Tetrahedron Vol. 34, pp. 3579–3589
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0040-4020/78/1215-3579/$02.00/0

NUMERICAL ANALYSIS OF THE STEREOSELECTIVITY OF PHOTOREDUCTION OF CYCLOHEXANONES AND OF ITS VARIATIONS. CONFIRMATION OF THE INVOLVEMENT OF A PYRAMIDAL RADICAL

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(*Received in the UK* 1 *June* 1978; *Accepted for publication* 13 *July* 1978)

Résumé—Une méthode générale d'analyse numérique des résultats expérimentaux a été appliquée à l'étude de la stéréosélectivité de la photoréduction des cyclohexanones.

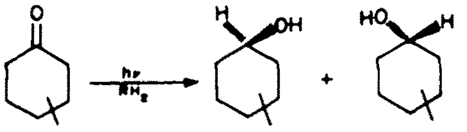
Cette méthode a permis de séparer avec un haut degré de fiabilité les deux hypothèses proposées précédemment pour expliquer les variations de stéréosélectivité.

(1) la participation d'un radical plan plus ou moins solvaté, (2) la participation de deux radicaux pyramidaux diastéréoisomères transporteurs de l'information stéréochimique. C'est cette dernière hypothèse qui doit être retenue. Le rapport des vitesses d'inversion spontanée des deux radicaux pyramidaux a pu être calculé dans ce cas, et comparé à la valeur expérimentale obtenue par ailleurs dans une expérience de deutériation sélective des cyclohexanols diastéréoisomères.

Abstract—A general method of numerical analysis of the experimental data was applied to the study of the stereoselectivity of photoreduction of cyclohexanones. The two assumptions, which were previously, put forward to account for the stereoselectivity variations, namely:

(1) the involvement of a more or less solvated planar radical, (2) the involvement of two diastereoisomeric pyramidal radicals which carry the stereochemical information could thus be separated with a high degree of reliability; the second assumption only is to be retained. The ratio of the spontaneous inversion rates of the two pyramidal radicals could be calculated and compared with the experimental value which was obtained independently from the selective deuteriation of the diastereoisomeric cyclohexanols.

In a previous paper, the photoreduction of cyclohexanones not α substituted, in hydrogen-donor solvents RH_2, was shown to lead to diastereoisomeric cyclohexanols.

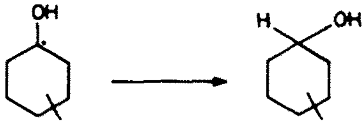


(I)

The study of the stereoselectivity of that photoreduction more generally pertains to that of asymmetric induction in the reduction of ketones. The stereoselectivity of the chemical reductions of cyclohexanones has been investigated in some detail, involving various methods: (a) reduction by hydrides: free[2] or hindered[3] borohydrides, free[4] or hindered[5] lithium aluminium hydrides, and complex hydrides;[6] (b) reduction by dissolved metals,[7] alkylboranes,[8] and organosilanes[9] Meerwein-Ponndorf-Verley reductions;[10] iridium phosphite catalysed reductions,[11] catalytic hydrogenation,[12] electroreduction;[13] (c) reduction by microorganisms,[14] etc.

Like in most cases mentioned above, the stereoselectivity of photoreduction depends on experimental conditions. Thus, when 2-propanol is the photoreducing agent, it varies with the ketone/alcohol molar ratio, with the incident light intensity, and with addition of radical scavengers.

Various assumptions were considered to account for these data. Among these, the observed effects could be interpreted by considering the radical step of the reaction only:



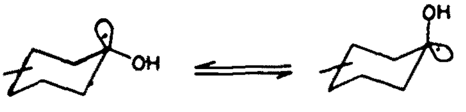
(II)

From the reaction entity, two possibilities can be considered:

(a) The hydroxycyclohexyl radical is planar: the stereoselectivity and its variations can then be explained in terms of a differing solvation of the two sides, according to their steric hindrance:

r r_s

(b) The radical centre is pyramidal: the radical then exists under two forms—axial and equatorial—corresponding to the two diastereoisomeric cyclohexanols respectively.



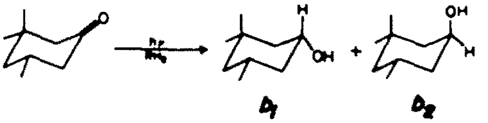
(III)

r_1 r_2

So as to choose between these two assumptions and to establish a reaction scheme liable to account quantitatively for the variations observed, the data were treated by the numerical method which had been used successfully in the investigation of the general mechanism of photoreduction of cyclohexanones by 2-propanol.[15] This quantitative analysis of stereoselectivity phenomena is reported in the present paper.

Method and experimental data

For the photoreduction of 3,3,5-trimethylcyclohexanone by 2-propanol, the quantum yield and the stereoselectivity of formation of cyclohexanols were measured under various experimental conditions (varying ketone and 2-propanol concentrations; cosolvent: benzene);



(IV)

The experimental stereoselectivity S_f is defined by the formula:

$$S_f = \frac{\text{3,3,5-trimethylcyclohexanol with axial OH (1,5-}\textit{trans}\text{)}}{\text{3,3,5-trimethylcyclohexanols (1,5-}\textit{cis}\text{)} + \text{(1,5-}\textit{trans}\text{)}} = \frac{b_2}{b_1 - b_2}$$

Forty-four values of S_f were measured (Table 1).

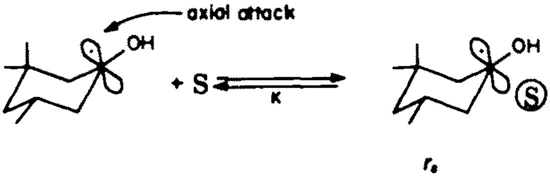
The aim is to express mathematically the stereoselectivity as a function of parameters which will generally be ratios of elementary rate constants. A computer treatment allows these parameters to be varied until the average relative error, between the theoretical value of the function and the corresponding experimental value, is minimal.

The values of the parameters thus optimised are discussed and may be correlated with data obtained from independent experiments. If the average residual error is low, i.e. of the same order of magnitude as the experimental error, and if the parameters obtained are physically reasonable, the assumption considered is retained as a working hypothesis. In the opposite case, it is discarded.

The two assumptions pertaining to the geometry of the hydroxycyclohexyl radical were tested by this method.

