvation equilibria shifts in the last term of Eqn. (4) as an artifact cannot be excluded.

To obtain a more reliable understanding of the data, DFT calculations were performed. The main question was whether an alkyne molecule can directly attack the organomagnesium compound via an $S_{\mathrm{E}}i$ type of reaction or whether a preliminary replacement of a solvent molecule is necessary. The species involved in a Grignard reagent and their coordination complexes with an alkyne were studied in the gas phase using the DFT B3LYP/6–31 + G* method. Solvation was modelled using the supermolecule approach (for details, see Calculation Methods). We present here only the most relevant data since an extensive computational investigation of the reaction is in progress, the results which will be published elsewhere.

In order to save computing time, Grignard reagents were modeled by MeMgBr, dimethyl ether was taken for

Table 2. Kinetic data for the reaction in various media at 20 °C

Solvent	Molar fraction of the ether	Concentration ($\mathrm{mol\ l^{-1}}$) PhMgBr	Concentration ($\mathrm{mol\ l^{-1}}$) Hex-1-yne	Initial rate ($\mathrm{d}C/\mathrm{d}t$) $\times 10^5$ ($\mathrm{mol\ l^{-1}\ s^{-1}}$)	$k_{\mathrm{II}} \times 10^5$ ($\mathrm{l\ mol^{-1}\ s^{-1}}$)	$k_{\mathrm{II}}[\mathrm{E}] \times 10^5$	Y	P
Et_2O	1.0	0.503	0.528	1.25	4.72	36.53	0.343	0.178
Et_2O + PhMe	0.92	0.503	0.528	1.24	4.68	33.39	0.338	0.182
Et_2O + PhMe	0.62	0.503	0.528	1.42	5.38	25.42	0.315	0.198
Et_2O + PhMe	0.23	0.503	0.528	4.13	15.6	26.36	0.274	0.216
Et_2O + PhCl	0.96	0.487	0.512	1.19	4.80	35.71	0.345	0.181
Et_2O + PhCl	0.92	0.473	0.496	1.24	5.28	37.70	0.346	0.183
Et_2O + PhCl	0.84	0.446	0.469	1.34	6.31	41.20	0.350	0.188
Et_2O + PhCl	0.22	0.503	0.528	2.85	10.7	18.08	0.372	0.223
$Et_2O + CH_2Cl_2$	0.94	0.487	0.512	1.20	4.82	35.86	0.352	0.180
$Et_2O + CH_2Cl_2$	0.88	0.473	0.496	1.19	5.11	36.48	0.359	0.181
$Et_2O + CH_2Cl_2$	0.77	0.446	0.469	1.19	5.71	37.28	0.372	0.184
$Et_2O + CH_2Cl_2$	0.15	0.503	0.528	1.85	6.46	10.92	0.414	0.200

Table 3. Complexation energies (ΔE), enthalpies (ΔH) and Gibbs free energies (ΔG) for the reaction $Z + HC{\equiv}CCH_3 \rightarrow Z{\cdot}HC{\equiv}CCH_3$ calculated at the B3LYP/6–31 + G* level of theory [all values are given in kcal mol^{-1} and are corrected for basis set superposition error (BSSE)]

Z	ΔE	ΔH	ΔG
$MgBr_2$	−8.35	−8.31	−0.25
$MgBr_2{\cdot}Me_2O$	−4.88	−4.38	4.50
MeMgBr	−5.37	−5.06	2.81
$MeMgBr{\cdot}Me_2O$	−2.84	−2.46	6.82
Me_2Mg	−3.92	−3.66	4.45
$Me_2Mg{\cdot}Me_2O$	−1.58	−1.08	7.07

Table 4. Estimated Gibbs free energies and equilibrium constants at 20 °C for the complex formation with propyne in dimethyl ether solution according to Eqns (7a) and (7b)

Complex	ΔG (kcal mol^{-1})	K
$MgBr_2{\cdot}Me_2O{\cdot}HC{\equiv}CCH_3$	8.68	3.3×10^{-7}
$MeMgBr{\cdot}Me_2O{\cdot}HC{\equiv}CCH_3$	7.14	4.7×10^{-6}
$Me_2Mg{\cdot}Me_2O{\cdot}HC{\equiv}CCH_3$	4.22	7.1×10^{-4}

the ether and propyne for alkynes. The gas-phase data are reasonably applicable to poorly polar ether solutions.

