cyclopropyl systems of comparable size give values comparable or larger than those observed in the experiment, and thus the calculation is taken as an upper limit to the rate.
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Metathetical Transposition of Bis-*tert*-alkyl Ketones. 1. A Model for a Study of Group Migration[1]

J. E. Dubois* and P. Bauer

Contribution from the Laboratoire de Chimie Organique Physique de l'Université de Paris VII, associé au C.N.R.S., 75005 Paris, France.

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Abstract: Partial rate constants k_p^{Rm} for the migration of alkyl groups are conventionally determined on the basis of approximations and hypotheses such that the set of values obtained is not necessarily consistent. The metathetical transposition of bis-*tert*-alkyl ketones constitutes a model reaction for which such assumptions are reduced to a minimum. A mechanistic study of this reaction shows a sequence of steps in common with two other reactions: the pinacol rearrangement of tetrasubstituted glycols and the fragmentation of the rearranged ketones. Kinetic and tracer studies (^2H and ^{13}C) on these three reactions, under strictly identical conditions of acidity which control the preequilibrium (ketone $\rightleftharpoons$ protonated ketone), bring out the usefulness of this model reaction for studying the influence of structural parameters controlling the migration of the group Rm; these structural parameters are in fact the environments $\mathcal{E}_{C_0}$ and $\mathcal{E}_{C_t}$ of the origin and terminal carbons defined by the migration. The constants k_p^{Rm} for Me and Et corresponding to particular environments E_{C_0} and E_{C_t} have been determined: k_p^{Me} (E_{C_0}:Me,Me/E_{C_t}:t-Bu) = 775×10^{-8} and k_p^{Et} (E_{C_0}:Et,Et/E_{C_t}:Et$_3$C) = 8×10^{-8} s^{-1}

Certain group properties, generally known as substituent effects, can, on the basis of a defining reaction, be assigned values which are widely applicable for the correlations of physicochemical data. For aliphatic groups the best known are the polar (σ^*) and steric (E_s) parameters.

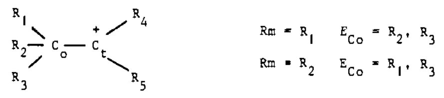
A group property of a rather different type is involved when considering the 1,2-alkyl shifts occurring in carbonium-ion rearrangements. It has not yet been possible to define for the alkyl groups a scale of migratory aptitudes[2] which would express the relative rates of migration of different groups. Thus ethyl vs. methyl migration aptitude varies from 35[3] to 17[4] in pinacol rearrangements and to 1 in the Wagner-Meerwein rearrangement.[5]

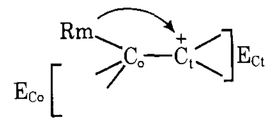
These results are probably partly due to the fact that the reactions which have been most often used to study the migration of alkyl groups (the Wagner-Meerwein rearrangement, the pinacol rearrangement, and ketone rearrangements in an acid medium[6]) are frequently unsuitable either because of a concerted mechanism leading to an overall phenomenon, not specifically a migration, or because of the impossibility of measuring the preequilibrium of carbonium or hydroxycarbonium ions which precede migration. For certain reactions, even the nature of the migratory group is uncertain.[7]

A suitable model system which allows the separation from overall kinetic data of data relating specifically to the migration step is not easy to find.

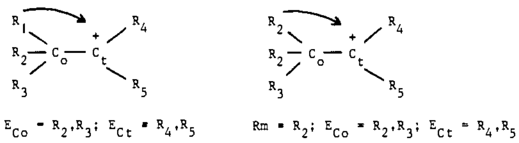
These problems have been the subject of numerous studies differing in both approach and method. In the experimental approach, the relative group migratory aptitudes are estimated from the product distribution. The results, however, cannot be extrapolated from one structure to another, since, in such intrastructural comparisons, any change in the nature of the migrating group Rm entails some modification of the environment E_{C_0} of the origin carbon C_0 (Scheme I). Furthermore, the migratory aptitude of a migrating group Rm depends on not one but two environments associated with two reaction sites: the environment E_{C_0} of the origin carbon C_0 and E_{C_t} of the terminal carbon C_t. Consequently, it is necessary to calculate the partial rate constants of migration (k_p^{Rm}) for constant environments using interstructural comparisons. In these studies the Rm group must migrate in comparable environments (Scheme II). Collins et al.[8] have shown the usefulness of this approach in studying the competition between aryl groups, but as already seen the results for alkyl groups are not conclusive.[3-5]

