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ENTROPIC EVIDENCE FOR THE FORMATION OF CARBONYL COMPOUND-DEPENDENT INTERMEDIATE COMPLEXES IN THE IVANOV REACTION

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Summary : Enthalpies and entropies of activation for the Ivanov reaction in THF are reported. On the basis of the positive and carbonyl compound-dependent entropies of activation, it is concluded that the reaction occurs via differently solvated complexes between the enolate and the carbonyl compound.

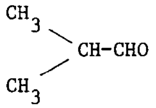
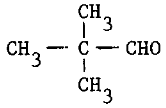
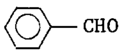
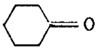
The intermediate formation of a complex between a Grignard reagent and a carbonyl compound has been observed in the Grignard reaction.[1] This complex formation is often believed to promote a metal-assisted intramolecular addition of RMgX to the carbonyl compound. To explain the stereochemical behaviour, similar interactions between carbonyl compounds and metal ions within the transition state have also often been postulated for aldolisation[2] and for different kinds of aldolisation-type reactions, such as the Refortmasky and Ivanov reactions.[3-5] Our recent results on the stopped-flow kinetics of the Ivanov reaction in THF give evidence that the reaction proceeds via the intermediate formation of a complex with a carbonyl compound-dependent structure.

At very low concentrations ($\simeq 10^{-3}$ M) of the Ivanov reagent (formed by the reaction of two equivalents of iPrMgCl with phenylacetic acid)[6] a first order with respect to both the carbonyl compound and the organometallic reagent was observed with several aldehydes and ketones, whereas at higher concentrations the kinetic behaviour was complicated by the formation of an unreactive dimer.[7] For four of the carbonyl compounds, temperature effects on the second-order rate constants were carefully studied and the enthalpic and entropic contributions were separated. The results reported in the Table show some unexpected and striking aspects :

(a) whereas the variations in the Gibbs energy of activation (which correspond to small differences in k_2) are small, the variations of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ from one carbonyl compound to another are quite larger ; this reflects a crude isokinetic relationship between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (Fig.1).

(b) the $\Delta S^{\ddagger}$ term is always positive (about zero for isobutyraldehyde) and is even strongly positive for cyclohexanone.

Table. Activation Parameters for the Ivanov Reaction[a]

Carbonyl compound	k_2 [b] ($M^{-1}s^{-1}$)	$\Delta G^{\ddagger}_{298}$ (kcal mol^{-1})	$\Delta H^{\ddagger}$ [c] (kcal mol^{-1})	$\Delta S^{\ddagger}$ [c] (cal $mol^{-1}K^{-1}$)
	465 ± 27	13.8	14.0 ± 0.2 [d]	+ 0.9 ± 0.7 [d]
 $CH_3-C(CH_3)_2-CHO$	74 ± 3	14.9	18.1 ± 0.7 [e]	+11.0 ± 2.0 [e]
	561 ± 30	13.7	17.2 ± 0.2 [f]	+11.7 ± 0.7 [f]
	19.4 ± 1.0	15.7	21.4 ± 0.3 [g]	+19.1 ± 1.0 [g]

[a] $PhCH{=}CH(OMgCl)_2$ + carbonyl compound. [b] Obtained as the mean ratios between the pseudo-first order rate constants and the concentrations of the carbonyl compounds at the end of the run (see note 7). Figures correspond to standard deviation. [c] Obtained by plotting Ln (k_2/T) vs. 1/T. k_2 values were corrected by taking into account thermal expansion of THF. Figures correspond to errors estimated by taking into account the uncertainty on k_2. [d] From data at 5, 10, 20, 25 and 30°C. [e] From data at 10, 20, 25 and 30°C. [f] From data at 5, 20, 25 and 30°C. [g] From data at 10, 20, 25, 30 and 40°C.

