Tetrahedron. Vol. 28, pp. 1653 to 1663. Pergamon Press 1972. Printed in Great Britain

DYNAMIC STEREOCHEMISTRY OF ALDOLIZATION—XX

STUDY OF THE STEREOCHEMICAL COMPOSITION VERSUS TIME; QUANTITATIVE DETERMINATION OF KINETIC AND THERMODYNAMIC STEREOSELECTIVITIES*

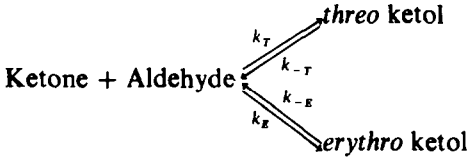
J.-E. DUBOIS and J.-F. FORT

Laboratoire de Chimique Organique Physique de l'Université de Paris VII,
Associé au C.N.R.S., 1, rue de la Brosse, 75 – Paris 5e – France

(*Received in the UK* 18 *October* 1971; *Accepted for publication* 19 *November* 1971)

Abstract—A kinetic study of a reversible diastereogenic aldol condensation is proposed in order to calculate unambiguously the kinetic and thermodynamic stereoselectivities (which correspond to the limiting compositions of the system). The diastereogenic step is found to be rate determining. Experimental and computer simulated concentration-time curves are in excellent agreement. Two examples of limiting stereochemical situations are considered, which demonstrate that the stereoselectivity may be, but not necessarily, rapidly changing during the reaction.

WE HAVE already reported that the stereochemical course of the aldol condensation is markedly dependent on experimental conditions;[1] but the reaction's reversibility makes the individual measurements of stereoselectivity under kinetic and thermodynamic control often not sufficiently precise.[2,3] In the present paper we propose a purely kinetic method for an unambiguous determination of stereoselectivities.



It is known, in fact, that when two diastereomers (henceforth abbreviated T and E) are produced under conditions of *irreversibility* ($k_{-T} = k_{-E} = 0$) the stereoselectivity is not dependent on reaction time and therefore the kinetic stereoselectivity S_{ki} can be measured by the concentration ratio of diastereomeric ketols:

$$S_{ki} = \frac{[T]}{[E]} \tag{1}$$

If, on the contrary, the reaction is highly *reversible* the proportion of stereoisomers is a function of the degree of advancement of the reaction (except if $k_{-T} = k_{-E}$); the kinetic and thermodynamic stereoselectivities S_{ki} and S_{th} correspond then to the

* 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 at the 21st meeting of the French Physical Chemistry Society, Paris, September, 1970.

stereochemical composition of the system at the very beginning of the reaction and at equilibrium:[4]

$$S_{ki} = \lim_{t \to 0} \frac{[T]}{[E]} \tag{2}$$

$$S_{th} = \lim_{t \to \infty} \frac{[T]}{[E]} \tag{3}$$

If it is assumed that the formation of *threo* and *erythro* products in a given run follow rate laws of the same form the kinetic and thermodynamic stereoselectivities are related to the specific rate constants of the reaction system:[5]

$$S_{ki} = \frac{k_T}{k_E} \tag{4}$$

$$S_{th} = \frac{k_T/k_{-T}}{k_E/k_{-E}} \tag{5}$$

We point out, in this paper, that we measure simultaneously, by a new and elaborate experimental method, the forward and reverse reaction rate constants of a diastereogenic mixed aldol condensation; the stereoselectivities S_{ki} and S_{th} now being calculated by relations (4) and (5). In fact we replace delicate measurements of limit concentrations by a reproducible method of reaction rate constants determination.

REACTION MODEL AND KINETIC METHOD

We have chosen to examine in detail the reaction of a cyclic ketone (2,2,5-trimethylcyclopentanone, henceforth abbreviated TMC) with an aliphatic aldehyde (RCHO) with the aim of understanding (by quantitative measurements) the factors which are responsible for the stereochemical course of the reaction. Our reaction model was