Scheme I





Scheme II

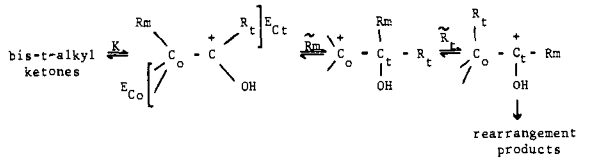


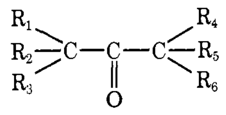
Theoretical approaches to the problem of molecular rearrangements have also been presented. Balaban et al.[9] have proposed a formal estimation of all rearrangement pathways using a method based on graph theory. Schleyer and his coworkers, considering the same kind of analysis, have determined preferred rearrangement pathways of acyclic compounds with blocked conformations[10] by calculating the energies of the intermediate carbonium ions by the Molecular Mechanics method,[11] outlined by Westheimer[12] and subsequently refined by other research groups. To our knowledge, this method has not so far been applied to the determination of the migratory aptitude of alkyl groups in acyclic compounds.

In order to try to solve this problem we have therefore undertaken a careful analysis of classical kinetic studies of migratory aptitudes in an attempt to discover a model reaction capable of yielding partial migration rate constants k_p^{Rm} unambiguously. Thus, what is sought is a multistep reaction in which the constant k_p^{Rm} can be deduced from the constant k corresponding to the step during which only the migration phenomenon occurs.

The metathetical transposition of bis-*tert*-alkyl ketones would seem to be a reasonable model for such a study (Scheme III), since in these compounds there are six alkyl groups capable of migration, each rearrangement apparently involving two successive migrations of a group Rm and a tertiary group R_t. Thus this reaction model is capable of yielding a great deal of information about the effect of the variable environments $\mathcal{E}_{Co}$ and $\mathcal{E}_{Ct}$ on the migration of a single alkyl group Rm, as well as on the sensitivity of various migrating alkyl groups, Rm, to a fixed environment E. The symbol $\mathcal{E}$ shall represent the variable environment and E the constant environment.

Scheme III





	Rm	R_t
path 1:	$\sim R_1$;	$\sim C-(R_4, R_5, R_6)$
path 2:	$\sim R_2$;	$\sim C-(R_4, R_5, R_6)$
path 3:	$\sim R_3$;	$\sim C-(R_4, R_5, R_6)$
path 4:	$\sim R_4$;	$\sim C-(R_1, R_2, R_3)$
path 5:	$\sim R_5$;	$\sim C-(R_1, R_2, R_3)$
path 6:	$\sim R_6$;	$\sim C-(R_1, R_2, R_3)$

It has been shown that, in contrast to certain ketone rearrangements in acid medium,[7] the reaction under consideration does not involve oxygen migration.[13] The identity of the group migrating in the slow step of the reaction may therefore be determined from the identity of the product formed.

Insofar as the constant k_p^{Rm} corresponds uniquely to a migration step, the metathetical transposition could constitute a valid model for the quantitative study of migration.