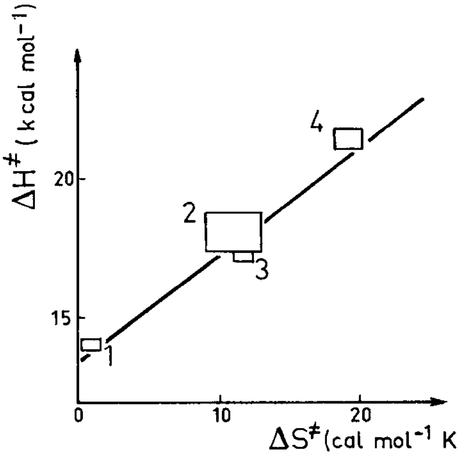


Fig. 1. Isokinetic Relationship for the Ivanov Reaction in THF (1: Isobutylraldehyde ; 2: Pivalaldehyde ; 3: Benzaldehyde ; 4: Cyclohexanone).

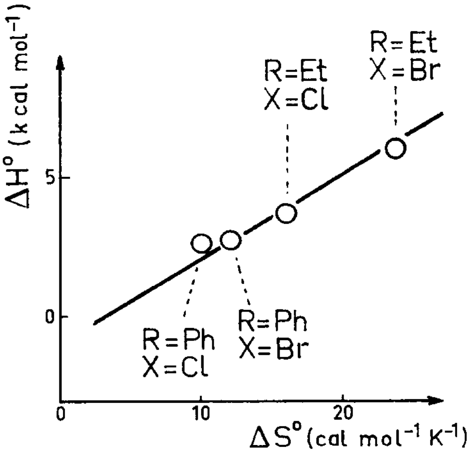
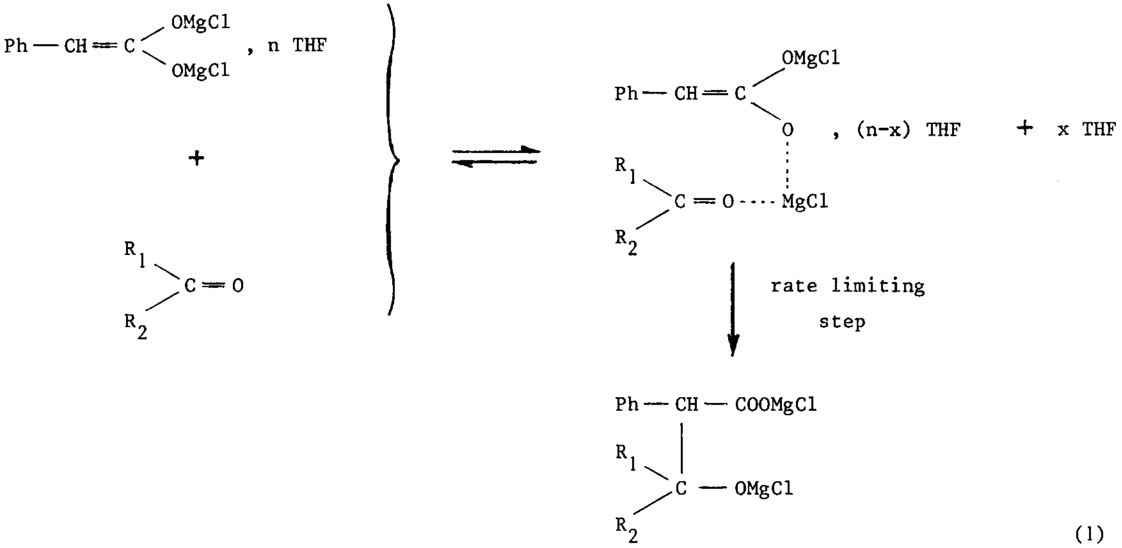


Fig. 2. ΔH° - ΔS° Relationship for the Schlenk Equilibrium of RMgX in THF (from data in ref. 10).

These results are clearly in disagreement with a mechanism in which the rate-limiting step would be a true bimolecular addition of the carbonyl compound to the metal-associated enolate ; however, they strongly favour a two-step mechanism : exoentropic preequilibrium association followed by a rate-limiting unimolecular electrocyclic rearrangement of the complex (eqn 1). Indeed, it is well known that bimolecular processes exhibit a negative entropy (usually < -10 cal $mol^{-1}K^{-1}$) which stems from the decrease of the translational degrees of freedom in going from the reactants to the transition state.