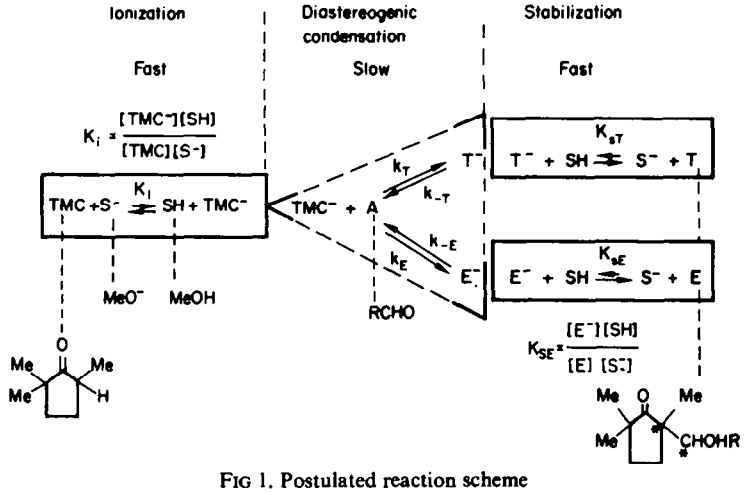


FIG 1. Postulated reaction scheme

chosen in order that the equilibration of diastereomeric ketols occur only via the retroaldolization path (epimerization being prevented by the lack of α carbonyl acidic hydrogen in the reaction products).[6]

In protonic solvents, the generally accepted reaction scheme for the base-catalysed mixed aldol condensation is described in Figure 1.

We make the assumption that the rates of the condensation step are slow compared to the rates of the ionization and stabilization steps.* The enolate and ketolate intermediates are considered to be in very low concentration relative to reactants and products (the conditions for the steady state approximation are therefore fulfilled).

The two diastereomeric ketols are found to be stable products (versus dehydration) under the reaction conditions so that the dehydration sequence need not be considered here.

We take into account two competitive reactions: the aldehyde self-condensation (the rate of which is found to be comparable to the mixed condensation rate) and the hemiacetal formation which is supposed to be rapid compared to the carbonylic condensations.[8]

According to these hypotheses the simplified and non-integrated kinetic equations, describing the transformation, are the following:

$$\left.\begin{aligned} \frac{d[T]}{dt} &= k'_T\,[\mathrm{TMC}]\,[A] - k'_{-T}[T] \\ \frac{d[E]}{dt} &= k'_E\,[\mathrm{TMC}]\,[A] - k'_{-E}[E] \end{aligned}\right\} \qquad (6)$$

The analytical aldehyde concentration is represented by $[A]$ (sum of the free aldehyde concentration and the hemiacetal concentration); the variation in analytical aldehyde concentration is followed versus time, in order to account for the self condensation of this carbonyl compound.

Each rate constant k' is, in fact, a complex expression including an acido-basic equilibrium constant, an absolute rate constant (condensation or retroaldolization) and the base concentration:

$$k'_T = K_i \frac{1}{1 + K_h[SH]} \frac{[SH]}{[SH]}\, k_T \qquad (7)$$

$$k'_{-T} = K_{sT} \frac{[S^-]}{[SH]}\, k_{-T} \qquad (8)$$

The rate constants k'_E and k'_{-E} are deduced from k'_T and k'_{-T} by substituting E to T in relations (7) and (8) (K_h is the equilibrium constant of the hemiacetal formation).

We have developed a computer program which, by a "quasilinearization" method,[9] gives simultaneously the four rate constants k'_T, k'_E, k'_{-T}, k'_{-E} and the theoretical concentration-time curves for reactants and diastereomeric products. The stereoselectivities S_{kt} and S_{th} are then exactly obtained by the ratios of these apparent rate constants according to (4) and (5). All that is needed are the initial concentrations,

* In the literature, examples provide evidence that the condensation step may or may not be the slow step, depending on the reactant structures and the reaction medium.[7]

and the variations in diastereomeric ketol and analytical aldehyde concentrations versus time.

RESULTS

In order to justify the proposed theoretical kinetic treatment, the influence on initial aldehyde concentration was experimentally investigated. In Table 1 are listed

TABLE 1. INFLUENCE ON INITIAL ALDEHYDE CONCENTRATION

$[A]_0$[a] M	$10^4 \times k'_T$ $M^{-1}s^{-1}$	$10^4 \times k'_{-T}$ s^{-1}	$10^4 \times k'_E$ $M^{-1}s^{-1}$	$10^4 \times k'_{-E}$ s^{-1}	S_{ki}[b]
0·0665	2·25	2·18	8·00	2·15	0·281
0·118	2·18	2·45	7·58	2·48	0·288
0·231	2·02	2·20	6·96	2·20	0·289
0·327	1·98	1·88	6·85	1·88	0·289
average	2·11	2·18	7·35	2·18	

[a] 3-methyl butanal was used as aldehyde.