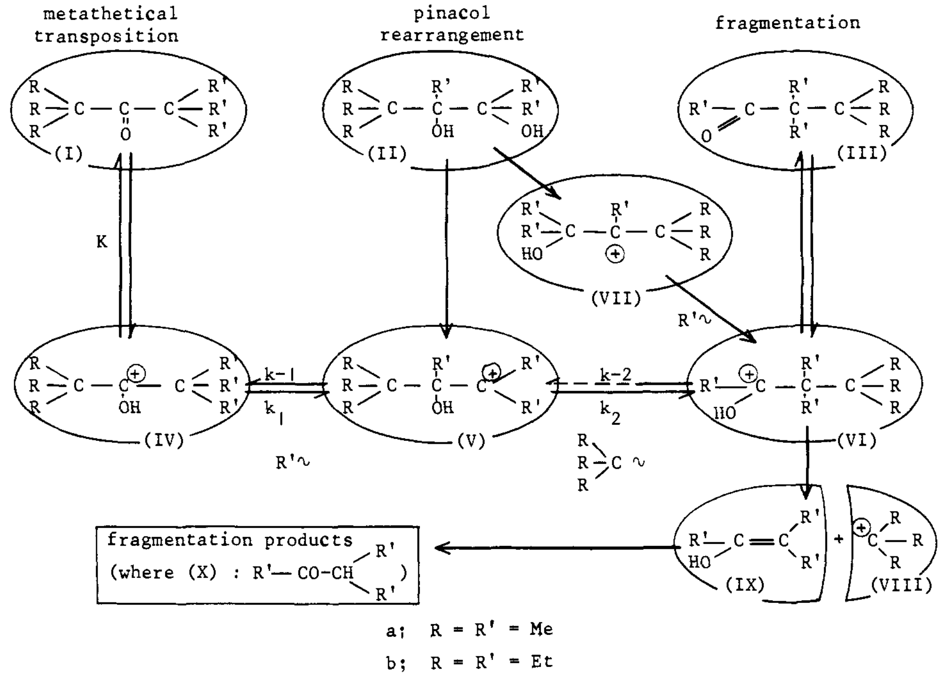
Results and Discussion

We have attempted to show that the mechanism of metathetical transposition is multistep and may be represented by Scheme IV. To this end we have used Collin's approach, which consists in enclosing the said mechanism within a reaction system having several ions in common. The mechanism in Scheme IV might be considered as the result of equilibria involving three hydroxycarbonium ions (IV $\rightleftharpoons$ V $\rightleftharpoons$ VI). Each of these ions is common to three reactions: the metathetical transposition of bis-*tert*-alkyl ketones (I), the pinacol rearrangement of glycols (II), and the fragmentation reaction of isomeric rearranged ketones (III). These three reactions can take place under identical experimental conditions. In this mechanistic scheme, the information required to elucidate the mechanism of metathetical transposition and calculate k_p^{Rm} corresponding to the migration step is obtained from kinetic studies, tracer studies, a product identification for all three reactions.

In reality, the evidence of the multistep mechanism for the ketone rearrangement is based on the existence of the α-hydroxycarbonium ion V, which, prior to this study, has been accepted by certain authors[14] and rejected by others.[15]

We shall therefore begin by attempting to prove the existence of the multistep mechanism by providing supporting evidence for the existence of ion V. We shall then elaborate our reaction medium–structure–reactivity study to validate the method of calculating k_p^{Rm} associated with the step IV $\rightleftharpoons$ V. In this way we shall be able to compare k_p^{Rm} values for different groups Rm for a series of bis-*tert*-alkyl ketones[16] and to use these values in structure–reactivity relationships.

Scheme IV



a; R = R' = Me
b; R = R' = Et

Existence of the α-Hydroxycarbonium Ion. We have chosen to approach this aspect of the problem by means of an H/D exchange study between the solvent nd the ketone.

Tracer Studies. The metathetical transposition of the bis-*tert*-alkyl ketones in concentrated sulfuric acid is followed by the fragmentation of the rearranged product (Scheme IV).

The dissolution of Ib and IIIb[17] in 96% D_2SO_4 allows the observation of isotopic exchange with the reaction medium. This exchange is measured by comparing the increase of the NMR signal which corresponds to the sulfuric acid protons to the internal standard signal of dioxane. The exchange observed over a 20-min period (Table I) from 1 mol of IIIb is ten times greater than the one observed from 1 mol of Ib. However, kinetic studies indicate that the amount of IIIb reacting over the same period of time is at least 100 times greater than the amount for Ib.

Thus, if the metathetical transposition occurred in the absence of ion Vb (whose α-hydrogen atoms of the carbonium center can exchange isotopes with the medium), the observed exchange from Ib[18] can only derive from IIIb or IIIb-derived products[19] and should therefore equal at most $^1/_{100}$ of the one from IIIb, i.e., 0.2. Since the Ib exchange is ten times greater, it can only stem from α-hydroxycarbonium ion Vb.[20]

Influence of Preequilibrium Constants. The determination of the constants $k_{\mathrm{p}}^{\mathrm{Rm}}$ requires a knowledge of the constant K for the preequilibrium protonation of each ketone studied. It has been observed, however, for hexamethylacetone, that beyond a certain sulfuric acid concentration (95%) the overall rate of ketone disappearance is independent of H_0.[21] We have verified this result[22] for a number of hexasubstituted ketones and it seems to be general for nonenolizable ketones. We can, therefore, avoid having to measure K by choosing acid concentrations greater than the limiting concentration (95%).

The reaction scheme consists of an equilibrium involving three ionic intermediates, ions IV, V, and VI, which may be generated rapidly from three different compounds:[23] ion IV from the bis-*tert*-alkyl ketone I; ion V from the glycol I; and ion VI from rearranged ketone III (Figure 1).

We will analyze successively the behavior of ion IV (zone A) formed by the metathetical transposition of I, ion VI (zone B) from a study of the fragmentation of rearranged ketone III, and that of ion V (zone C) from a study of the pinacol rearrangement of glycol II. In this last case the existence of a parallel reaction pathway giving rise to ion VI from ion VII (zone D) requires a complementary tracer study (^{13}C) to determine the importance of this pathway.

