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DYNAMIC STEREOCHEMISTRY OF ALDOLIZATION—XXI

DEFINITION OF THE "RESTORING ENERGY" OF A SYSTEM OF REVERSIBLE COMPETITIVE REACTIONS†

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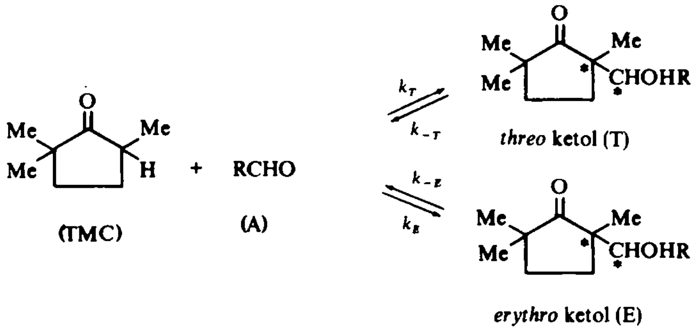
Abstract—A new quantity, called "restoring energy" (E_r), has been defined in order to measure the distance between kinetic and thermodynamic stereoselectivity; the reverse reaction, whose rate constant ratio is related to the magnitude of E_r, restores the diastereomeric system to its equilibrium composition. Solvent and cation catalyst appear to have a marked influence on the "restoring energy" of the aldol condensation. Final products being taken as reference, these results are interpreted in terms of difference in type of interactions between two postulated transition state models (cyclic and open-chain).

IN THE preceding paper we described, for a reversible diastereogenic aldol condensation, a new approach for quantitative determination of kinetic and thermodynamic stereoselectivities.[1] Our two examples of stereochemical pathways point out that, under certain conditions, the thermodynamically less stable isomer can be formed predominantly in the first reaction period.



$$S_{ki} = \frac{k_T}{k_E} \quad (1)$$

$$S_{th} = \frac{k_T/k_{-T}}{k_E/k_{-E}} \quad (2)$$

It may be interesting to define a quantity which measures, at the beginning of the reaction, the distance from the thermodynamic diastereomeric composition (chosen as reference); we propose here to define this new quantity (measured in energy units) by the following relation:

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† Abstracted from the Thesis (Doctor Engineer) of J. F. Fort to be submitted before the University of Paris in 1971 N° CNRS Ao 6401. A preliminary communication of this work was presented the 21st meeting of the French Physical Chemistry Society, Paris, September, 1970.

$$E_r = RT \left| \mathrm{Ln} \frac{S_{ki}}{S_{th}} \right| \qquad E_r = 0 \Leftrightarrow S_{ki} = S_{th} \tag{3}$$

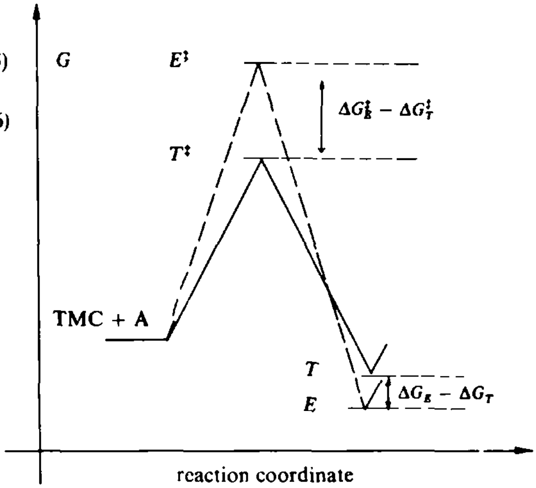
Or substituting (1) and (2) into (3):

$$E_r = RT \left| \mathrm{Ln} \frac{k_{-T}}{k_{-E}} \right| \tag{4}$$

The quantity E_r represents, in fact, the difference between the activation free energies of the reverse reactions:

$$E_r = |\Delta G^{\ddagger}_{-E} - \Delta G^{\ddagger}_{-T}| \tag{5}$$

$$E_r = |(\Delta G^{\ddagger}_{E} - \Delta G^{\ddagger}_{T}) - (\Delta G_E - \Delta G_T)| \tag{6}$$



Potential energy diagram for a diastereogenic mixed aldol condensation. The enolization step (which is common to the two pathways) and the stabilization steps are neglected in order to simplify the figure: it will be seen, in the discussion, that the stabilization steps do not change the order of stability of the ketolates

In other terms, the rate constant ratio for the reverse reactions is a function of the distance between the stereochemical composition under kinetic and thermodynamic control (relations (3) and (4)); then, a "restoring effect" toward the equilibrium composition is observed (an analogy is made with the mechanical *restoring force* which arises when a spring is stretched out of its equilibrium position). We propose therefore to name the quantity E_r the "restoring energy" of the system: many of the same principles can be applied to other systems and other reactions.†

We have already presented evidence that an important "restoring effect" seems to operate, under certain conditions, for the aldol condensation;[1] in the present paper, we report results which contribute to the understanding of those factors which are responsible for such an apparently surprising stereochemical course.