(1)

Enthalpy-entropy compensation, corresponding to a linear relationship between enthalpies and entropies, has been observed in ligand-exchange reactions when a ligand replaces x liganded solvent molecules, and when x varies throughout a series of ligands or metals.[9] A similar explanation is probably valid for the Ivanov reaction. Indeed, if one assumes that the enthalpy and entropy variations primarily arise from changes in the thermodynamic parameters of the preequilibrium, $\Delta H^{\ddagger}$-$\Delta S^{\ddagger}$ compensation is due to differences in the number of the expelled THF molecules. (The $\Delta H^{\ddagger}$ variations correspond chiefly to differences in the number of THF-Mg^{2+} bonds which are broken, and the $\Delta S^{\ddagger}$ increase is related to the increase of the translational partition functions)

An interesting comparison can be made between the data reported here and the data by Smith and Becker[10] on the thermodynamics of the Schlenk equilibrium in THF for simple Grignard reagents (eqn 2)

$$R_2Mg + MgX_2 \rightleftharpoons 2\ RMgX \qquad (2)$$

These authors reported that ΔS^{o} is strongly positive in THF (up to 23.7 cal $mol^{-1}K^{-1}$), whereas it is about zero in Et_2O, and that ΔH^{o}-ΔS^{o} partial compensation occurs when R or X is changed.

[This latter property can be depicted by a rough ΔH^o-ΔS^o relationship (Fig.2)] . These results were interpreted by considering changes in the coordination numbers of the magnesium ion. Indeed, Smith and Becker pointed out that magnesium in magnesium halides should be coordinated up to 6 ligand molecules in THF, instead of 4 in Et_2O, and that the coordination number of magnesium is propably reduced in going from the left side to the right side of the reaction. The analogies in the entropic values ($\Delta S^{\ddagger}$ for the Ivanov reaction compared to ΔS^o for the Schlenk equilibrium), as well as in the ΔH-ΔS plots, suggest that a similar behaviour occurs for the first step of the Ivanov reaction ; i.e. a change in the coordination number usually accompanies carbonyl compound coordination to magnesium. This change depends on the structure and the reactivity of the carbonyl compound : the amount of loosening of complexed THF molecules is small for the most reactive isobutyraldehyde and larger for cyclohexanone. It can also be concluded that magnesium in the Ivanov reagent is more than tetracoordinated (probably hexacoordinated) in THF.

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(7) Kinetic measurements were performed by fast-mixing the Ivanov reagent (concentration : *ca*.5 x 10^{-2} M in THF) with an equal volume of a carbonyl compound solution (concentration > 0.1 M in THF) and by following the increase in transmittance at 310 nm (l = 0.1 cm). At this wavelength, the absorbance, mainly due to the organometallic reagent, is so large (λ_{max} = 307 nm ; $\varepsilon = 10^4$ M^{-1} cm^{-1}) that the transmittance is zero during most of the run. Under these conditions, it is only possible to follow the decrease of the Ivanov reagent concentration during about the five last percents of the reaction, *i.e.* from *ca.* 10^{-3} M. For this part of the transmittance-time curve, it was shown that the enolate concentration decrease agrees with the first-order kinetic equation. Since in this part of the run, the concentration of the carbonyl compound is roughly constant, these conditions correspond to pseudo-first order conditions. The variations of the experimental rate coefficient were examined as a function of the carbonyl compound concentration : it was shown that k_1 is proportional to the concentration at the end of the run. (It was verified that the product of the reaction does not interfere with the kinetics).

When measurements were performed at 345 nm, *i.e.* when the absorptivity of the organometallic reagent is much smaller, it was observed that the first-order rate law was not valid throughout the whole range of concentrations, even when the concentrations of the carbonyl compound were large enough so that they were always in large excess. Under these conditions, the variations in transmittance fit a complex kinetic law derived by assuming the formation of a dimer species in the Ivanov reactant (literature data on dimer formation from simple ketone enolates indicates this might result from the association of two enolate ions with the same magnesium ions) in fast equilibrium with the monomer, and also by assuming that this dimeric form is unreactive. By means of this equation, second-order rate constants for the reaction of the monomeric Ivanov reagent were obtained. They agreed with those calculated at low concentrations.

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