Hypothesis of a planar radical centre

Numerical analysis of the experimental value of stereoselectivities. If the hydroxycyclohexyl radical is "equatorial" side of the 1-hydroxy3,35-trimethyl- in fast equilibrium.



$$K = \frac{[r_s]}{[r][S]} \qquad \text{(V)}$$

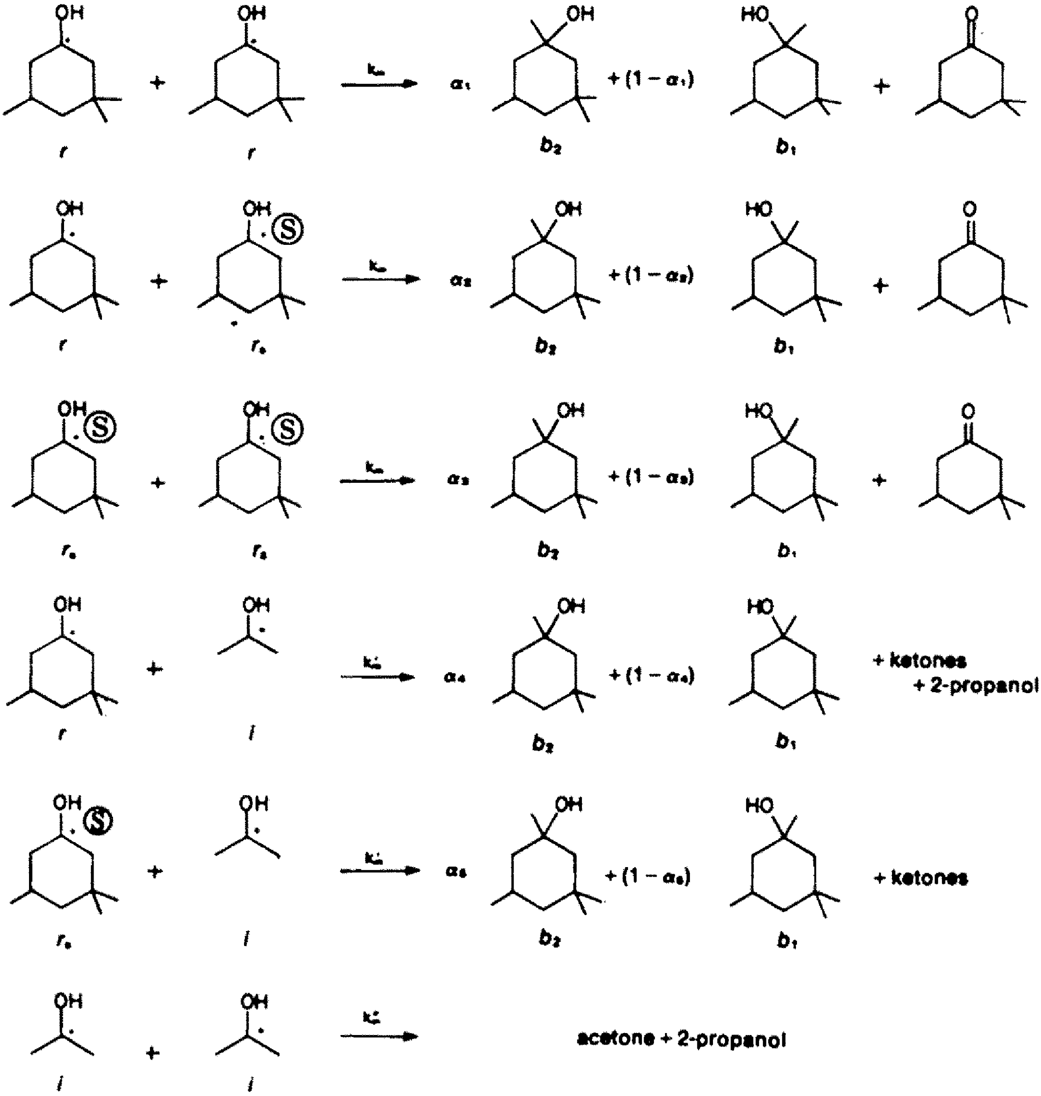
The disappearance of these radicals through dismutation leads to more or less important amounts of axial-OH (1,5 *trans*) or equatorial-OH (1,5 *cis*) cyclohexanol according as they are more or less solvated. The "equatorial" side of the 1-hydroxy3,3,5-trimethylcyclohexyl radical, which is less hindered, is likely to be more readily solvated. The equatorial attack of the solvated radical, which leads to the axial-OH (1,5 *trans*)

Table 1. Variation of the quantum yield Φ and of the stereoselectivity S_f for the photoreduction of 3,3,5-trimethylcyclohexanone in 2-propanol against the initial concentrations of the reactants

S_f	Φ	[ketone]	[RH_2]	S_f	Φ	[ketone]	[RH_2]
0.620	0.284	1.000	7.690	0.670	0.133	0.763	3.850
0.590	0.221	1.000	5.000	0.640	0.095	0.413	3.850
0.620	0.181	1.000	3.500	0.600	0.138	0.450	5.210
0.410	0.027	0.050	1.620	0.620	0.180	0.781	5.210
0.725	0.249	1.980	6.540	0.665	0.210	1.346	5.210
0.630	0.157	0.680	4.880	0.710	0.230	1.825	5.210
0.640	0.160	0.680	5.150	0.390	0.219	0.033	12.990
0.600	0.206	0.680	6.580	0.400	0.184	0.033	11.360
0.630	0.276	0.680	11.240	0.410	0.119	0.033	8.690
0.660	0.329	1.000	10.990	0.410	0.114	0.033	8.620
0.650	0.318	1.000	10.420	0.410	0.065	0.033	4.950
0.630	0.309	1.000	9.090	0.450	0.035	0.033	3.180
0.390	0.071	0.050	4.760	0.540	0.051	0.759	1.480
0.390	0.052	0.050	3.920	0.500	0.031	0.328	1.480
0.400	0.046	0.050	3.270	0.480	0.026	0.156	1.480
0.400	0.032	0.050	2.270	0.440	0.023	0.031	1.480
0.460	0.012	0.050	0.910	0.640	0.027	0.200	1.310
0.560	0.181	0.500	6.540	0.610	0.035	0.200	1.630
0.640	0.220	0.952	6.540	0.630	0.040	0.200	1.940
0.660	0.233	1.316	6.540	0.600	0.044	0.200	2.220
0.695	0.198	1.431	3.850	0.570	0.063	0.200	3.270
0.670	0.152	0.997	3.850	0.580	0.067	0.200	3.560

alcohol, is thus more difficult than that of the free radical. This phenomenon can therefore induce differences in stereoselectivity when the molar ratio ketone/2-propanol is varying.

The various dismutation reactions of the hydroxylated radicals can be written as follows:



(VI)

(VII)

(VIII)

(IX)

(X)

(IX)

$$S_f = \text{final stereoselectivity} = \frac{db/dt}{\dfrac{db_1}{dt}+\dfrac{db_2}{dt}} = \frac{\alpha_1 k_m[r]^2 + 2\alpha_2 k_m[r][r_s] + \alpha_3 k_m[r_s]^2 + \alpha_4 k'_m[r][i] + \alpha_5 k'_m[r_s][i]}{k_m[r]^2 + 2k_m[r][r_s] + k_m[r_s]^2 + k'_m[r][i] + k'_m[r_s][i]}$$

Here also solvated and unsolvated radicals are all assumed to dismutate at the same rate.