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† We are not the first to draw attention to the great interest regarding comparison of kinetic and thermodynamic stereoselectivities.[2]

RESULTS

Influence of solvent and cation catalyst

The results listed in Tables 1 and 2 present evidence that the magnitude of the "restoring energy" is a function of solvent polarity and of the size of cation catalyst. Two opposite types of situations, which can be produced by different combinations of parameters, are to be considered:

If the solvent is weakly-polar and the cation catalyst small (THF–MeOH (90:10) with MeOLi), that is to say if we can suppose that the ketone enolate is tightly bonded to the cation in an ion-pair,[3,4] then the magnitude of the "restoring energy" is found to be important (E_r = 1·95 kcal/mol at 20° in the preceding experimental conditions).

TABLE 1. INFLUENCE OF SOLVENT

Solvent[a]	S_{ki}	S_{th}	k'_{-T}/k'_{-E}	E_r kcal/mol
THF–MeOH 90:10	9·27[b]	0·315	29·4	1·95
THF–MeOH 0:100	0·289[b]	0·286	1·01	0·01

[a] Catalyst: MeOLi; Temperature: 20°; Aldehyde: 3-methylbutanal.
[b] Average values of at least three runs were taken.

TABLE 2. INFLUENCE OF CATION CATALYST

Catalyst[a]	S_{ki}	S_{th}	k'_{-T}/k'_{-E}	E_r kcal/mol
MeOLi[b]	9·27	0·315	29·4	1·95
$MeON(Me)_4$[c]	0·180	0·173	1·04	0·02

[a] Solvent: THF–MeOH (90:10); Aldehyde: 3-methylbutanal.
[b] Temperature: 20°.
[c] Temperature: 0°.

A large "restoring energy" is also found when the reaction is performed in DME or benzene as solvents with MeOK or MeONa as catalysts.[5]

On the other hand, the "restoring energy" is found to be nearly zero when the dissociation of the enolate salt is promoted by an appropriate choice of solvent (see Table 1, pure methanol; a similar stereochemical situation is observed when the reaction is performed in H_2O or in DMSO[5]) or cation catalyst (see Table 2, $MeON(Me)_4$).

Intermediate situations, between these limiting cases, have been obtained with binary solvent mixtures (THF–MeOH) of variable composition; as can be seen from Fig 1, kinetic stereoselectivity is a decreasing function of the solvent composition while thermodynamic stereoselectivity remains nearly constant;† the magnitude of

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† Going from THF–MeOH (90:10) to pure methanol slows down reaction rate significantly (experimental section): on the other hand as the cation is varied in size from Li^+ to $N(CH_3)_4^+$, in the same solvents, an important acceleration is observed. These results are in agreement with the literature.[6]

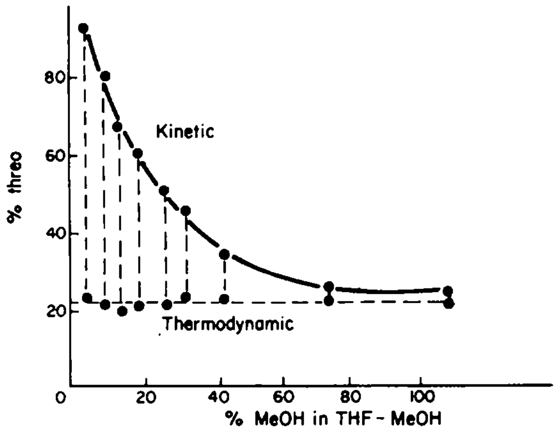

Fig 1. Influence of binary solvent mixture composition on the stereochemical course. Aldehyde: 3,3-dimethylbutanal; catalyst: MeOLi; Temperature: 20°C

the "restoring energy" is therefore found to be a decreasing function of the dielectric constant of the medium.[7] All these observations demonstrate that the "restoring energy" shows a pronounced sensitivity to the nature of the enolate salt in the reaction medium.