[b] Kinetic and thermodynamic stereoselectivities are found to be nearly the same in that particular case (MeOH as solvent, MeOLi as catalyst)

the apparent calculated rate constants for several initial aldehyde concentrations: the four observed rate constants vary little with a five fold change in initial aldehyde concentration, the measured deviation being of the order of magnitude of the experimental errors (the calculated rate constants are reproducible to $\pm$ 6–8% and the stereoselectivities to better than 1%).* A good first order dependence on ketone and base concentration is also found as can be seen in the experimental section. In all cases we find excellent agreement between calculated and experimental concentration-time curves which can be considered a good justification of the proposed mathematical model (Eq 6). The above results are consistent only with, as postulated, a slow reversible condensation step.

EXAMPLES OF STEREOCHEMICAL PATHWAYS

We give here, as examples, the results for two radically opposed stereochemical situations obtained by a simple change of the solvent parameter.

Rapidly changing stereoselectivity (Fig 2)

When the condensation is performed in a weakly polar solvent (for example THF–MeOH, 90:10), we find that the less thermodynamically stable ketol is formed predominantly at the beginning of the reaction. Consequently the stereoselectivity changes considerably during the reaction between the two limiting values S_{ki} and S_{th}. The concentration-time curves, on Fig 2, are typical of such a situation: the less thermodynamically stable isomer† concentration passes through a maximum (at that time the degree of advancement is found to be 50%) and then decreases to its equilibrium value.

* The magnitude of these rate constants is in agreement with other kinetic values found in the literature.[10]

† The configuration of the diastereomers has been established by analogy of physical and dynamic (reactivity in the aldol condensation) properties with ketols of well known configuration and similar structure.[6] We ascribed the threo configuration to the ketol which is found to be highly favored under kinetic control in that non-dissociating medium.[11]

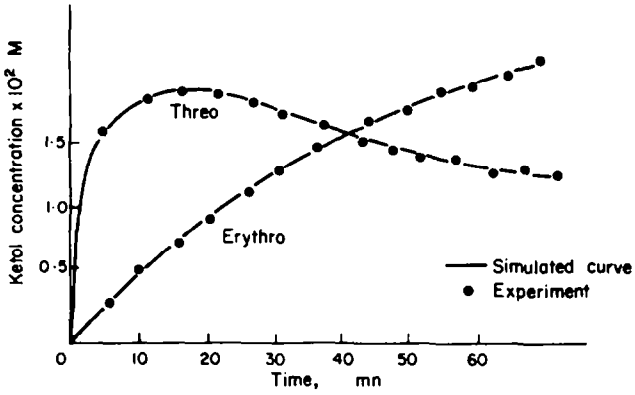


FIG 2. Rapidly changing stereoselectivity

solvent: THF-MeOH (90:10); [RCHO] = 0·130 M; [TMC] = 0·127 M; [MeOLi] = 0·024 M; T = 20°C; 3-methylbutanal was used as aldehyde.

$$\begin{cases} k'_T = 61{\cdot}7\ 10^{-4}\ M^{-1}\ s^{-1} \\ k'_{-T} = 34{\cdot}0\ 10^{-4}\ s^{-1} \\ k'_E = 6{\cdot}65\ 10^{-4}\ M^{-1}\ s^{-1} \\ k'_{-E} = 1{\cdot}15\ 10^{-4}\ s^{-1} \end{cases} \Longrightarrow \begin{cases} S_{ki} = 9{\cdot}27 \\ S_{th} = 0{\cdot}315 \end{cases}$$

Stable stereoselectivity (Fig 3)

With the same reactants but in a polar solvent (pure methanol) we observe a stereoselectivity which is always equal to the thermodynamic one:

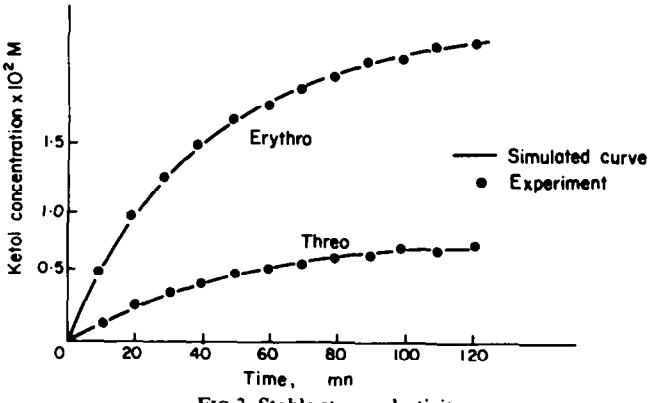


FIG 3. Stable stereoselectivity

solvent: MeOH; [RCHO] = 0·117; [TMC] = 0·116 M; [MeOLi] = 0·385 M; T = 20°C 3-methylbutanal was used as aldehyde.