So as to calculate this stereoselectivity, a relationship must be found between the steady state concentrations of the hydroxisopropyl (i) and hydroxycyclohexyl (r and r_s) radicals. For each of these radicals, their rate of formation $2\Phi I_a$ (where Φ is the quantum yield of formation of the alcohols and I_a the light intensity used) is then equal to their rate of disappearance. Steady states:

$$r \qquad 2\Phi I_a - 2k_m[r+r_s]^2 - 2k'_m[r+r_s][i] = 0$$

$$i \qquad 2\Phi I_a - 2k''_m[i]^2 - 2k'_m[r+r_s][i] = 0.$$

Whence $k_m(r+r_s)^2 = k''_m(i)^2$ and $[i] = \sqrt{k_m/k''_m}\,([r]+[r_s])$ so that expressions like $k'_m[i][r]$ or $k'_m[i][r_s]$ can be replaced by: $k_m\beta(1+K[S])[r]^2$ or $k_m\beta(1+K[S])K[S][r]^2$ respectively, where $\beta = k'_m/k_m \cdot \sqrt{k_m/m''_m}$.

The stereoselectivity, is then expressed as a function of the seven parameters previously defined:

$$S_f = \frac{\alpha_1 + \alpha_4\beta + K[S](2\alpha_2 + \alpha_4\beta + \alpha_5\beta) + K^2[S]^2(\alpha_3 + \alpha_5\beta)}{1 + \beta + 2K[S](1+\beta) + K^2[S]^2(1+\beta)}.$$

It is noteworthy, that no assumption was made *a priori* as to the values of these parameters. However, owing to their physical definition, they have to satisfy some conditions: $0 \leq \alpha \leq 1$; $K > 0$; $\beta \geq 0$. Two particular cases of this general hypothesis were calculated independently.

(1) The planar radicals are solvated by 2-propanol: $[S] = [RH_2]$.

(2) The planar radicals are solvated by the cyclohexanone: [S] = [ketone].

After the minimisation calculation (see Experimental), the numerical values of the parameters α_i, K, β, and of the residual error F are the following ones:

	(1)	(2)
α_1	−0.41	−4.65
α_2	2.73	−10.58
α_3	−6.67	−26.561
α_4	1.07	0.41
α_5	−0.89	1.08
β	1.26	68.06
K	0.031	5.13
F	1.75	0.238

These two assumptions cannot fit the experimental data. In the first case, five parameters (α_1, α_2, α_3, α_4, α_5) have erratic values and the relative error on each datum point averages 20%. In the second case, though the residual error is low (7%) four parameters possess erratic values α_1, α_2, α_4, α_5.

These results therefore lead to discard the hypothesis that a planar radical centre, which is more or less solvated by the initial ketone or by 2-propanol, is the origin of variations of the stereoselectivity of photoreduction.

Hypothesis of a pyramidal radical centre

Some EPR studies have provided clear cut evidence for pyramidal radical structures (16 to 22), in particular for the hydroxyisopropyl radical.[23] The calculations of Fujimoto and Fukui[24] predicted that the 2-norbornyl radical was pyramidal.

In the case of the hydroxycyclohexyl radical, the pyramidal structure, put forward by Kaplan[25] was corroborated by *ab initio* (SCF, STO 3G) calculations carried out for us by Devaquet.[26] Devaquet could show that the most stable structure corresponds to a pyramidalisation angle of *ca.* 40° (tetrahedral $\alpha = 54°.5$) and that, in the course of the inversion undergone by these radicals, the radical centre becomes planar, with an energy of activation of *ca.* 3.5 kcal mole^{-1}. These data are shown on Fig. 1.

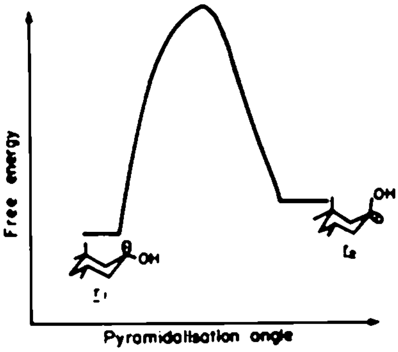


Fig. 1. Free energy diagram for free inversion.

(a) *Configurational stability of the 3,3,5-trimethylhydroxycyclohexyl radicals*

The hypothesis of a pyramidal radical centre implies that the activation energy of the hydrogen fixation reaction is lower than, or of the same order of magnitude as, the energy of activation required for the inversion of the radicals. Hydrogen fixation on the radicals is indeed a dismutation reaction whose activation energy is likely to be very low.[15]

So as to show that the hydroxycyclohexyl radicals possess some configurational stability, competitive kinetics were carried out between radical deuteriation and the inversion of the radicals formed from pure diastereoisomeric 3,3,5-trimethylcyclohexanols.

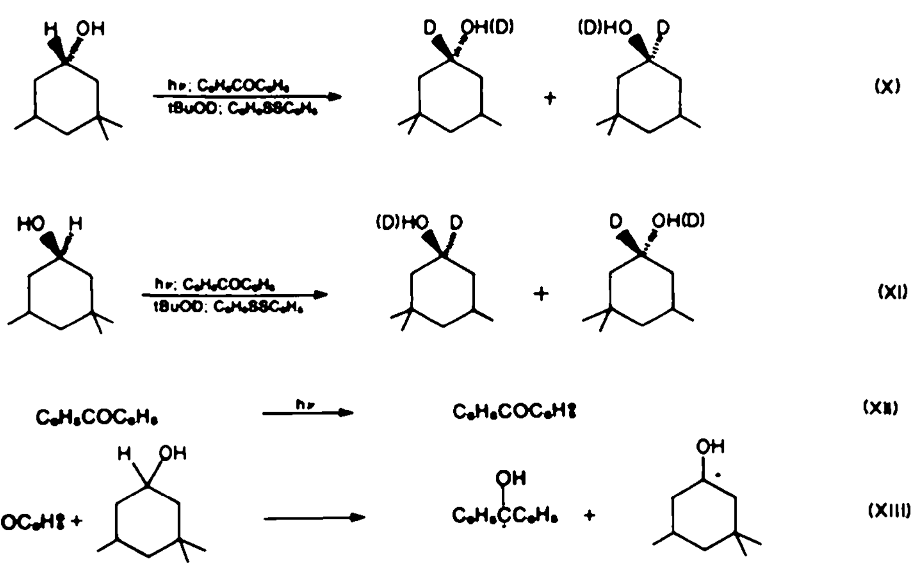
The aim of the reaction is to give rise to the hydroxycyclohexyl radical photochemically (hν; $C_6H_5COC_6H_5$) from both diastereoisomeric 3,3,5-trimethylcyclohexanols.