Influence of temperature

Measurements of stereoselectivities in limiting solvent compositions were extended to varying temperatures. The results are summarized in Table 3, (for rate constant variations see experimental section). The temperature dependence of kinetic stereoselectivity gives the values for the difference in enthalpy and entropy of activation between the two transition states:† it is possible to measure only the difference in the activation parameters because of the complexity of the individual rate constants. However, from a stereochemical point of view these differences are the most significant quantities.

The differences in the activation parameters are computer calculated from the relation:

$$2{\cdot}303\, R \log (k'_T/k'_E) = -\frac{\Delta H^{\ddagger}_T - \Delta H^{\ddagger}_E}{T} + \Delta S^{\ddagger}_T - \Delta S^{\ddagger}_E$$

Although the temperature interval is too small to provide accurate activation parameters, the changes of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ with changes in solvent are large enough to have mechanistic implications. These data suggest that in nonpolar solvents the kinetic stereoselectivity is governed primarily by the enthalpy term (the activation entropy difference being nearly equal to zero) while in polar solvents the entropy term has to be considered.

Conformational preferences in diastereomeric ketols

An IR analysis of final products indicates that the *threo* diastereomeric ketol is completely chelated, the OH band ($\nu_{OH} = 3520\ cm^{-1}$) remaining unchanged by

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† The ground state reactants are identical so that k'_T/k'_E is directly proportional to the free energy difference between the two diastereomeric transition states.

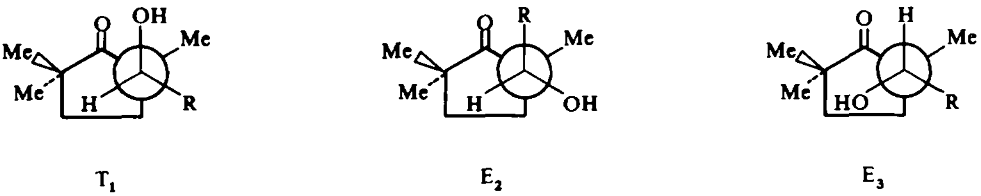
TABLE 3. INFLUENCE OF TEMPERATURE ON KINETIC STEREOSELECTIVITY

Solvent composition	S_{ki} 10·0	15·0	20·0	25·0°	$\Delta H^{\ddagger}_{T} - \Delta H^{\ddagger}_{E}$ kcal/mol	$\Delta S^{\ddagger}_{T} - \Delta S^{\ddagger}_{E}$ eu
THF-MeOH 90:10		9·65	9·27	8·96	− 1·3 ± 0·1	− 0·1 ± 0·2[a]
THF-MeOH 0:100	0·234	0·262	0·281	0·311	+ 3·2 ± 0·2	+ 8·5 ± 1

[a] The uncertainties indicate the probable errors. Catalyst: MeOLi; Aldehyde: 3-methyl butanal.

dilution; the most populated conformation must be that in which the OH and CO substituents are brought together as in T_1 (Fig 2).

On the other hand, the free OH band ($\nu_{OH} = 3625\ cm^{-1}$) of the *erythro* diastereomer increases to the detriment of the associated band ($\nu_{OH} = 3518\ cm^{-1}$) with dilution: the required stable conformations should then be predominantly E_2 and E_3.[8]



T_1 E_2 E_3

FIG 2. Highly populated conformations (in a Newman projection according to the new C– C bond). Infrared spectra were taken in dilute CCl_4 solutions; the substituant *R* was isobutyl

The solvent in which these measurements has been performed is quite different from the usual reaction medium; nevertheless it seems reasonable to suppose that for these strong intramolecular H-bonding systems the stability of the H-bond (and therefore the conformational equilibrium) would be little disturbed by effect of solvent.[9]

Other physical constants (retention time in VPC, b.p., refractive index) can be rationalized in terms of very important differences in properties of the OH groups.[10]

Thus it can be concluded that the possible conformations of the diastereomeric ketols are very differently populated.

DISCUSSION

A mechanistic interpretation may be proposed based on postulated structures of the two transition states involved and a comparison with the stereochemistry of final products.