$$\begin{cases} k'_T = 2{\cdot}06\ 10^{-4}\ M^{-1}\ s^{-1} \\ k'_{-T} = 2{\cdot}28\ 10^{-4}\ s^{-1} \\ k'_E = 7{\cdot}13\ 10^{-4}\ M^{-1}\ s^{-1} \\ k'_{-E} = 2{\cdot}26\ 10^{-4}\ s^{-1} \end{cases} \Longrightarrow \begin{cases} S_{ki} = 0{\cdot}289 \\ S_{th} = 0{\cdot}286 \end{cases}$$

The first example illustrates quantitatively that the stereochemical composition under kinetic control may be quite different from the thermodynamic one; this phenomenon has often been observed in the literature for a wide variety of reactions.[12] But the second example clearly indicates that this observation is not always valid, for the simple modification of one parameter is sufficient to transform radically the stereochemical course of the reaction.

In conclusion, this new approach to aldol condensation stereochemistry gives us unambiguously kinetic and thermodynamic stereoselectivities under conditions for which the reverse reaction (retroaldolization) cannot be neglected. This method, applicable to all such kinetic system, gives precisely the rates of reaction and the calculated stereochemical composition during the transformation.

In the next paper these novel results are rationalized in terms of a detailed mechanism.

EXPERIMENTAL

Apparatus. Quantitative VPC was performed by using a Girdel-75-FS-1 (ionization detector) gas chromatograph; all peaks were automatically integrated with a base line correcting AOIP integrator.

Calculations were performed on an IBM 360 at the University of Orsay computing center.

The NMR spectra were recorded on a Varian A60 high resolution NMR spectrometer using TMS as an internal reference.

IR spectra were taken with a Perkin–Elmer 225 spectrometer.

Conductometric titrations were performed with a Philips cell connected to a Wayne-Kerr bridge.

Kinetic vessel. A new reaction apparatus, flushed with dry argon and protected against the ingress of atmospheric moisture, were constructed and tested in order to perform several kinetic runs under the same reaction conditions. The principle of the apparatus is shown in the following figure:

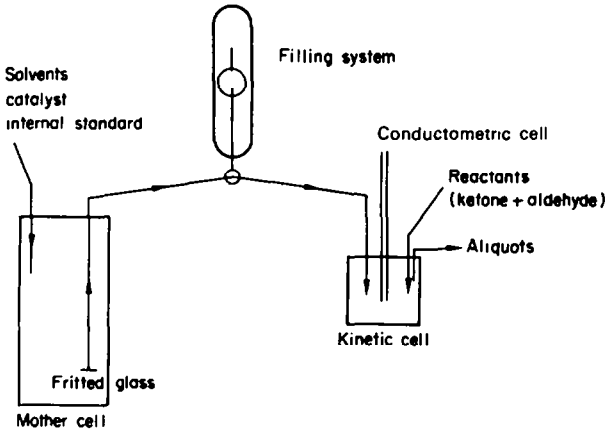


FIG 4. Kinetic apparatus

The kinetic runs were performed in a completely closed and thermostated apparatus consisting principally of two cells: the first one, of large capacity (400 ml), was used to store the catalytic solution, the second one (25 ml) for kinetic measurements only. A known and reproducible volume of solution was transferred, automatically and under argon, through a "filling system" from the mother cell to the kinetic cell before each run. The kinetic cell was connected to a conductivity bridge which gave the conductance of the solution; if any degradation of the catalytic solution occurred it was possible to detect it by this method. Reactants were added to the kinetic cell with a syringe through an injection cap; the same method was used to withdrawn aliquots.

Materials. The solvents were heated under reflux over sodium (THF and toluene) or magnesium (MeOH), then distilled under inert gas and stored in a glove box. The solvents so obtained were found to contain less than 0·05% water by the Karl Fischer method.

Lithium methoxide and tetramethylammonium methoxide. The preparation of lithium methoxide and tetramethylammonium methoxide has already been described;[13] the same procedure was used.

The 3-methylbutanal (iso-valeraldehyde Eastman Organic Chemicals) was distilled under argon before each kinetic run.