As shown in Table 3, the solvation of the magnesium compounds causes a substantial decrease in the complexation energies. It should be noted that the ΔG values differ considerably from the ΔE and ΔH values, thus indicating a significant contribution of enthropy. The complexes are weak and ΔG of their formation is positive. Complexation of an alkyne with bisolvated magnesium species appeared to be energetically unfavourable (see also Fig. 1) and should be ruled out.

As a consequence, the reaction proceeds through the replacement of a solvent molecule by the alkyne and subsequent rate-limiting conversion of the complex to products:

$$Z \cdot 2E + A \overset{K}{\rightleftharpoons} ZEA + E \tag{5a}$$

$$ZEA \xrightarrow{k} \text{products} \tag{5b}$$

$$v = k[ZEA] = kK\frac{[Z \cdot 2E][A]}{[E]} \tag{6}$$

where Z denotes a magnesium compound, A the alkyne and E an ether molecule.

The equilibrium constant K can be estimated from the equilibria

$$Z \cdot 2E \rightleftharpoons ZE + E \tag{7a}$$

$$A + ZE \rightleftharpoons ZEA \tag{7b}$$

combining the data from Table 3 and the Gibbs free energies of solvation calculated in our previous work.[16] The results are presented in Table 4. When the Lewis acidity of the species decreases, the replacement of the ligands becomes easier. However, all the equilibria are shifted far to the left.

The nature of the phenylmagnesium bromide solution can also be represented by the Schlenk equilibrium:

$$2PhMgBr \rightleftharpoons Ph_2Mg + MgBr_2 \tag{8}$$

shifted towards PhMgBr in diethyl ether ([PhMgBr]/[Ph_2Mg] $\approx$ 8, from Refs 17 and 18). A semiquantitative treatment of the Lewis acidities of Grignard entities[7] indicated somewhat lower acidity of PhMgBr and Ph_2Mg species in comparison with corresponding methyl compounds. Moreover, diethyl ether, as a weaker Lewis acid due to the steric demands, should enhance the acidity of the magnesium center compared with dimethyl ether. Consequently, the equilibrium constants for the complex formation in the phenylmagnesium bromide–hex-1-yne system must be greater to some extent than those in Table 4. Nevertheless, the concentrations of the complexes in

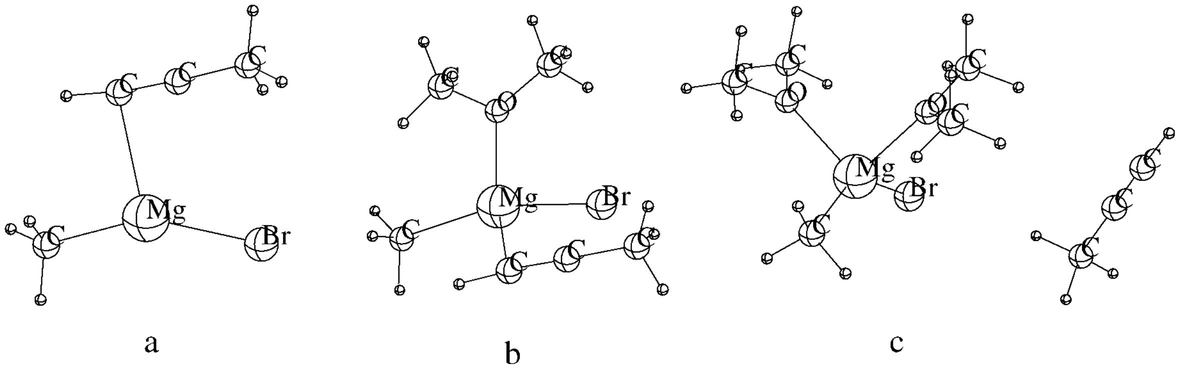

Figure 1. The optimized (at the B3LYP/6–31 + G* level of theory) structures of the propyne complexes with (a) unsolvated methylmagnesium bromide, (b) monosolvated methylmagnesium bromide and (c) disolvated methylmagnesium bromide

the reaction solution remain extremely low. This seems to be the reason for the rather feeble reactivity of alkynes, although the rate of product formation from an alkyne–Grignard complex appears to be unexpectedly large.