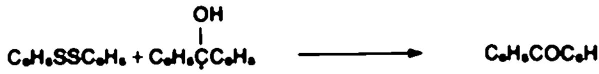
Phenyl disulfide $C_6H_5SSC_6H_5$ is also involved in the reaction; its role is to transfer deuterium by the following mechanism.[27]

At the end of reaction, the total percentage of deuteriated alcohols (retention % + inversion %), then the percentage of isomerised alcohol (inversion %) were measured.

Whatever the initial diastereoisomer, the inversion percentage was always found to be lower than the retention percentage.

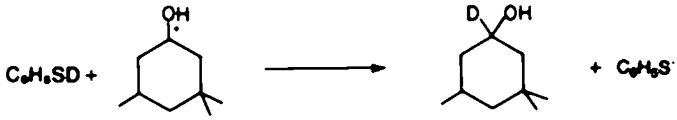
The value of the retention %/inversion % ratio is 5 ± 1





$C_6H_5SSC_6H_5 + C_6H_5\dot{C}(OH)C_6H_5 \longrightarrow C_6H_5COC_6H_5 + C_6H_5SH + C_6H_5S^{\cdot}$ (XIV)

$C_6H_5SH + t\text{-}BuOD \longrightarrow C_6H_5SD + t\text{-}BuOH$ (XV)



(XVI)

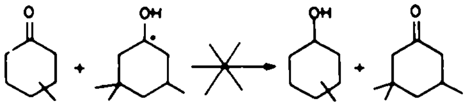
$C_6H_5S^{\cdot} + C_6H_5S^{\cdot} \longrightarrow C_6H_5SSC_6H_5$ (XVII)

for *trans* 3,3,5-trimethylcyclohexanol and 11 ± 2 for the *cis* isomer.

This result corroborates that the hydroxycyclohexyl radicals, once they are generated, keep the "memory" of the configuration of the parent cyclohexanol; their inversion rate is slow with respect to their reduction rate.

(b) *Solvation*

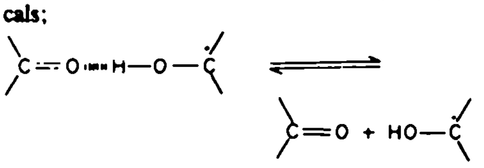
The stereoselectivity was shown to be varying as the ketone concentration was increasing or when another ketone was added to the photoreducing medium. In the case of 3,3,5-trimethylcyclohexanone and of 4-t-butylcyclohexanone, an increase in the proportion of *trans*-cyclohexanol was observed.[1] This result was first interpreted in terms of a selective hydrogen exchange between the carbonyl compound and the hydroxycyclohexyl radicals formed through photoreduction.



(XVIII)

As a matter of fact, this assumption is ruled out by another experimental result. When the added ketone (e.g. 2-methylcyclohexanone) is not photoreducible, the corresponding alcohol cannot be obtained whereas the same variation of stereoselectivity is observed.

This led us to consider that the ketone is not involved in a hydrogen exchange process but participates in a process of selective solvation of the hydroxylated radicals;



(XIX)

These solvation processes are analogous to those put forward by Schenck.[28] They should lower the inversion barrier of the radicals if reference is made to what is known for tricoordinated atoms.[29]

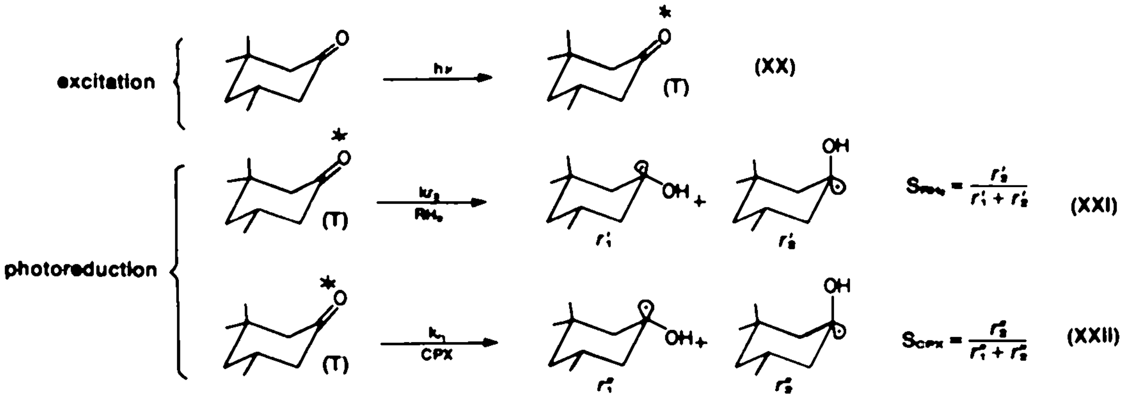
The two pyramidal diastereoisomeric radicals are not likely to be solvated in the same way; in particular, the equatorial-OH (*cis*) radical [r_1] can be expected to be more solvated (and thus to be more readily inverted) than the axial OH (*trans*) radical [r_2]. Analogous steric selections were observed by Shapiro[30] who could show that $Eu(Fod)_3$ complexes the equatorial OH cyclohexanols more strongly than their axial-OH isomers.