The 2,2,5-trimethylcyclopentanone (not commercially available) was synthesized via the three following steps:

Dieckmann condensation. To dry toluene (1500 ml) Na in pieces (28 g) was added: the mixture was refluxed for 60 mn under vigorous stirring in order to disperse the Na. Ethyl adipate (one mole) was then added and refluxed for 2 hr: a mixture of EtOH and toluene (200 ml) was then distilled at 110° (some toluene was added again if necessary). The reaction medium was cooled in ice and MeI (320 g) was rapidly added; the mixture was refluxed for 8 hr (became yellow) and then poured onto ice, extracted with toluene and dried over $MgSO_4$. After the drying agent remained by filtration and the toluene extract evaporated, the 2-carbethoxy-2-methylcyclopentanone was distilled under reduced pressure (b.p. = 70–80/2 mm, n_D^{25} = 1·4440). The average yield was found to be 72%.

Total methylation. To dry ether (500 ml) was added 34 g of 2-carbethoxy-2-methylcyclopentanone and 120 g MeI: the mixture was cooled in ice and 16 g of $NaNH_2$ was slowly added and then stirred for 4 hr at room temp. The reaction medium was poured onto ice, acidified (with H_2SO_4 until ph 1–2), neutralized (with $NaHCO_3$) and extracted with ether (3 times with 50 ml). The organic layer was treated with $Na_2S_2O_3$, with saturated NaCl and dried over $MgSO_4$. The solvent was evaporated and the 2-carbethoxy-2,5,5-trimethylcyclopentanone distilled under reduced pressure (b.p. = 90–95°/5 mm n_D^{25} = 1·4390). The average yield was found to be 45%.

Decarboxylation. To 25 ml water was added 38 g 2-carbethoxy-2,5,5-trimethylcyclopentanone and 28 ml of N HCl: the mixture was refluxed for 24 hr. The organic layer was extracted with ether (3 times with 15 ml), neutralized ($NaHCO_3$) and dried over $MgSO_4$. The ether was evaporated and the 2,2,5-trimethylcyclopentanone roughly distilled under reduced press. A slow distillation on a Nester Faust column was performed to obtain a pure ketone (b.p. = 70°/50 mm, n_D^{25} = 1·4260, ν(C=O) 1730 cm^{-1}. Found: C, 75·95; H, 11·30. $C_8H_{14}O$ requires: C, 76·14; H, 11·18%). The average yield of this step was found to be 63%.

The total average yield (on 10 syntheses) was found to be more than 20%. With this method we obtained a ketone completely free from other methylated cyclopentanones.[14]

The 2-(1-hydroxy-3-methylbutyl)-2,5,5-trimethylcyclopentanone diastereomeric ketols (*threo* and *erythro*) were prepared by a classical aldol condensation in a nonpolar solvent mixture, the reaction being stopped near the maximum of concentration of the *threo* isomer. To 100 ml THF–MeOH (95:5) was added 8 ml 2,2,5-trimethylcyclopentanone, 6 ml freshly distilled iso-valeraldehyde and 3 ml N MeOLi (in MeOH): the reaction medium was neutralized (with KH_2PO_4N) 1 hr after the beginning (the *threo* percentage was then found to be nearly 55%). The mixture was filtered and the organic layer extracted with ether. By reduced pressure distillation 3 ml ketone was recovered and 6·7 g diastereomeric ketols. The two ketols were separated by a slow and delicate distillation on a small Nester–Faust column. *Threo* and *erythro* ketols were obtained in small quantity (500 mg) completely free from each other.

Threo ketol. b.p. = 51°/10^{-2} mn; n_D^{25} = 1·4532: IR (CCl_4 $\nu_{(C=O)}$ = 1721 cm^{-1}; NMR (CCl_4) ppm, 3·57 (1) (—C<u>H</u>OH—): (Found: C, 73·58; H, 11·29. $C_{13}H_{24}O_2$ requires: C, 73·60; H, 11·30%).

Erythro ketol. b.p. = 65°/10^{-2} mm; n_D^{25} = 1·4555: IR (CCl_4) $\nu_{(C=O)}$ = 1732 cm^{-1}; NMR (CCl_4) ppm, 3·74 (1) (—C<u>H</u>OH—): (Found: C, 73·58; H, 11·29. $C_{13}H_{24}O_2$ requires: C, 73·60; H, 11·30%).