When the ketone enolate is not dissociated from the cation catalyst, (weakly polar solvents, small cation catalyst) we proposed a rigid transition state model[11] in which the metal ion M^+ (for example Li^+) plays a prominent "bridging" role:[12, 13]

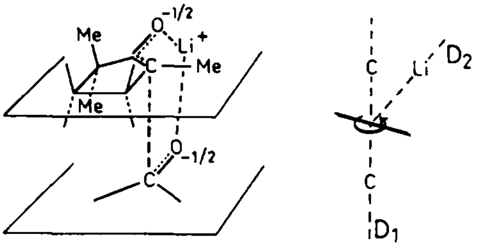


Fig 3. Cyclic transition state model

This cyclic model[14] points out that, for the attack to be favoured, the reactants must be oriented relative to one another in a particular way: first of all, orientation along the direction D_1 (which is perpendicular to the enantiomeric faces of the reacting species[15]) in order to maximize the p-orbital overlap of the prochiral C atoms;[16] secondly orientation of the oxygenated substituents according to D_2 (Fig 3) imposed by the formation of a "bridged structure" with the metal ion M (which is equivalent to a loss of rotational freedom around the direction D_1). We propose here a "reactant-like" transition state-model, which can be considered as reasonable,[17] but the following type of argument is independent of the real degree of rehybridization of orbitals in the transition state.

The free energy difference between the two diastereomeric transition states in competition is then simply a function of steric interactions between two substituents of each prochiral C atom, the same conformation being imposed for the two transition states:

Threo transition state (favourable)

Erythro transition state (unfavourable)

Fig 4. Steric interactions

The stable conformations in final products differ from the transition state imposed conformation so that the free energy difference between the diastereomeric ketols is very different from that between the two postulated transition states; the "restoring energy" is therefore expected to be large, as we found experimentally.

It would be interesting to know if the inversion of stability occurs in the condensation step or in the stabilization step (in other terms, to know if the order of stability of the ketolates resembles the order of stability of the diastereomeric transition states or the final product). Experiments, with the same reaction model, in aprotic solvents where the ionization and stabilization steps do not occur, give the same type of stereochemical course as found here;[18] the inversion is therefore characteristic of the condensation step (or the ketolate *threo* is the less stable isomer).

When the ketone enolate is assumed to exist as free anions in the reaction medium (polar solvents or $(Me)_4N^+$ counterion), we suppose that in the transition state the degree of free rotation around D_1 is great (the degree of rehybridization of orbitals may also be more important).

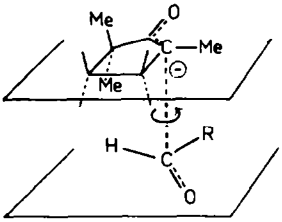


FIG 5. Open-chain transition state model

In this case, the interactions are not easily estimated, even qualitatively, because of insufficient information concerning the population of possible conformations. The free energy difference between the two transition states in competition is a function of steric and polar interactions between the three substituents of each prochiral C atom; nearly the same types of interactions are found in final products so that the "restoring energy" is expected to be quite low, as we found experimentally.

The temperature dependence measurements of kinetic stereoselectivity may be considered, in our opinion, as additional evidence of these two limiting transition state models. If we assume that in the two cyclic transition states a similar degree of rigidity is reached, then a small activation entropy difference between the two transition states, as is experimentally observed, is to be expected (same entropy loss between initial and activated states). In the two open-chain transition states, on the other hand, the population of the possible conformations is assumed, as in final products, to be different (equivalent to a different degree of rotational freedom), then a much greater activation entropy difference between the two activated states has to be involved (as found experimentally).

Also consistent with the above interpretation are the published results relative to the Diels–Alder reaction where the activation entropy difference between the two diastereomeric (*endo* and *exo*) cyclic transition states is found to be small independently of the reactant structures.[19]

In conclusion, all these data will be interpreted in terms of two competing and limiting mechanisms:

Mechanism Ad_N2_C (bimolecular nucleophilic addition via a cyclic transition state)

The enolate salt exists, in the reaction medium, as ion pairs and the cation catalyst enters the transition state structure forming a bridge between the two reacting species. The interactions in the transition state are very different in type from that in the final products; the "restoring energy" is therefore important. The "restoring effect" is probably involved when, in a reactant-like transition state, a great and specific constraint is operative.

Mechanism Ad_N2_O (bimolecular nucleophilic addition via an open-chain transition state)

The ketone enolate exists as free anions and in the transition state the degree of rotational freedom around the direction of attack is much greater than in mechanism Ad_N2_c. The "restoring energy" is quite low because the interactions in the transition state and in final products are much more alike.

EXPERIMENTAL

Apparatus and materials. Measurements were carried out and materials were prepared and purified essentially as described previously.[1]

Influence of solvent. The kinetic results have already been reported with the concentration-time curves of the preceding paper:[1] these experiments were performed according to the described procedure.