The overall information thus obtained should allow the identification of the slow step in the equilibrium involving the three ions, the determination of the rate constant of this step, and the calculation of the constant $k_{\mathrm{p}}^{\mathrm{Rm}}$.

Zone A: Metathetical Transposition of Ketones Ia and Ib. In 96% H_2SO_4 the disappearance of ketones Ia and Ib is a first-order one and the rate constants are, respectively, 4450×10^{-8} and 33×10^{-8} s^{-1}.[24]

Zone B: Fragmentation of Ketones IIIa and IIIb. Ketones IIIa and IIIb in the reaction medium give only the fragmentation products Xa and Xb.[25] No trace of ketones Ia or Ib nor glycols IIa or IIb was found.[26] This result tends to prove the absence of reversibility of the metathetical transposition.

Zone C: Pinacol Rearrangement of Glycols IIa and IIb. Two mechanisms have been proposed for the pinacol rearrangement: a multistep one[27] via hydroxycarbonium ions and a concerted one.[28] However, in the latter case the studies were carried out in 50% H_2SO_4 and it can be safely supposed that this mechanism, which implies the previous formation of a carbonium hydrate, leads to an exchange of ions with the water of the medium. Under our experimental conditions (96% H_2SO_4), it is likely that the concerted mechanism should, insofar as it depends on the water content of the medium, here be replaced by the multistep mechanism. We shall therefore adopt the hypotheses of the multistep mechanism which implies passing through ions V and VII.

Table I. H/D Isotope Exchange of Ketones Ib and IIIb in 96% D_2SO_4 at 25 °C[a]

Compd[b]	Concn, M	Concn of products having reacted after 20 min, M	Ratio of H_2SO_4/dioxane integrations at 20 min	Obsd exchange
Ib	1	<0.01[c]	4	2
IIIb	1	1	22	20
Only medium[d]			2	

[a] The spectra are carried out on a Jeol C60 HL NMR spectrometer. Internal reference dioxane. [b] The roman numerals correspond to the compounds in Scheme IV. [c] After 20 min, the value found for Ib is 0.006 mol ± 0.0015. [d] The medium is comprised of a dioxane solution in 96% D_2SO_4. The sample is kept under argon throughout the entire manipulation.

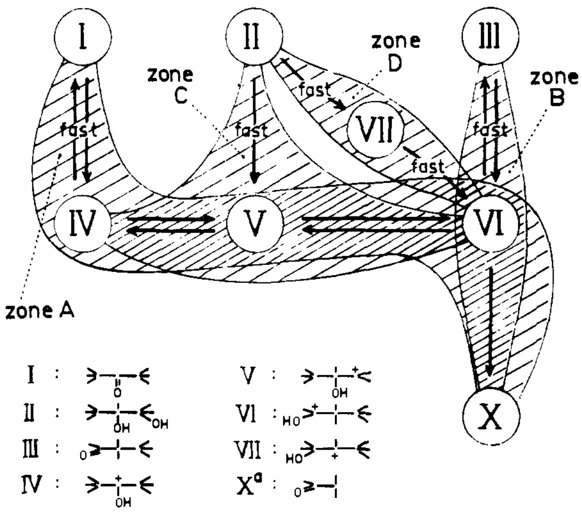
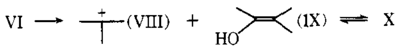


Figure 1. Zones of the reaction model studied under distinct physicochemical methods: (a) The X ketone results from fragmentation of ion VI:



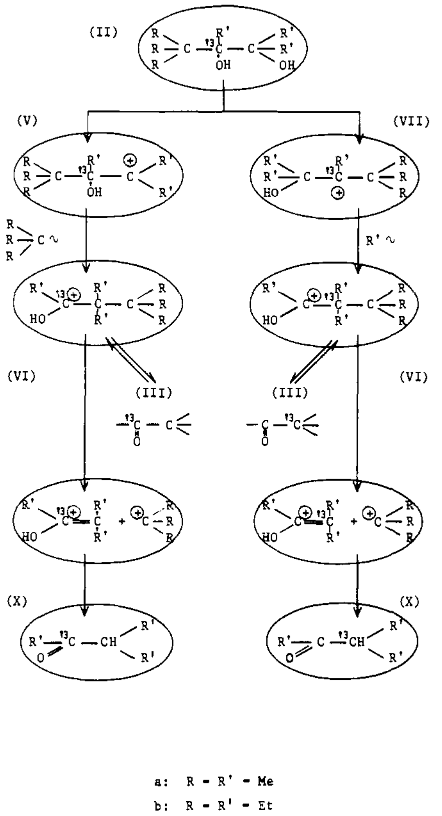
The pinacol rearrangement of glycols IIa and IIb was studied under the same experimental conditions as the preceding reactions (metathetical transposition of Ia and Ib and fragmentation of IIIa and IIIb). Glycols IIa and IIb have a lifetime smaller than 30 s: IIa gives 4% of Ia and 96% of IIIa, and IIb gives 28% of Ib and 72% fragmentation products (percent of ketone Xb).