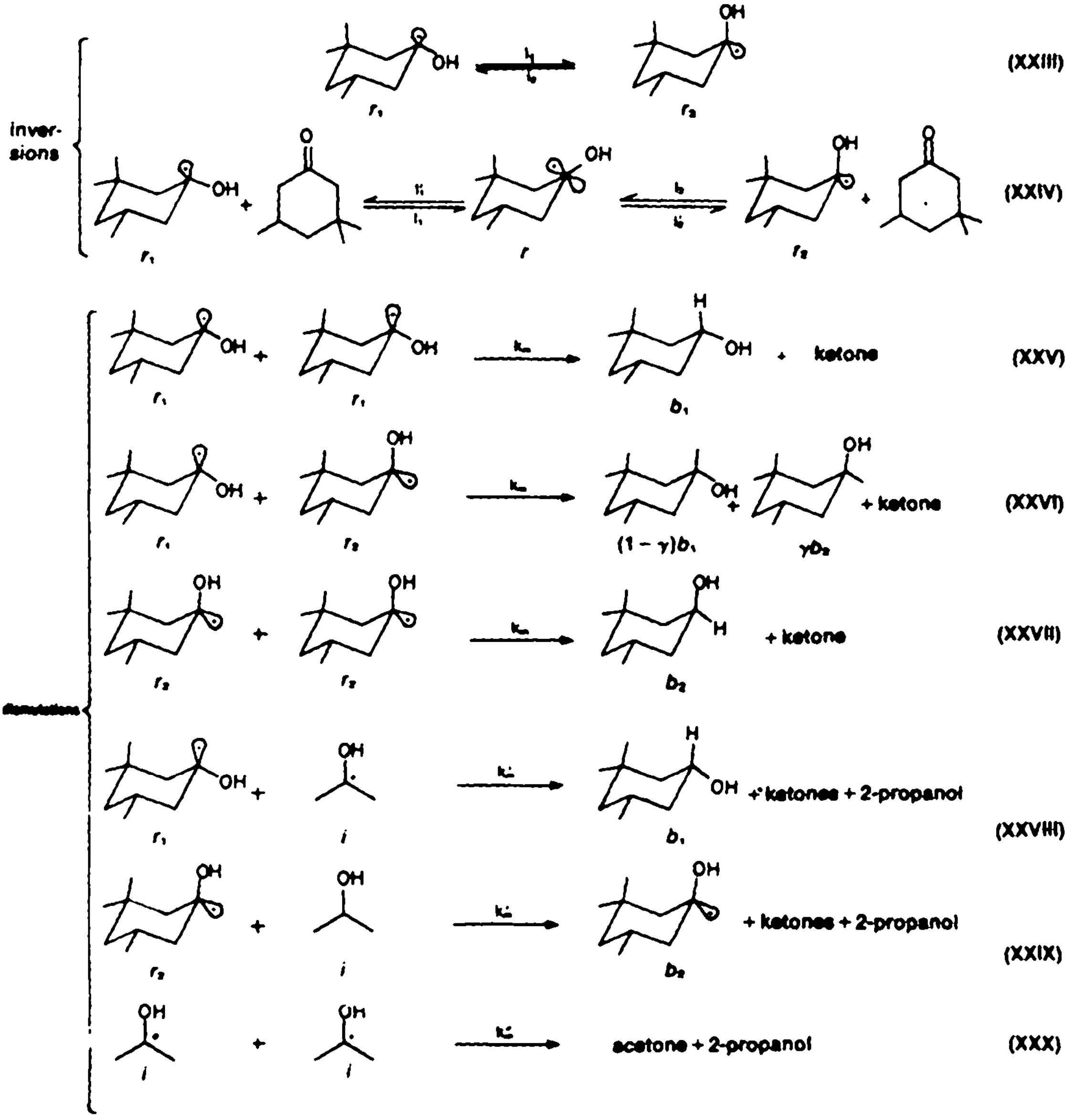
Likewise, the study of the chromatographic retention times of the diastereoisomeric cyclohexanols[31] also led to converging results: the equatorial-OH cyclohexanols interact more strongly with the stationary phase and their retention time is longer.

As for free inversion, an energy diagram can be drawn for the inversion assisted by diastereoisomeric pyramidal radicals; a solvated planar intermediate is likely to occur as in the inversion of solvated carbanions.[32]

(c) *Numerical analysis of the experimental stereoselectivities*

Within the scope of our hypothesis, the radicals are generated from the cyclohexanone triplet state interacting with two reducing agents (2-propanol or CPX, *vide infra*) with an initial stereoselectivity S_i which is modified by the inversion reactions of the radicals. A steady stereoselectivity S_s is thus reached before the occurence of the dismutation reactions which lead to the cyclohexanols with a stereoselectivity S_f. The final stereoselectivity S_f is the only one which can be reached experimentally. The various steps are summarized in the following scheme:





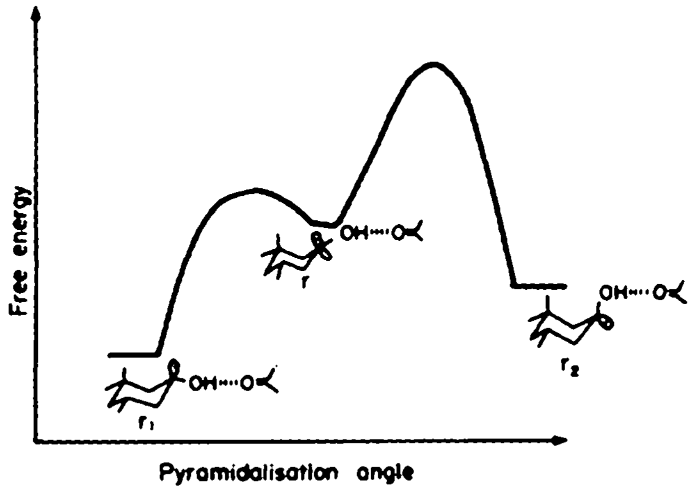


Fig. 2. Free energy diagram for assisted inversion.

In all the calculations which are to follow, the stereoselectivities S are defined from the axial-OH entity, where R is equatorial (*trans*), and which is referred to by the subscript 2.

The calculation of the final stereoselectivity S_f is carried out by following the above reaction scheme which can be divided into 3 steps:

$$T \longrightarrow S_i \longrightarrow S_s \longrightarrow S_f$$

corresponding to the calculation of the initial S_i, steady S_s, and final S_f stereoselectivities, respectively.

(1) *Calculation of the initial stereoselectivity S_i*

The initial stereoselectivity S_i is determined at the level of the interaction between the triplet and the photoreducing agents. In a previous work,[15] indeed, we showed that two kinds of photoreducing agents were involved: 2-propanol and a 1:1 stoechiometric complex between ketone and alcohol (probably an enol-alcohol complex named CPX)

$$[\mathrm{CPX}] = [\mathrm{ketone}]\,[\text{2-propanol}].$$

The rate constants for the triplet-complex (kr_1) and the triplet-2-propanol (kr_2) interactions, as well as the equilibrium constant K′ for the ketone-2-propanol complex, were determined:

$$k_{r_1} = (1.35 \pm 0.3) \times 10^9\ \mathrm{M^{-1}\,s^{-1}}$$

$$k_{r_2} = (0.7 \pm 0.2) \times 10^6\ \mathrm{M^{-1}\,s^{-1}}$$

$$K' = (1.5 \pm 0.2) \times 10^{-3}\ \mathrm{M^{-1}}.$$

Depending upon the ketone concentration in the photoreducing medium, the relative importance of the two kinds of photoreduction is varying. The initial stereoselectivity S_i is the weighed mean of the stereoselectivities arising from the photoreduction by 2-propanol, S_{RH_2}, and from the photoreduction by the complex, S_{CPX}.

$$S_i = \frac{k_{r_2}[\mathrm{RH_2}]S_{RH_2} + k_{r_1}K'[\mathrm{ketone}][\mathrm{RH_2}]S_{CPX}}{k_{r_2}[\mathrm{RH_2}] + k_{r_1}K'[\mathrm{ketone}][\mathrm{RH_2}]}$$

$$= \frac{0.34S_{RH_2} + [\mathrm{ketone}]S_{CPX}}{0.34 + [\mathrm{ketone}]}.$$

(2) *Calculation of the steady stereoselectivity S_s*

The calculation of this stereoselectivity directly derives from the steady-state equation for radical r_2.

$$0 = \frac{dr_2}{dt} = \left(\frac{dr_2}{dt}\right)_T + \left(\frac{dr_2}{dt}\right)_{f.\perp} + \left(\frac{dr_2}{dt}\right)_{a.\perp} + \left(\frac{dr_2}{dt}\right)_d$$

The different terms of this expression were calculated successively.

