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ADAMANTANONE : A MODEL TO ASSESS THE POSITION OF THE TRANSITION STATE IN NUCLEOPHILIC ADDITION REACTIONS TO CARBONYL COMPOUNDS.

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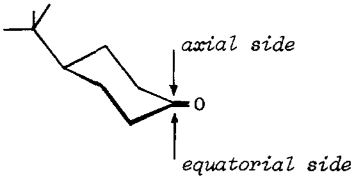
As we have previously pointed out[1], the position of the Transition State along the reaction coordinate is a matter of controversy among workers in the field of nucleophilic addition reactions to carbonyl compounds.

Some authors claim that the transition state is always "Reactant-like" whatever may be the nucleophile ; others think, on the contrary, that the structure of the transition state depends upon the nucleophile and can be either "Reactant-like", or "Product-like" or somewhere in between.

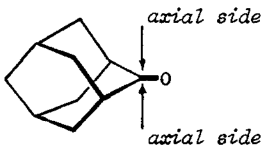
In the preceding paper we have set forth three kinds of arguments, based upon extra-thermodynamic relationships and ratios of rate constants, which plead in favor of a shift of the activated complex along the reaction coordinate according to the nature of the incoming nucleophile. These arguments are alltogether consistent with this idea and we believe that this "mutual consitency" cannot be fortuitous. However, considered separately , none of them afford compelling evidence for the hypothesis under consideration.

We have tried to devise an experiment which would give us an unambiguous answer to the problem and found that adamantanone is a good model for this purpose, providing we could compare the rate of nucleophilic addition to adamantanone with the rates of attack on both sides of cyclohexanone.

Both sides of the adamantanone molecule are the same and are like the axial sides of the cyclohexanone as can be seen from the following figure :



4-t-butylcyclohexanone



adamantanone

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The rates of axial and equatorial attack k_a and k_e on 4-t-Butylcyclohexanone are usually quite different ; if we know the overall rate constant k and the percent of the two epimers formed during the reaction we can easily have a good estimate of k_a and k_e.

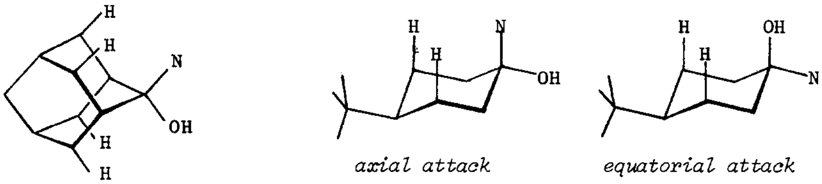
Let us see now what happens in the case of adamantanone : we shall examine only two extreme cases, arising when the transition state is either reactant-like or product-like :

a) the transition state is "Reactant-like".

The nucleophile is still quite far from the central carbon atom which is in a sp_2 hybridization state. When the nucleophile approaches the adamantanone molecule - whatever may be the direction of the approach - it "sees" the axial side of cyclohexanone : the rate of addition on adamantanone, k_α, must then be approximatively equal to 2 k_a.

b) The transition state in "Product-like"

The situation is completly different in this case ; the central carbon atom is now in a sp_3 **state** and both the -OH group and the nucleophile N are axial with respect to one side or the other of adamantanone (fig. 2). At best when the nucleophile is small - as for example in the borohydride ion reduction - we are actually in the situation resulting from an <u>equatorial</u> attack of the cyclohexanone and the rate constant k_α will be $\simeq \underline{2\ k_e}$.



axial attack *equatorial attack*

<u>Fig. 2</u>

If the nucleophile is something else than a H atom, the rate constant k_α will be $< 2\ k_e$.

To sum up, we may say :

- if the transition state is "Reactant-like" $k_\alpha \simeq 2\ k_a$
- if the transition state is "Product-like" $k_\alpha \simeq 2\ k_e$
- if the transition state is somewhere between reactants and product k_α will have an intermediate value between 2 k_a and 2 k_e.

In table I we report our results for the addition reactions of 3 nucleophiles to 4-t-Butylcyclohexanone and adamantanone.

In the first reaction, reduction by BH_4^- ion, $k_\alpha = 5.14$ and is slightly higher than $2\ k_e = 4.30$ but much smaller than $2\ k_a = 17.10$, in the second reaction, SO_3^{--} ion addition $k_\alpha = 0.16$ and is equal, whithin experimental error, to $2\ k_a = 0.14$.