Initial conditions

Solvent	[TMC] M	$[A]^a$	[MeOLi] M	T°C
THF-MeOH (90:10)	0·127	0·130	0·024	20·0
THF-MeOH (0:100)	0·116	0·117	0·385	20·0

[a] The aldehyde was the iso-valeraldehyde (3-methylbutanal).

[b] The increase in the base concentration was imposed by the great rate retardation observed in pure methanol.

Results

Solvent	$10^4 k'_T$ $M^{-1}s^{-1}$	$10^4 k'_{-T}$ s^{-1}	$10^4 k'_T$ $M^{-1}s^{-1}$	$10^4 k'_{-E}$ s^{-1}	$\frac{(k'_T + k'_E)}{[S^-]}$ $10^2 \times M^{-2}s^{-1}$	$\frac{(k'_{-T} + k'_{-E})}{[S^-]}$ $10^2 \times M^{-1}s^{-1}$
THF-MeOH (90:10)	61·7	34·0	6·65	1·15	28·5	14·7
THF-MeOH (0:100)	2·06	2·28	7·13	2·26	$0·239^a$	0·117

Solvent	S_{kt}	S_{th}
THF-MeOH (90:10)	9·27	0·315
THF-MeOH (0:100)	0·289	0·286

[a] The factor of retardation, defined by the ratio of these rate constants, were 120 and 126 respectively for the total forward and reverse reaction. Qualitatively, the aldehyde self condensation appears to be slowed down by a greater factor.

Influence of catalyst. The experiments with the tetramethylammonium methylate were not performed in the kinetic conditions; kinetic and thermodynamic stereoselectivities were obtained by diastereomeric concentration ratios at the beginning of the reaction and at equilibrium. These results were not refined enough to provide accurate values with temperature changes but they were sufficiently precise to have a good value of the "restoring energy" (the stereoslectivity being nearly constant during the reaction). The kinetic procedure will be used in order to obtain accurate activation parameters.

Initial conditions

Catalyst	Solvent	[TMC] M	[A][a] M	T°C
MeOLi (0·024 M)	THF-MeOH 90:10	0·127	0·130	20·0
MeON(Me)$_4$ (0·015 M)	THF-MeOH 90:10	0·129	0·128	0·0

[a] The aldehyde was the iso-valeraldehyde.

Results

Catalyst	S_{kt}	S_{th}
MeOLi	9·27	0·315
MeON(Me)$_4$	0·180	0·173

Influence of binary solvent mixture composition. The purpose of these experiments was only to see, in a qualitative way, the stereochemical composition under kinetic and thermodynamic control for several solvent compositions, so that the new kinetic procedure has not been used in that particular case. The experiments were performed in a classical way: in a little flask, flushed with argon, were added the dry solvent mixture of known composition, the catalyst (in the same solvent), the ketone and the aldehyde. Several aliquots were withdrawn at the beginning and at the end of the reaction; they were analyzed by VPC in the already described conditions.[1]

Results

Solvent mixture THF-MeOH % MeOH	% threo ketol[c] under kinetic control	% threo ketol[c] under thermodynamic control
5	95[a]	23
11	80	21
17·5	68	18
21·5	60	20
27	52	18
31	45	21
40	30	24
70	23	22
100	23	22

The average initial concentrations were the following:

[TMC] = 0·120 M

[A][b] = 0·130 M

[MeOLi] increasing between 10^{-2} (5% MeOH) and 10^{-1} (100% MeOH): T = 20°C.

[a] These ratios were measured with an accuracy of ±3%; they are not to be compared with other kinetic results. These data indicate qualitatively that the "restoring energy" is a decreasing function of the dielectric constant.

[b] The aldehyde was the 3,3-dimethylbutanal.

[c] At least five points at low conversion were taken in a run.

Influence of temperature. The general procedure, already described,[1] was used in order to measure the temperature influence on reaction rate constants and on stereoselectivities. At each temperature two conductometric titrations were performed in order to determine the base concentration.

THF-MeOH (90:10)

T°C	$10^4 \times k'_T$ $M^{-1}s^{-1}$	$10^4 \times k'_{-T}$ s^{-1}	$10^4 \times k'_E$ $M^{-1}s^{-1}$	$10^4 \times k'_{-E}$ s^{-1}	S_{ki}	S_{th}
25	72·3	47·0	8·05	1·72	8·96	0·327
20	61·7	34·0	6·65	1·16	9·27	0·315
15[a]	13·0	7·25	1·35	0·227	9·65	0·302

The average initial concentrations were:
(iso-valeradehyde) = 0·130 M
[TMC] = 0·127 M
[MeOLi][a] = 0·024 M.