Formation of radical r_2: $(dr_2/dt)_T$

$(dr_2/dt)_T$ is the rate of formation of radicals r_2 from the triplet, that is $2\Phi I_a S_i$, where Φ is the overall quantum yield of photoreduction, I_a the light intensity absorbed, and S_i the initial stereoselectivity defined above. The origin of the factor 2 lies in the nature of the terminating reactions as, on the average, two hydroxycyclohexyl radicals are required to obtain one cyclohexanol.[15]

Free inversion of radical r_2: $(dr_2/dt)_{f\perp}$

Equation (4) leads to: $(dr_2/dt)_{f\perp} = i_1[r_1] - i_2[r_2]$ where i_1 and i_2 are the rates of free inversion of radicals, r_1 and r_2 respectively.

Assisted inversion of radical r_2: $(dr_2/dt)_{a\perp}$

As eqn (XXIV) corresponds to a reaction of inversion which is assisted by the cyclohexanone, on account, of the difference in the energy level (a few kcal) between the free pyramidal radicals and the solvated planar intermediate, it is reasonable to assume that the steady-state concentration of the planar radical *p* is negligible.

From this assumption, the participation of that intermediate in the dismutation reactions (formation of cyclohexanol) was disregarded. The steady-state equation for radical *p* could then be written from eqn (XXIV), considering only equilibrium:

$$(l_1[r_1] + l_2[r_2])\,[\mathrm{ketone}] - (l'_1 + l'_2)[p] = 0$$

The variation of concentration of radical r_2 during the assisted inversion is:

$$(dr_2/dt)_{a\perp} = L_1[r_1] - L_2[r_2]\,[\mathrm{ketone}]$$

where $$L_1 = \frac{l_1 l'_2}{l'_1 + l'_2}$$

and $$L_2 = \frac{l_2 l'_1}{l'_1 + l'_2}$$

Reaction of dismutation: $(dr_2/dt)_d$

The three kinds of radicals being present (r_1, r_2, $(CH_3)_2\dot{C}OH$) lead to the dismutation reactions. As to radical r_2, the value of the outgoing flow is given by:

$$\left(\frac{dr_2}{dt}\right)_d = -2k_{dd}[r_2]^2 - 2k_{dd}[r_1][r_2] - 2k'_{dd}[r_2][i]$$

which corresponds to the dimutation reactions where radical r_2 is involved:

$$r_2 + r_2 \xrightarrow{k_{dd}}$$

$$r_2 + r_1 \xrightarrow{k_{dd}} \text{cyclohexanol} + \text{ketones.}$$

$$r_2 + i \xrightarrow{k'_{dd}}$$

In the same way as in the above calculations, the hydroxycyclohexyl radicals r_1 and r_2 are all assumed to dismutate at the same rate whereas the mixed dismutation, $r + i$, is operating at a different rate.

Thus

$$\left(\frac{dr_2}{dt}\right)_d = -2k_{dd}[r_2]^2 - 2k_{dd}[r_1][r_2] - 2k_{dd}([r_1] + [r_2])[r_2]\beta$$

with $\beta = k'_{dd}/k_{dd}\sqrt{k_{dd}/k''_{dd}}$ as previously.

The steady stereoselectivity S_s is now calculated by writing that the concentration of radical r_2 is steady during the photoreduction reaction:

$$\sum \frac{dr_2}{dt} = 0$$

that is: $2\Phi L_a S_1 + i_1[r_1] - i_2[r_2] + (L_1[r_1] - L_2[r_2])\,[\text{ketone}] - 2k_{\infty}\,[r_2]^2 - 2k_{\infty}\,[r_1][r_2] - 2\,k_{\infty}\,[r_2]\,([r_1] + [r_2])\beta = 0$. As both hydroxycyclohexyl radicals are also in the steady state:

$$2\Phi L_a - 2k_{\infty}[OH^{\cdot}]^2 - 2k'_{\infty}\beta[OH^{\cdot}]^2 = 0$$

whence

$$[OH^{\cdot}] = [r_1] + [r_2] = \sqrt{\frac{\phi L_a}{k_{\infty}(1+\beta)}}.$$

Since

$$S_s = [r_2]/[r_1] + [r_2], \quad [r_1] = (1 - S_s), \quad [OH^{\cdot}]$$

and

$$[r_2] = S_s \cdot [OH^{\cdot}].$$

The light intensity L_a, which is absorbed by 3,3,5-trimethylcyclohexanone, can be related to the incident light intensity to: $L_a = L_0(1 - 10^{-7.5}\,[\text{ketone}])$ for a mean length of one centimeter, where 7.5 is the molar extinction coefficient of the ketone at the wavelength of irradiation (310 nm).

After parametrisation, the expression of the steady stereoselectivity is:

$$S_s = \frac{S_1\sqrt{1+\beta}\sqrt{\Phi\cdot(1-10^{-7.5[\text{Ketone}]})} + v_1[\text{Ketone}] + j_1}{\sqrt{1+\beta}\sqrt{\phi(1-10^{-7.5[\text{Ketone}]})} + v[\text{Ketone}] + j}.$$

The meaning of these four new parameters can be precised now:

$$j = \frac{i_1 + i_2}{2\sqrt{(k_{\infty}L_0)}} \qquad j_1 = \frac{i_1}{2\sqrt{(k_{\infty}L_0)}}$$

$$v = \frac{L_1 + L_2}{2\sqrt{(k_{\infty}L_0)}} \qquad v_1 = \frac{L_1}{2\sqrt{(k_{\infty}L_0)}}$$

(a) j measures the rate of free inversion of the hydroxycyclohexyl radicals and refers to both radicals r_1 and r_2; (b) j_1 refers to radical r_1 only; (c) v measures the rate of assisted inversion of the hydroxycyclohexyl radicals: as above, this value, without any subscript, refers to both radicals r_1 and r_2; (d) v_1 refers to radical r_1 only.