The equilibrium (5a) is shifted far to the left and the equilibrium can be taken into account by multiplying the observed rate constants by molar concentration of the free ether:

$$k_{\mathrm{II}} = \frac{kK}{[\mathrm{E}]} \tag{9}$$

Rate constants corrected in this way (Table 2) were correlated according to Eqn. (1) and the following equation was obtained:

$$\begin{gathered}\log\,[k_{\mathrm{II}}[\mathrm{E}]] = \\ -1.02(\pm 0.54) - (2.6 \pm 0.9)Y - (8.4 \pm 2.0)P \quad (10) \\ R = 0.841, \quad SE = 0.101, \quad n = 12.\end{gathered}$$

The concentration of free ether in the solution can be only roughly estimated, because the contribution of the Schlenk equilibrium [Eqn. (8)] and of the association equilibria of the species involved cannot be taken into account. This seems to be the reason for the relatively poor correlation of the data. However, the polarity and polarizability terms in Eqn. (10) are statistically significant and their signs are now coherent. Decelerating effects of solvent polarity and polarizability indicate a smaller polarity of the transition state in comparison with the reagents, thus presenting evidence in favour of a cyclic structure of the transition state.

The fast reactions of ketones can hence be rationalized on the basis of extensive complex formation with Grignard reagents. As the values for the equilibrium constants are large (for a review, see Ref. 19), with an excess of one of the reagents the other is almost completely bound and the changes in the solvent composition, similar to those in the present work, only slightly affect the positions of the equilibria. This explains why good linear log *k* vs Kirkwood function plots have been obtained for the reactions of ketones.[3–6] Moreover, the refractive indexes of ethers and of non-donating additives used in those studies differed only slightly and therefore the contribution of solvent polarizability remained undetected.

CONCLUSIONS

The reaction between an alkyne and Grignard reagent involves two consecutive steps, the first consisting in the replacement of a coordinated solvent molecule by the alkyne, followed by a unimolecular reaction of the complex. The complex formation equilibrium is shifted far towards the initial reagents and therefore, despite a fast rearrangement of the complex to products, the overall reaction is slow.

Addition of non-donating solvents accelerates the reaction, presumably by shifting the replacement equilibrium in favour of the complex formation. In addition, a susceptibility of the reaction rate to changes in the solvent polarity and polarizability was revealed by a correlation analysis. This points to a smaller polarity of the transition state in comparison with the reagents, thus presenting evidence in favour of a cyclic structure of the transition state.

EXPERIMENTAL

Materials. All the procedures with the reagents and solutions were carried out under dry argon. The Grignard reagents in diethyl ether were prepared in the conventional manner. The reagents in binary solutions were obtained by diluting the Grignard reagents with appropiate amounts of the ether and/or of the non-donating solvent.

Kinetic measurements. The reaction was carried out in a glass vessel mantled with foam plastic and placed in a thermostated housing. The equipment was sealed with a thermostated lid. The reaction cell was provided with a mechanical stirrer and a thermistor, which was connected through a bridge circuit to a recording potentiometer.

All parts of the equipment and the reagents were thermostated. The reaction vessel was purged throughly with pure argon, 15 ml of the Grignard reagent were cannulated into the cell and the stirring was started. After thermal equilibrium, 0.92 ml of hex-l-yne was introduced and the temperature change of the reaction solution (usually 0.1–0.2 °C) was recorded as a plot of temperature versus time. Because the system was nearly adiabatic, the heat exchange with the internal part of the calorimeter caused only a little heat loss.

The zero-order initial rate constants in $\mathrm{mol\,l^{-1}\,s^{-1}}$ were obtained dividing the rate constants, determined as the slope of the tangent to the kinetic curve at the initial point, by the molar temperature rise of the reaction. The latter was determined from a separate run with the same reagent containing about 10 mol% triethylamine. The rapid and complete reaction of 30 μl of hex-l-yne raised the temperature by about 0.6 °C and provided the total heat of the reaction under the experimental conditions. The second-order rate constants were obtained dividing the initial rate constants by initial concentrations of hex-l-yne and the Grignard reagents.

CALCULATION METHODS

All calculations were carried out using the Gaussian 98 program package.[20]

Optimizations and vibrational analysis were done using DFT with hybrid B3LYP functional and the 6–31 + G* basis set. All stationary points were found to be true minima (number of imaginary frequencies, NImag = 0). The calculated frequencies were also used for calculations of enthalpies and Gibbs free energies. The stability of the complexes was calculated considering the basis set superposition error estimated according to the counterpoise correction method of Boys and Bernardi.[21]

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