Table I

Reagent					
	k total	% axial attack	k_a	k_e	k_α
BH_4^-	10.7 (1)	80	8.55	2.15	5.14 (1)
SO_3^{--}	0.7 (2)	10	0.07	0.63	0.16 (2)
NH_2OH	464.10^4 (3)	?	?	?	44.10^4 (3)

(1) In $l.mole^{-1}.mn^{-1}$ at 25°C in H_2O/dioxane 50/50

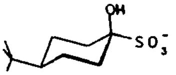
(2) In $l.mole^{-1}.sec^{-1}$ at 25°C in H_2O at pH = 4.000

(3) In $l.mole^{-1}.mn^{-1}$ at 25°C in H_2O/EtOH 95/5 at pH = 1.00.

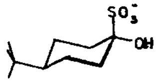
These data prove beyond any reasonable doubt that the transition state is Product-like in the former reaction and reactant-like in the latter, as already suggested in the preceding paper. Due to the uncertainty on the percent of axial attack, usually calculated from the amount of the two epimers isolated at the end of the reaction we cannot expect a very close agreement between k_α and either 2 k_e or 2 k_a : in fact an exact agreement would be merely fortuitous since 2 k_a and 2 k_e represent only two limiting values for k_α.

In the third case, NH_2OH addition, the percent of axial attack is not known, and is not easy to measure , from the rate constants observed we can predict that the attack is equatorial to an extent of about 95 %.

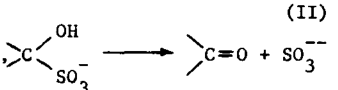
We believe that the adamantyl system can be useful not only to elucidate carbonyl addition reaction but also for the reverse reaction, the passage from a sp_3 to a sp_2 carbon atom. We have checked this idea in one case, the hydrolysis of bisulfite addition compounds for which we had measured the rate constants for both epimers of the 4-t-butylcyclohexanone^2.. These rate constants are respectively 4.45 $10^{-4}.sec^{-1}$ for epimer I and 26 $10^{-4}.sec^{-1}$ for epimerII:



(I)



(II)

In this reverse reaction,  $\mathrm{>C(OH)SO_3^-} \longrightarrow \mathrm{>C{=}O} + SO_3^{--}$, the transition state must be near the ketone and we can estimate the rate constant of the adamantyl derivative if we assume that, other things being equal, the difference in reactivity reflects the difference in steric strain relief between the two epimers. In epimer I, when the reaction goes to completion, there is a strain relief equal to the conformational energy of the -OH group, i.e. - ΔG_{OH}=+0.87 Kcal^3 in epimer II the steric strain relief is equal to - $\Delta G_{SO_3^-}$ = + 2.25 Kcal^2. In adamantanone both the OH group and the SO_3^- group are axial with respect to one side of the molecule ; the relief of strain, when the system proceeds from reactants to product in thence + (0.87 + 2.25)=+3.12Kcmole.

A simple calculation allows us to predict that the adamantanone bisulfite addition compound must hydrolyse faster than the fastest of the two epimers of 4-t-butylcyclohexanone and according to the energy relief calculated above at a rate > $110.10^{-4}.sec^{-1}$. The experiment has given us $227.10^{-4}.sec^{-1}$[4], i.e. about two times the calculated figure.

We are inclined to believe that this result is in accordance with theory since the strain relief in adamantyl system is certainly higher than 3.12 Kcal/mole ; in 4-t-butylcyclohexanone the $\widehat{CCC}$ angle is equal to 111°5 and the resulting "flattening" of the chair diminishes somewhat the interactions between an axial substituent and the axial 3 and 5 - H atoms.

Two conclusions can be drawn from the results reported here :

1) Our assumption of the dependance of the position of the transition state along the reaction coordinate upon the nucleophile is essentially correct.

2) Adamantyl system is a good model to assess the position of the transition state in reaction involving a change of nydridization of the central carbon atom in the rate-limiting step. It does not matter whether the change is from sp_2 to sp_3 or the reverse, the limitation being that the steric effects are the main factors of reactivity.

The adamantyl system can be used even for very different types of reactions. DALTON, POND and TURRO[5] have recently measured the rate of oxetane formation by photoaddition of trans dicyanoethylene to a number of substituted cyclohexanones and to adamantanone. From their data it is easy to estimate the rate constant k_a of an axial attack, which is in the range $2.4 - 2.6\ 10^{-9}\ M^{-1}.sec^{-1}$; the rate constant of addition to adamantanone, $5.0\ 10^{-9}\ M^{-1}.sec^{-1}$, is exactly what can be expected $\simeq 2\ k_a$, for a reactant-like transition state, as assumed by the authors and there is, may be, no need to look for any other explanation to account for the "rate increase" of adamantanone.

References

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