GENERALIZED CURTIN-HAMMETT PRINCIPLE AND THE ELUCIDATION OF TRANSITION STATE TYPE.

APPLICATION TO STEREOSELECTIVITY IN LAH REDUCTION OF ALKYL-ARYL-KETONES.

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We have recently pointed out (1,2) the need for an equation relating stereoselectivity to some parameters which could be susceptible of experimental determination or, at least, accurate estimation. Such equation would lead to the quantitative prediction of asymmetric induction in kinetic controlled reactions.

Equation [1] is the result of a generalization of Curtin-Hammett principle (2) to any num-

$$\frac{N_A}{N_B} = \frac{\sum\limits_{i} \exp(-G_i^{A\neq}/RT)}{\sum\limits_{i} \exp(-G_i^{B\neq}/RT)} \qquad [1]$$

ber of significant transition states. Its application eliminates some of the limitations inherent to previous interpretations of asymmetric induction in open-chain compounds (3,4,5). As applied to the reactions in Table I, N_A, N_B stand for percentages of diastereomeric products and $G_i^{A\neq}$, $G_i^{B\neq}$ are free energy levels of the various transition states leading respectively to A and B, evaluated with reference to a common level. Such reference level is taken as the free energy content of a hypothetical transition state with no steric interactions of the kind that differentially unstabilize each of the actual transition states.

TABLE I. Percentage of erythro carbinol in LAH reduction of $R-C_6H_4-CO-CHR_1-CR_2R_3R_4$ (Et$_2$O, 35°C)

Entry	Nature of ketone					% Erythro (calc.)		% Erythro (exp.)	Ref.
	R	R_1	R_2	R_3	R_4	Reactant-like TS$\neq$	Product-like TS$\neq$		
1	H	Me	Me	Me	Me	97	74	100±3	6
2	H	Me	H	Me	Me	76	60	86±3	1
3	H	Me	H	H	Me	61	55	55±3	6
4	H	Me	H	H	Ph	67	49	47±3	7
5	p-Me	Me	H	H	Ph	67	49	47±3	8
6	m-Me	Me	H	H	Ph	67	49	47±3	8
7	o-Me	Me	H	H	Ph	66	48	45±3	8,9
8	H	H	H	Me	Ph	46	49	48,7±0,2	2

In the calculation of N_A/N_B the following steps are involved: a) establishment of the various transition states leading to each of the diastereomeric products; b) analysis of interactions present in each transition state; c) evaluation of the energy of such interactions and of $G^{A^{\neq}}_i$ and $G^{B^{\neq}}_i$ levels relative to a reference level; d) application of equation [1].

As an illustration we are going to elaborate the case that corresponds to entry 1 of Table I. The ways of attack leading to the six different transition states are indicated in Fig. 1 ("H" stands for reducing agent). The evaluation of interactions as well as their sum, $G^{\neq}_i$, for the various transition states of trigonal type are summarized in Table II. It is to be noted that for the remaining entries of Table I, eighteen different transition states are to be taken into account.
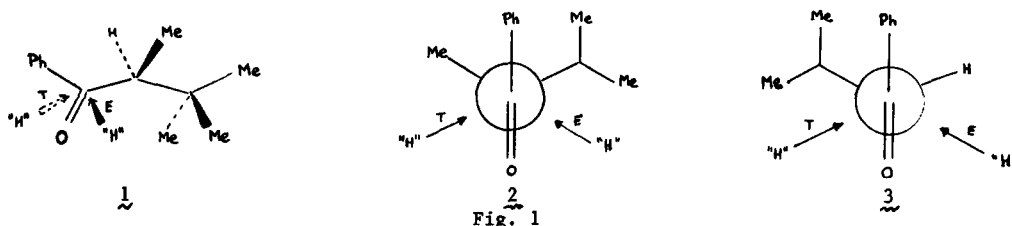

Fig. 1

To understand the origin of the figures in Table II, some previous considerations about the nature of the transition states are necessary. From a critical analysis of recent literature (10,11), reactant-like and product-like transition states may be considered as the geometrical extremes of a wide spectrum, to which a "trigonal type" or "tetrahedral type" geometry can be respectively assigned. For a four centre transition state (12), both types are visualized in Fig. 2 concerning the degree of breaking and new formation of bonds and in Fig. 3 with regard to a tentative geometrical delimitation of them.
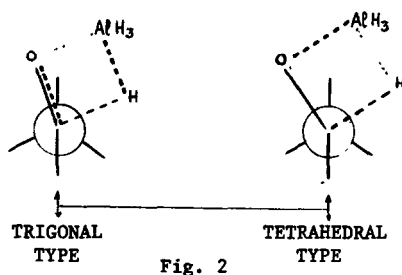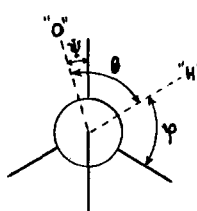

Fig. 2   Fig. 3

Steric interactions which differentially unstabilize the transition states may be already present in the initial state or be of new formation. Among the former, some have the same value at the initial and final states, value which has also been taken for the transition state. Such are the (1,2)gauche interactions of Ar with C-2 substituents, which were evaluated as the equivalent (1,3)parallel ones (i.e. $(R \leftrightarrow Me)_{1,2}$gauche $<>$ $(R \leftrightarrow H)_{1,3}$parallel), taken, in turn, from literature values for model cyclohexane derivatives (13).