Procedure for a kinetic run. The mother cell was filled with the solvents, the catalyst and the internal standards at the beginning of a series of runs. After that moment the reaction apparatus was kept completely closed and under argon. A known volume of filtered catalytic soln (the filtration occurred at the exit of the mother cell) was transferred (pushed by an argon press) through the filling system from the mother cell to the kinetic cell: this operation was repeated several times to fill the kinetic cell (in which the soln was always homogeneous). Three runs, in a series, were used in order to determine the catalytic concentration (by a conductometric titration): the catalyst concentration was found to be constant in a series so that for each kinetic measurement the average value of the three titrations was taken. For a kinetic run, the ketone was added with a syringe through an injection cap: time zero was taken at the moment of the aldehyde addition. The syringes were weighted before and after injection in the kinetic cell. Aliquots were withdrawn at several times (which for calculation reasons needed to be separated by a

constant unit of time) during the condensation with a syringe through the same injection cap. This soln was rapidly neutralized in a tube which was immediately sealed up (even one year after the aliquot was made no evolution of the diastereomeric mixture could be detected). Analysis of this homogeneous aliquot was made by VPC.

Kinetic run in THF–MeOH (90:10)

Mother cell. At the beginning of the series of measurements, the mother cell was filled with 300 ml of dry THF–MeOH (90:10), 6 ml dioxane (internal standard for VPC), 2·7 ml of a N solution of 1,2,4,5-tetraisopropyl benzene in THF–MeOH (90:10) (internal standard for VPC), and 700 mg of MeOLi.

Conductometric titrations. The kinetic cell was filled with four volume units of the "filling system" (volume unit = 4·31 ml) and 4 ml doubly distilled water was added in order to make the titration end point easier to detect. HBr (Merck, ultra pure) was used as titrant (1·92 N in decarboxylated water): the titration end point was then the intersection of two good straight lines. The average volume of titrant needed for the three titrations was 0·222 ml (or $0{\cdot}0427 \times 10^{-2}$ mol).

Kinetic runs. For each run the kinetic cell was filled with four volume units (or 17·24 ml), 284 mg of TMC was added and then 198·5 mg of freshly distilled iso-valeraldehyde. Aliquots were withdrawn from 0 time to 80 min at 5 min intervals; aliquots (0·1 ml) were neutralized with 0·05 ml of a methanolic soln of MeCOOH(M)–MeCOONa(M).

VPC analysis was performed directly on the aliquots under the following conditions:

For the diastereomeric ketols: column 150 cm packed with 5% Xe 60 on gas chrom Q 100–120 mesh, temp 103° (injector 150°), carrier gas N_2 45 ml/mn, internal standard 1,2,4,5-tetraisopropylbenzene, retention time 9 mn (internal standard), 20 mn (*three ketol*), 27 mn (*erythro* ketol).

For the reactants: same column, temp 35° (injector 150°), carrier gas N_2 10 ml/mn, internal standard dioxane, retention time 4 mn (iso-valeraldehyde), 7 mn (dioxane), 33 mn (TMC).

The diastereomeric peaks were completely resolved and symmetrical (no decomp was detected): each peak was reported to a constant surface of internal standard. The surface-concentration relation was determined by the following method: the surface of the ketone peak at zero time was associated with the initial concentration of ketone (and the same for the aldehyde peak); at the end of the kinetic run (time 80 mn for example) the total surface of the ketol peaks was associated with the calculated ketol concentration (this concentration being related to the decrease in ketone concentration).

Results. The experimental and calculated values of the concentration-time curves on Fig 2 are listed in the following Table:

T_{mn}	[A] M	[TMC] M	$[T]_{exp}$ $\times 10^2$M	$[T]_{cal}$ $\times 10^2$M	$[E]_{exp}$ $\times 10^2$M	$[E]_{cal}$ $\times 10^2$M
0	0·1300	0·1270	0·000	0·000	0·000	0·000
5	0·1102	0·1087	1·565	1·548	0·269	0·268
10	0·1046	0·1038	1·840	1·858	0·484	0·480
15	0·1014	0·1018	1·860	1·887	0·665	0·670
20	0·0989	0·1002	1·840	1·847	0·841	0·845
25	0·0968	0·0994	1·780	1·791	0·987	1·007
30	0·0942	0·0984	1·703	1·733	1·153	1·157
35	0·0917	0·0971	1·678	1·676	1·308	1·295
40	0·0897	0·0964	1·621	1·620	1·438	1·423
45	0·0874	0·0963	1·592	1·569	1·577	1·542
50	0·0861	0·0962	1·535	1·524	1·638	1·651
55	0·0840	0·0944	1·513	1·485	1·750	1·753
60	0·0831	0·0942	1·440	1·450	1·840	1·849
65	0·0810	0·0938	1·420	1·413	1·905	1·936
70	0·0785	0·0930	1·380	1·371	2·020	2·016
75	0·0770	0·0923	1·358	1·332	2·113	2·089
80	0·0752	0·0923	1·310	1·301	2·160	2·157

Kinetic run in THF–MeOH (0:100)

Mother cell. At the beginning of the series of measurements the mother cell was filled with 300 ml of

dry MeOH, 7·5 ml dioxane, 5 ml of a N/2 soln (in THF–MeOH, 50:50) of 1,2,4,5-tetraisopropylbenzene and 4·5 mg MeOLi.