(3) *Calculation of the final stereoselectivity* S_f

The final stereoselectivity S_f, which refers to the cyclohexanols formed, is the only one which can be reached experimentally.

$$S_f = \frac{db_2}{db_1 + db_2}.$$

As there is, indeed, no equilibrium reaction between the cyclohexanols formed during the photoreduction reaction,

$$S_f = \frac{k_{\infty}[r_2]^2 + 2\gamma k_{\infty}[r_1][r_2] + \beta k_{\infty}[r_2]([r_1] + [r_2])}{k_{\infty}([r_2] + [r_1])^2 + \beta k_{\infty}([r_2] + [r_1])^2}$$

$$= \frac{S_s^2 + 2\gamma(1 - S_s)(S_s) + \beta S_s}{1 + \beta}$$

where γ $(0 < \gamma < 1)$ measures the proportion of axial-OH cyclohexanol, b_2, which is formed during the dismutation $r_1 + r_2$ (*vide supra*).

(4) *Results*

In a computer calculation, the parameters contained in the theoretical expressions were fitted so that the relative error on the theoretical and experimental final stereoselectivities S_f could be minimal. The numerical values of the optimised parameters are the following ones:

$$S_{RH_2} = 0.3 \pm 0.06$$
$$S_{CPX} = 0.7 \pm 0.2$$
$$v = 4 \pm 0.4$$
$$v_1 = 2.6 \pm 0.1$$
$$j = 0.45 \pm 0.1$$
$$j_1 = 0.16 \pm 0.04$$
$$\gamma = 0.5 \pm 0.04$$
$$\beta = 1.2 \pm 0.25$$

These parameters comply with the following conditions: $0 < S_{RH_2} < 1$; $0 < S_{CPX} < 1$; $0 < v_1 < v$; $0 < j_1 < j$; $0 < \gamma < 1$; $\beta > 0$. The residual error on each datum point is so small as to be close to 7%, on the average. The hypothesis of a pyramidal radical, whose inversion rate depends on a solvation process, therefore, allows the observed variations of stereoselectivity during the photoreduction of 3,3,5-trimethylcyclohexanone by 2-propanol to be accounted for.

These data can be correlated with some values which were found, experimentally in independent experiments. In the minimisation calculation indeed, the two parameters j_2 and $j = j_1 + j_2$ are the free inversion rate constants of the diastereoisomeric pyramidal radicals; j_2 refers to radical r_2; j_1 to radical r_1

$$\frac{j_2}{j_1} = 1.9 \pm 0.6.$$

This result can be compared with the values of the retention/inversion ratios that were measured independently for the selective radical deuteriation of the diastereoisomeric 3,3,5-trimethylcyclohexanols (*vide supra*):

$$\frac{\text{retention}}{\text{inversion}}\begin{cases} = 5 \pm 1 \text{ for } \textit{cis}\text{ 3,3,5-trimethycyclohexanol} \\ = 11 \pm 1 \text{ for } \textit{trans}\text{ 3,3,5-trimethylcyclohexanol} \end{cases}$$

The retention term is proportional to the hydrogen abstraction rate: it also corresponds to the dismutation, whose rate constant is k_{∞} which is the same for both radicals r_1 and r_2.

Under these conditions, the ratio of the rates of inversion, j_1 and j_2, of radicals r_1 and r_2 can be calculated readily:

$$\frac{\text{retention}}{\text{inversion}\,(r_1)} \times \frac{\text{inversion}\,(r_2)}{\text{retention}} = \frac{11 \pm 1}{5 \pm 1} = \frac{j_2}{j_1}.$$

In both cases: $1.7 < (j_2/j_1) < 3$ which is another decisive argument favouring the pyramidal structure of the hydroxycyclohexyl radicals.

DISCUSSION

The above results corroborate our earlier assumptions.[15] In particular, the involvement of two different reducing entities in the photoreduction of cyclohexanones in 2-propanol—namely, 2-propanol and a photoreducing complex CPX (which is likely to be formed from the enolic species of the cyclohexanone and 2-propanol)—allows the observed stereoselectivity variations to be accounted for. These two competitive processes do not seem to induce the same initial stereoselectivity:

$$S_{RH_2} = 0.30 \pm 0.06$$

$$S_{CPX} = 0.76 \pm 0.20.$$

The only involvement of CPX cannot account for the overall stereoselectivity variations observed. The investigation of the photoreduction of 3,3,5-trimethylcyclohexanone in cyclohexane had shown that the stereoselectivity depended on the ketone concentration. As a matter of fact, in cyclohexane, the photoreducing complex CPX was not involved as the quantum yield of photoreduction remained constant. All the cyclohexanol formed therefore resulted from a direct interaction of the cyclohexanone triplet with cyclohexane, which induced the only initial stereoselectivity S_{RH2}. The stereoselectivity variation, that was observed in cyclohexane, is to be assigned to the inversion reactions of the pyramidal radicals; this variation was smaller than with 2-propanol.[1] Therefore, two simultaneous and independent phenomena can induce stereoselectivity variations depending upon the initial ketone concentration.

The simplifying assumptions that were used for the calculations relative to the inversion reactions of the pyramidal radicals can be made clearer now: the model (free of solvated) inversion mechanisms chosen are analogous to those put forward by Niemeyer[32] for the inversion of carbanions.

The free energy diagram chosen for free inversion was consistent with the *ab initio* calculation of Devaquet;[26] on the contrary, in the case of assisted inversion (solvated radicals), a solvated planar reaction intermediate was considered, but its effect on the final stereoselectivity is negligible (no dismutation from the solvated planar radical occurs). The introduction of this intermediate allows the steric selection to be accounted for in a simple way, as it depends on the solvation of the pyramidal radicals; the equatorial—OH radical r_1, being more stable and more solvated too, will be inverted more readily, through assisted inversion, whence the shift towards the cyclohexanol which is no longer the thermodynamic product. However, a difference between, our model and that of Niemeyer is to be pointed out: the solvation of the hydroxylated radicals, contrarily to that of carbanions, occurs at the hydroxylated group (and not directly on the reaction entity).

Nevertheless, a preferential stabilisation might operate through interaction between the radical centre and the π system of the carbonyl group. Such an assumption, which would account for the minimum in the free energy diagram for the inversion of the solvated radicals, cannot be ascertained experimentally. As the occurrence of this minimum apparently fits better the interconversion of the pyramidal radicals, this latter assumption only was considered.

In the photoreduction of 3,3,5-trimethylcyclohexanone in 2-propanol, both inversion processes of the pyramidal radicals are competing: their relative importance determines the final stereoselectivity.

Stereoselectivity control thus depends on the solvation of the hydroxycyclohexyl radicals:

(a) The energy of the non solvated radicals is such that the energy barrier allowing their interconversion is higher than the activation energy required for their dismutation; this case is closely related to a configurational control.