[a] In the THF-MeOH solvent system, the lower limit for the base solubilization was found to be 10% of MeOH. In fact, at 15° a large drop in catalyst concentration was observed (the concentration was then approximatively determined as 0·008 M) because of the insolubility of the catalyst in the mother cell (the solution was always homogeneous in the kinetic cell). The calculated rate constants were therefore much lower but the stereoselectivities remained unaffected by this phenomenon.

The computer calculated activation parameter differences were the following:

$$\Delta H^{\ddagger}_T - \Delta H^{\ddagger}_E = -1{\cdot}3 \pm 0{\cdot}1^{b} \text{ kcal/mol}$$
$$\Delta S^{\ddagger}_T - \Delta S^{\ddagger}_E = -0{\cdot}1 \pm 0{\cdot}2 \text{ eu}$$
$$\Delta G^{\ddagger}_T - \Delta G^{\ddagger}_E = -1{\cdot}2 \text{ kcal/mol at } 20^\circ$$

$$\Delta H_T - \Delta H_E = 1{\cdot}35 \pm 0{\cdot}1 \text{ kcal/mol}$$
$$\Delta S_T - \Delta S_E = 2{\cdot}4 \pm 0{\cdot}2 \text{ eu}$$
$$\Delta G_T - \Delta G_E = 0{\cdot}7 \text{ kcal/mol at } 20^\circ$$

[b] The uncertainties indicates the probable errors. The correlation coefficient was 0·999.

THF-MeOH (0:100)

T°	$10^4 \times k'_T$ $M^{-1}s^{-1}$	$10^4 \times k'_{-T}$ s^{-1}	$10^4 \times k'_E$ $M^{-1}s^{-1}$	$10^4 \times k'_{-E}$ s^{-1}	S_{ki}	S_{th}
25	3·63	4·58	11·65	4·58	0·311	0·311
20	1·82	2·47	6·28	2·47	0·289	0·289
15	1·17	1·10	4·47	1·09	0·262	0·261
10	0·702	0·657	3·00	0·657	0·234	0·234

The average initial concentrations were:
(iso-valeraldehyde) = 0·126 M
[TMC] = 0·130 M
[MeOLi] = 0·403 M.

The computer calculated thermodynamic parameter differences were the following:

$$\Delta H^{\ddagger}_T - \Delta H^{\ddagger}_E = 3{\cdot}2 \pm 0{\cdot}2 \text{ kcal/mol}^{a}$$
$$\Delta S^{\ddagger}_T - \Delta S^{\ddagger}_E = 8{\cdot}5 \pm 1 \text{ eu}$$
$$\Delta G^{\ddagger}_T - \Delta G^{\ddagger}_E = 0{\cdot}7 \text{ kcal/mol at } 20^\circ$$

[a] The same results were found for the parameter differences between the diasteromeric products. The correlation coefficient was found to be 0·996.

IR analysis of diastereomeric ketols. The effect of dilution on the bonded OH band in the IR spectrum was studied in order to distinguish between intra and intermolecular association: solutions of the two ketols in carbon tetrachloride in the concentration range 0·5–0·05 M exhibited strong peaks in the 3500–3650 cm^{-1} IR region, in the addition to the sharp CO peak at about 1725 cm^{-1}. The relative apparent extinction coefficients ($\varepsilon^a_b/\varepsilon^a_f$) were calculated from the ratio of the maximum absorbance of the bonded peak to the maximum absorbance of the free peak: it is a rough measure of the type of association.

Ketol	$\nu_{OH_{free}}$ cm^{-1}	$\nu_{OH_{bonded}}$ cm^{-1}	$\varepsilon^a_b/\varepsilon^a_f$	$\nu_{C=O}$ cm^{-1}
Threo (0·5 M)[a]	3635[c]	3520	10	1721
Threo (0·05 M)[b]	3635	3520	7·6	1722
Erythro (0·5 M)[a]	3625	3518	1·2	1732
Erythro (0·05 M)[b]	3625	3518	0·5	1732

[a] 0·1 mm path length cells were used.

[b] 1 mm path length cells were used.

[c] Sharp peaks and broad peaks were measured with an accuracy of ± 1 cm^{-1} and ± 3 cm^{-1} respectively.

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