Conductometric titrations. The kinetic cell was filled with four volume units and MeCOOH was used as titrant: the titration end point was the intersection of two good straight lines. The average volume of titrant needed for three titrations was 0·393 ml (or $6{\cdot}87 \times 10^{-3}$ mole of titrant).

Kinetic runs. For each run the kinetic cell was filled with five volume units (or 21·55 ml), 325 mg of TMC was added and then 225 mg freshly distilled iso-valeraldehyde. Aliquots were withdrawn from 0 time to 120 min at 10 min intervals: aliquots (0·1 ml) were neutralized with 0·06 ml of a methanolic soln of MeCOOH [3M]–MeCOONa [3M]. VPC analysis was undertaken directly on the neutralized aliquots under the preceding conditions.

Results. The experimental and calculated values of the concentration-time curves on Fig 3 are listed in the following Table:

T_{min}	$[A]$ M	[TMC] M	$10^2 \times [T]_{exp}$ M	$10^2 \times [T]_{cal}$ M	$10^2 \times [E]_{exp}$ M	$10^2 \times [E]_{cal}$ M
0	0·1177	0·1164	0·000	0·000	0·000	0·000
10	0·1115	0·1103	0·144	0·149	0·498	0·515
20	0·1057	0·1049	0·266	0·265	0·916	0·914
30	0·1013	0·1008	0·359	0·354	1·237	1·221
40	0·0976	0·0974	0·435	0·423	1·500	1·458
50	0·0951	0·0951	0·485	0·477	1·672	1·643
60	0·0941	0·0946	0·497	0·519	1·713	1·789
70	0·0917	0·0923	0·549	0·552	1·893	1·904
80	0·0900	0·0909	0·578	0·578	1·992	1·993
90	0·0889	0·0901	0·593	0·598	2·043	2·061
100	0·0875	0·0889	0·619	0·613	2·131	2·113
110	0·0868	0·0885	0·628	0·624	2·165	2·153
120	0·0860	0·0880	0·636	0·633	2·193	2·183

Kinetic dependence on initial aldehyde concentration

The experimental procedure has already been described (see standard procedure in THF–MeOH (0:100)): the initial conditions for the four kinetic runs of the Table 1 were the following

$[A]_0$ M	$[TMC]_0$ M	$[MeOLi]_0$ M	T°C
0·0665	0·127	0·389	20·0
0·118	0·116	0·387	20·0
0·231	0·124	0·382	20·0
0·327	0·121	0·378	20·0

Kinetic dependence on ketone

The experimental procedure has already been described: the initial conditions and the calculated rate constants are listed in the following Table:

$[TMC]_0$ M	$[A]_0$ M	[MeOLi] M	$10^4 \times k'_T$ $M^{-1}s^{-1}$	$10^4 \times k'_{-T}$ s^{-1}	$10^4 \times k'_E$ $M^{-1}s^{-1}$	$10^4 \times k'_{-E}$ s^{-1}	S_{ki}
0·0650	0·129	0·406	1·78	1·87	6·17	1·85	0·289
0·125	0·127	0·403	1·81	2·47	6·30	2·47	0·288
0·260	0·123	0·395	1·93	2·45	6·65	2·47	0·290
0·404	0·121	0·387	1·47	2·19	5·05	2·19	0·290
	average values		1·75	2·24	6·04	2·24	
	solvent: MeOH: T = 20·0°C						

For a six fold change in initial ketone concentration, the measured variations are of the order of magnitude of the experimental errors.