(b) The solvated radicals, having a lower inversion barrier invert more easily than they react; according to the Curtin-Hammett principle, the final stereoselectivity is then determined by the activation energies of the reactions.[33]

EXPERIMENTAL

Products. 3,3,5-trimethylcyclohexanone (purum Fluka) was doubly distilled on a Buchi spinning band column (b.p.$_{760}$ 182°). The 2-propanol and benzene were Fluka spectroscopic grade solvent. Benzophenone was twice recrystallized from a 1:1 benzene–EtOH mixture; m.p. 48°. Phenyl disulfide was purified by recrystallization from EtOH; m.p. 61°. t-BuOD was obtained through heavy water hydrolysis of potassium t-butylate; it was then dried on a 4 Å molecular sieve and purified by microdistillation b.p. 82°. The deuteriation percentage was measured by PMR (60 MHz).

Analysis. The samples were analysed by gas chromatography using a flame ionization detector. The rates of conversion were never greater than 20% (a range over which the stereoselectivity is constant with respect to time).

Five independent injections were carried on and the mean of three median values, was considered. The comparison of the data obtained by this method with those resulting from the PMR determination (60 MHz) of the carbinolic protons of the cyclohexanols allowed its validity to be tested. The PMR determination allows the occurence of unidentified products, whose retention time is identical of that of the cyclohexanols formed, to be ruled out. The experimental error on the measure of the stereoselectivity is, on the average, close to ±3% (absolute error).

Configurational stability of the 3,3,5-trimethylhydroxycyclohexyl radicals

The diastereoisomeric 3,3,5-trimethylcyclohexanols were purified by preparative GPLC (Carlo Erba: column: Ucon Polar 10% and KOH 10% on Chromosorb W 30/90; 9 m long; t = 110°; flow: 100 ml/mn). A benzene soln of cyclohexanol (0.1 M), benzophenone (0.1 M), phenyl disulfide (0.01 M) and t-buOD (10 M) was irradiated in a photochemical reactor "Rayonet" Model RPR 100 equiped with 16 RPR 3500 Å lamps. The degassed solns were put in sealed tubes which were dipped in a 1:1 acetone-water mixture so as to irradiate benzophenone only. Stereoselectivity was measured at 10% in reaction progress for 1,5 *trans* cyclohexanol and at only 2% for the other diastereoisomer so as to minimise side reactions as much as possible. The cyclohexanols were then determined both by GLPC and PMR so as to measure the deuteriation rate. Benzyl acetate was used as an internal standard in both cases. On the PMR spectra the carbinolic CH of the cyclohexanols was measured with respect to the CH_2 of benzyl acetate. Experimentally, the ratio H_H = (alcohol/acetate) PMR/(alcohol/acetate)GLPC is close to 0.45 for the hydrogenated product whereas it is zero for the fully deuteriated product.

The deuteriation percentage of the alcohols then is [0.45 − H/0.45] × 100. The inversion percentage of the cyclohexanols is equal to the percentage of conversion to the other diastereoisomer C. The retention/inversion ratio is [(0.45 − H)/0.45) − C]/C.

Various controls were carried on in this experiment so as to ascertain the validity of these results:

(1) It was checked that the diastereoisomeric cyclohexanol formed resulted from an inversion and not from a photoreduction of the cyclohexanone which might be formed: (a) the cyclo-

hexanone was not irradiated (b) it was found only in negligible amounts in the medium.

(2) The H_H ratio of 0.45 is the mean of 22 independent runs.

(3) The deuteriation percentage of t-BuOD was controlled and occasional corrections were effected.

(4) Lastly, the values of the retention/inversion ratio are the mean of three independant runs for each diastereoisomeric cyclohexanol.

Computing techniques

The iterative method used is that due to Powell:[34] "an efficient method of finding the minimum of a function of several variables without calculating derivatives." Calculations were performed with a subprogram entitled VA 04 A on a C.I.I. IRIS 80 computer. The function F to minimise was the mean quadratic errors on S_t:

$$F = \sum_{i=1}^{N=44} \left(\frac{S_{th} - S_{t_{exp}}}{S_{th}}\right)^2$$

where N is the number of experimental points, S_{th} is the theoretical value calculated from our formula and $S_{t_{exp}}$ is the corresponding experimental value of the stereoselectivity.

The difficulty, in this method, lies in the choice of the initial values of the parameters which are to be minimised. As a matter of fact, the method is the more efficient as the initial values of the parameters are closer to the values at the minimum. The choice was made as objectively as possible, taking into account the physical and experimental reality. These initial values are:

Planar radical centre

$\alpha_1 = \alpha_4 = 0.4$: non solvated radicals (*cf* stereoselectivity in diluted medium)
$\alpha_3 = \alpha_5 = 0.8$: solvated radicals (*cf* stereoselectivity in concentrated medium)
$\alpha_2 = 0.6$: intermediate case
$\beta = 2$: (mean value)
$K = 0.01$: weak solvation.

Pyramidal radical centre

Two batches of initial values were successively chosen, the second one leading to a slightly lower value of F:

First batch

$$\left.\begin{aligned} S_{RH_3} &= 0.5 \\ S_{CPX} &= 0.5 \\ v &= 1 \\ j &= 0.5 \\ v_1 &= 1 \\ j_1 &= 0.5 \\ \alpha &= 0.5 \\ \beta &= 1 \end{aligned}\right\} \text{mean values with no inversion from radical } r_2$$

Second batch

$S_{RH_3} = 0.3$: (*cf* stereoselectivity in diluted medium)
$S_{CPX} = 0.7$: (*cf* stereoselectivity in concentrated medium)
$$\left.\begin{aligned} v &= 4 \\ j &= 2.4 \end{aligned}\right\}\text{: value from the preceding minimisation}$$
$v_1 = 1$
$j_1 = 0.5$
$\alpha = 0.5$ (mean value)
$\beta = 1$ (mean value)

However, the influence of the initial values of the parameters on their final values was not systematically investigated since the various parameters interact on each other.

We also tried to estimate the accuracy on each parameter with the help of a method taking into account the experimental absolute error on the stereoselectivity (±3%): ±3% were added randomly to the whole series of the experimental values of S_t. Ten different random distributions were tested.

In each case a new minimisation calculation was carried on leading every time to new parameters whose value oscillated around the optimal value. The value of the maximum deviation was chosen by considering a Gauss distribution of the values of a parameter. Even though F values that are slightly smaller than the minimal value found may exist, the final value of the parameters will not be affected significantly.

As the subprogram VA 04 A optimises the parameters taken one at a time with the help of an iterative method, it seemed that the order of input of the parameters might be important. In the particular case of the pyramidal radical, the subprogram VA 04 A was compared with another subprogram (DAVIDO) which optimises all the parameters together. With identical initial values, very close final values were found.

Acknowledgement—We should like to thank G. Viel (C.I.C.T., Toulouse) for performing all the calculations.

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