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THE STRUCTURE OF THE TRANSITION STATE IN NUCLEOPHILIC ADDITION REACTIONS TO CARBONYL COMPOUNDS.

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We have been interested for some time in the nucleophilic addition reactions to carbonyl compounds[1-6], the interpretation of our kinetic data has lead us to conclude that the position of the transition state along the reaction coordinate is not the same for all reactions and depends instead upon the nucleophilic reagent.

This point, however, is a matter of controversy among workers in this field ; the "old" dichotomy first proposed by DAUBEN[7] - Steric approach control versus product development control - has been sharply criticized in recent years[8-12] and CHEREST and FELKIN[12] have postulated that the transition state is always "Reactant-like", whatever may be the nucleophile.

Most of the discussions however are based on the observation of the stereochemical course of reactions such as carbonyl reductions by complex metal hydrides and Grignard reagents additions. The explanations given so far fail to account satisfactorily for the kinetic data which, in our opinion, are at least as important as the stereochemical ones. We wish to develop, herein, three kinds of arguments which are consistent with the idea that the transition state can be either "Reactant-like" or "Product-like" or somewhere in between depending upon the nature of the incoming nucleophile.

1) the reaction constant ρ

In table I are listed the ρ values of seven nucleophilic addition reactions taken from the literature or from our own measurements (entries 4 and 7).

The ρ's are always > 0 which indicates an increase in the electron density around the central carbon atom when the system proceeds from reactants to transition state ; the charge, initially > 0 and approximatively equal to $+ 0.4$ [19] decreases during the formation of the activated complex ; although no close relation exists between the value of ρ and the variation of the charge density, a very crude estimate can be made[20] : a variation of charge of 1 unit must correspond to a ρ value of 6 to 10. Thus the charge born by the central carbon atom in the transition state is still largely positive in reactions 5 to 7 and very close to zero - probably slightly negative - in the BH_4^- ion addition reaction.

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Table I

	Reactions	ρ	References
1	$R-\phi-CO-CH_3$ + BH_4 Na	+ 3.06	13
2	$R-\phi-CO-\phi-R'$ + BH_4 Li	+ 2.81	14
3	$R-\phi-CHO$ + HCN	+ 2.33	15
4	$R-\phi-CHO$ + SO_3^{--}	+ 1.27	16
5	$R-\phi-CO-CH_3$ + ϕ MgBr	+ 0.41	17
6	$R-\phi-CO-\phi-R'$ + CH_3Mg I	+ 0.36	18
7	$R-\phi-CO-CH_3$ + NH_2OH	+ 0.32	6

Others things being equal, the greater the ρ and the greater the charge variation, the farther the transition state is from the initial state : thus the transition state is certainly more "Product-like" in the reduction by BH_4^- ion than in cyanohydrin formation. The case of the SO_3^{--} ion addition is even more striking ; this nucleophile bears two negative charges, nevertheless the ρ value of the bisulfite addition compound formation is only 1.27 and the transition state is probably very similar to the reactants. In the last three reactions the attacking nucleophile is neutral : the very low value of ρ indicates a very small difference in the electronic density on the central carbon atom between the reactants and the transition state and we can conclude - in complete agreement with the findings of KARABATSOS and ALTHUIS[21] - that the transition state is "Reactant-like".

2) The linear free-energy relationship $\delta\Delta G^{\neq} = \alpha\ \delta\Delta G^{\circ}$

The existence of a linear relationship between the free energies of activation and of reaction $\Delta G^{\neq}$ and ΔG° has been often observed although there is no a priori theoretical reason for the existence of such a correlation.

When this kind of relationship occurs it means that the different factors which influence the reactivity - electronic, steric and so on - act in the same way for all the compounds which lie on the correlation line. Moreover the slope of this line, α, is related to the position of the transition state along the reaction coordinate ; α is always somewhere between 0 and 1 : a "low" value of α indicates a "Reactant-like" transition state, a "high" value a "Product-like" transition state.

From results found in the literature[22] and from our own date we have been able to establish a linear free - energy relationship for three nucleophilic addition reactions , the correlation coefficient, the number of compounds which obey the correlation and the slope α are given in the table II.

The slope is much higher in the cyanide ion addition than in the two other cases and this is another argument in favour of a transition state more "Produdt-like" in the case of the cyanohydrine formation reaction.

Table II

Nucleophile	Number of Ketones	Correlation coefficient	α
SO_3^{--}	12	0.99	0.49
NH_2Oh	7	0.99	0.56
CN^-	17	0.95	0.74

3) Ratio of rate constants

For compounds which lie on the same correlation line, i.e. for which the same reactivity factors are operating, the difference in reactivity must depend upon the position of the transition state along the reaction coordinate.

The ratios of the rate constant of cyclohexanone to those of cyclopentanone, cycloheptanone and acetone, for four nucleophilic addition reactions, are given in the table III. There is a marked trend in these ratios, the difference in reactivity between any two compounds increasing in the order : SO_3^{--} NH_2OH CN^- BH_4^-. The different factors we invoked to explain the reactivity of the ketones i.e. hyperconjugation in the initial state, steric effects, torsional strain etc... are more efficient in differentiating two compounds when the transition state is farther from the starting materials. Thus, in the cases of SO_3^{--} ion and NH_2OH additions in which the transition state is "Reactant-like" the stereoelectronic effects will be the most important factors of reactivity ; on the other hand, when the transition state is "Product-like", as in the other two reactions, steric effects (torsional strain or steric effects of approach) will take on more importance in explaining the difference in reactivity.

Table III

	SO_3^{--}	NH_2OH	CN^-	BH_4^-
k_{C_6} / k_{C_5}	15	23	24	46
k_{C_6} / k_{C_7}	12	23	50	158
$k_{C_6} / k_{C_{acetone}}$	2.5	5.5	14	20

The ratio k_{C_6} / k_{C_7} deserves particular attention : this ratio varies widely with the nucleophile and can be a useful criterion to assess the position of the transition state along the reaction coordinate.

The arguments developed above are altogether consistent with the fact that the transition state, in nucleophilic addition reactions, can be either "Reactant-like" or "Product-like", depending upon the nucleophile. In the four reactions we have examined so far, SO_3^{--} ion and

NH_2OH additions are "reactant-like" and BH_4^- ion reduction and cyanohydrin formation are "product-like". In the following paper we shall describe experiments, made on a model compound; which confirm and reinforce our views on this problem.

We believe moreover that even for the same nucleophile the transition state is not always necessarily at the same place on the reaction coordinate ; we have not, at the present time, compelling evidence to support this view which stems from the examination of the $\delta\Delta G^{\neq}$ / $\delta\Delta G^{\circ}$ relationships. When a linear relationship occurs between these quantities for most of the compounds, the fact that some compounds do not lie on the regression line means that "something else" happens, this being probably due to a "shift" of the transition state.

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