Kinetic dependence on base

The experimental procedure has already been described (see procedure in THF–MeOH (0:100)): successive dilutions were obtained by adding dry methanol to the mother cell. For each dilution two titrations and one kinetic run were performed. The initial conditions and the calculated rate constants are listed in the following Table:

$[MeOLi]_0$ M	$[TMC]_0$ M	$[A]_0$ M	$k_T/[S^-] \times 10^4$ $M^{-2}\,s^{-1}$	$k'_{-T}/[S^-] \times 10^4$ $M^{-1}\,s^{-1}$	$k'_E/[S^-] \times 10^4$ $M^{-2}\,s^{-1}$	$k'_{-E}/[S^-] \times 10^4$ $M^{-1}\,s^{-1}$	S_M
0·900	0·128	0·134	6·12	7·32	18·3	6·98	0·335
0·675	0·128	0·132	6·27	7·04	21·0	7·33	0·298
0·500	0·125	0·134	5·67	6·74	19·0	6·67	0·298
0·370	0·127	0·130	4·77	5·27	17·0	5·32	0·281
0·270	0·126	0·129	4·20	5·80	15·8	5·80	0·266
	average values		5·40	6·43	18·2	6·42	
	solvent: MeOH; T = 20·0°C						

For a three fold change in initial base concentration, the calculated variations of $k'/(S^-)$ are of the order of the experimental error; nevertheless a second order deviation is observed which may be attributed to a change in the reaction medium as the base concentration increases. A significant variation of the stereoselectivities is also detected which may be rationalized in terms of variations in the solvatation power of the reaction medium (see, for example, ref 15).

In order to prevent any specific accelerating effect,[16] the ionic strength was not stabilized by addition of new salts.

Acknowledgment—We would like to thank the French Institute of Petroleum for the award of a Fellowship to one of us (J. F. Fort).

REFERENCES

[1] J. E. Dubois and M. Dubois, *Chem. Commun.* 1567 (1968)
[2] A. T. Nielsen, *J. Org. Chem.* **30**, 3650 (1965); A. T. Nielsen and W. J. Houlihan, *Organic Reactions* Vol. 16, p 11. Wiley, New York (1968)
[3] M. Dubois, Thesis, University of Paris (1969); J. L. Luche and H. B. Kagan, *Bull. Soc. Chim. Fr.* 2260 (1971)
[4] A. Schriesheim and C. A. Rowe, Jr., *Tetrahedron Letters* 405 (1962)
[5] E. Ruch and I. Ugi, *Topics in stereochemistry*. Vol. 4, p 100. Wiley, New York (1969)
[6] J. E. Dubois and M. Dubois, *Bull. Soc. Chim. Fr.* 3553 (1969); J. E. Dubois and M. Dubois, *Ibid.* 3120 (1969)
[7] M. Ballester and P. D. Bartlett, *J. Am. Chem. Soc.* **75**, 2042 (1953); L. Traynor, Ph.D., University of Michigan (1964); C. D. Gutsche, D. Redmore, R. S. Buricks, K. Nowotny and C. A. Armbruster, *Ibid.* **81**, 1235 (1968); P. L. Nayak and M. K. Rout, *J. Indian Chem. Soc.* **47**, 807 (1970); B. Deschamps and J. Seyden-Penne, *Tetrahedron* **27**, 3959 (1971)
[8] P. Le Henaff, *Bull. Soc. Chim. Fr.* 4687 (1968)
[9] R. Bellman, J. Jacquez, R. Kalaba and S. Schwimmer, *Mathematical Biosciences* 71 (1967)
[10] D. S. Noyce and W. Reed, *J. Am. Chem. Soc.* **81**, 624 (1959); R. P. Bell and P. T. McTigue, *J. Chem. Soc.* 2983 (1960); R. W. Hay and K. R. Tate, *Austral. J. Chem.* 1651 (1966); J. A. Markisz and J. D. Gettler, *Canad. J. Chem.* **47**, 1965 (1969)
[11] J. E. Dubois and J. F. Fort, unpublished results
[12] J. E. Dubois and M. Dubois, *Tetrahedron Letters* 4215 (1967); J. E. Dubois and P. Fellmann, *C.R. Acad. Sc. Paris* **266** (C), 139 (1968); M. Schlosser, *Topics in stereochemistry* Vol. 5, p 26. Wiley, New York (1970); M. Schlosser, *Bull. Soc. Chim. Fr.* 453 (1971) and refeces cited
[13] W. K. Musker and R. R. Stevens, *J. Am. Chem. Soc.* **90**, 3515 (1968)
[14] F. G. Gault, J. E. Germain and J. M. Conia, *Bull. Soc. Chim. Fr.* 1064 (1957)

[15] G. Bram, F. Guibe and M. F. Mollet, *Tetrahedron Letters* 2951 (1970); T. Bottin-Strzalko, J. Seyden-Penne and B. Tchoubar, *C.R. Acad. Sc. Paris* **272** (C), 778 (1971)
[16] H. Ginsburg, G. Le Ny, G. Nee and B. Tchoubar, *Ibid.* **270** (C), 1415 (1970)