Interactions due to partial eclipsing of oxygen –absent at the final state– were taken as their value at the initial state multiplied by a correcting factor, $\underline{w}$, to wich values around $0 \cdot 9$ for "trigonal" and $0 \cdot 2$ for "tetrahedral" transition states were considered. Values of initial state interactions (see Table III) were taken from model literature compounds (14) or deduced from Dreiding models by applying Hill equation (15).

Similar considerations apply to newly formed interactions due to oxygen after coordination and its environment –altogether symbolized by "O"– which will reach their maximun value at the final state. These values were multiplied by a factor, $\underline{z}$, for which values around $0 \cdot 1$ for "trigonal" and $0 \cdot 8$ for "tetrahedral" transition states were considered. Newly formed interactions due to the attacking hydride and its environment –altogether symbolized by "H"– were directly estimated accordingly to the transition state type –the two sets of values are in Table III–.

TABLE II.- INTERACTIONS (Kcal/mol) IN LAH REDUCTION OF C_6H_5-CO-CHMeBu^t

REACTION	INTERACTIONS ALREADY PRESENT AT THE INITIAL STATE		NEW FORMED INTERACTIONS		$G_i^{E\neq}$	$G_i^{T\neq}$
	(1,3)parallel of Ar	(1,2)eclipsing of O= (a)	(1,3)parallel of "O" (b)	(1,3)parallel of "H"		
$\underset{\sim}{1}$ → Er	(Ph-H)=1·5	(O-Bu^t)=1·05	("O"-Me)≳3·2	|("H"-Me)≳5·1|+[("H"-H)≳0·6]	8·4	
$\underset{\sim}{1}$ → Th	(Ph-H)=1·5	(O-Bu^t)=1·05	[("O"-Me)≳3·2]+[("O"-H)≳1·5]	("H"-Me)≳5·1		7·8
$\underset{\sim}{2}$ → Er	[(Ph-H)=1·5]+[(Ph-Me)>4·1]	(O-H)=0·80	("O"-H)≳1·5	("H"-Me)≳5·1	11·5	
$\underset{\sim}{2}$ → Th	[(Ph-H)=1·5]+[(Ph-Me)>4·1]	(O-H)=0·80	("O"-Me)≳3·2	("H"-H)≳0·6		7·1
$\underset{\sim}{3}$ → Er	(Ph-Me)>4·1	(O-Me)=0·00	|("O"-Me)≳3·2]+[("O"-H)≳1·5]	("H"-H)≳0·6	4·9	
$\underset{\sim}{3}$ → Th	(Ph-Me)>4·1	(O-Me)=0·00	("O"-H)≳1·5	[("H"-Me)≳5·1]+[("H"-H)≳0·6]		9·9

(a) To be multiplied by $\underline{w}$=0·95   ;   (b) To be multiplied by $\underline{z}$=0·05

TABLE III.- INTERACTIONS (Kcal/mol) AND CORRECTING FACTORS USED TO CALCULATE RESULTS SUMMARIZED IN TABLE I

TYPE OF TS$^{\neq}$ AND CORRECTING FACTORS	(1,3)PARALLEL INTERACTIONS OF "H"	(1,3)PARALLEL INTERACTIONS OF "O"	INTERACTIONS OF ECLIPSING OF =O
Trigonal 0·95 ≳ $\underline{w}$ ≳ 0·90 0·05 ≤ $\underline{z}$ ≤ 0·10	("H"-H) ≳ 0·6	("O"-H) ≳ 1·5	=O↔Me = 0·00 , 0·00 and 0·00
	("H"-Me) ≳ 5·1		=O↔H = 0·80 , 0·80 and 0·80
	("H"-Ph) ≳ 5·6	("O"-Me) ≳ 3·2	=O↔CMe$_3$ = 1·05 , 1·05 and 1·05
			=O↔CHMe$_2$ = 0·40 , 0·40 and 1·05
Tetrahedral 0·40 ≳ $\underline{w}$ ≳ 0·10 0·60 ≤ $\underline{z}$ ≤ 0·90	("H"-H) ≳ 0·1	("O"-Ph) ≳ 6·4	=O↔CH$_2$Me = 0·00 , 0·00 and 0·40
	("H"-Me) ≳ 1·0		=O↔CH$_2$Ph = 0·00 , 0·00 and 0·45
	("H"-Ph) ≳ 1·7		=O↔CHMePh = 0·40 , 0·45 and 0·60

Proposed values for "O" and "H" interactions (Table III) were attained by optimisation of essay values. Complementary variation of w and z factors (see Table III) only changes diastereo-mer percentage in less than ±2. This is in keeping with the geometrical limits portulated in Fig. 3, and in favour of the internal consistency of the method.

In a forthcoming paper we shall show that the same procedure may be applied to the elucidation of transition states in the reactions of Grignard reagents with aldehydes yielding the same diastereomeric carbinols obtained in the processes summarized in Table I.

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