However, these results must take into account the fact that the products of rearrangement of IIa and fragmentation to Xb can be formed by two separate pathways involving either of the intermediate ions V and VII (Scheme IV).

We must determine the relative importance of these pathways in order to estimate the importance of the reversibility of step IV → V. A ^{13}C tracer experiment solves this problem (Scheme V).

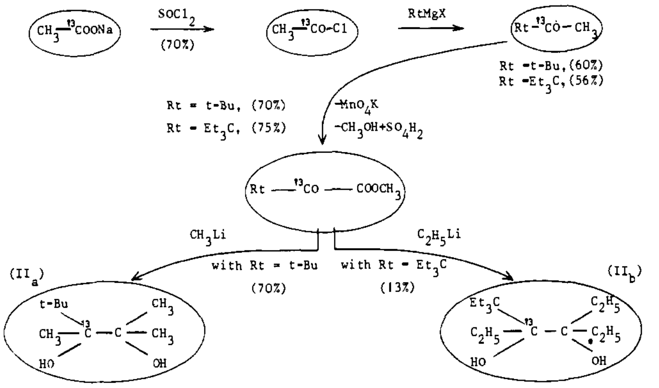
Zone D: Tracer Experiment (^{13}C). Using ^{14}C labeled compounds, Stiles and Mayer[28] showed that the pinacol rearrangement of IIa takes place entirely via ion Va in 50% H_2SO_4. This result need not necessarily hold true for glycols IIa and IIb in 96% H_2SO_4. We therefore decided to check this point using a different technique.

Scheme V



Glycols IIa and IIb were prepared using sodium acetate labeled on the carbonyl with 56-57% ^{13}C (Scheme VI). After a 30-s reaction time, labeled glycol IIa yields 96% of IIIa and IIb yields 72% of Xb.

Scheme VI



The isotope distribution in these products is analyzed by mass spectroscopy. The spectra corresponding to IIIa and Xb were measured three times and compared with those of unlabeled products obtained under the same conditions.

The high-resolution mass spectra of ketone IIIa shows the following peaks at *m/e* 43.045 ($-COCH_3$), 43.089 ($-CH(CH_3)_2$), and 44.048 ($-^{13}COCH_3$). No noticeable peak at *m/e* 44.092 ($-^{13}CH(CH_3)_2$) was observed. A comparison of the molecular peaks *m/e* 142.242 and 143.245 of the unlabeled and labeled ketone shows a ^{13}C concentration of 56%,[29] which corresponds to the ^{13}C concentrations in glycols IIa and IIb. A similar comparison of the peaks *m/e* 43.045 and 44.048 indicates an isotopic enrichment of 56% for the carbonyl carbon. Thus, for IIIa, all the ^{13}C present is found in the carbonyl group, thereby indicating (Scheme V) that the pinacol rearrangement of IIa takes place only via Va. This result amply confirms the works of Stiles and Mayer.

The mass spectrum of labeled ketone Xb exhibits peaks at *m/e* 57 ($-COC_2H_5$), 71 ($-CH(C_2H_5)_2$), 58 ($-^{13}COC_2H_5$), and a peak at 72 ($-^{13}CH(C_2H_5)_2$).[30]

A comparison of the molecular peaks[31] for labeled and unlabeled Xb shows a ^{13}C concentration of 56%[29] in the labeled ketone. The same type of comparison of peaks at *m/e* 57 and 58 as well as peaks at *m/e* 71 and 72 indicates an isotopic concentration of 52 and 4%, respectively. These results indicate that 93% of the pinacol rearrangement of glycol IIb (Scheme V) takes place via ion V and the remaining 7% via ion VII.[32]

Thus, in the pinacol rearrangement of IIa and IIb, the percentage A of reaction via ion V occurs 100 and 93%, respectively. If H represents the molar ratio between I and the sum of products (I + III + X) formed in 30 s by the pinacol rearrangement of II, the amounts of I obtained via ion V are: $H(100/A)$, i.e., 0.04 mol (4%) for Ia and 0.30 mol (30%) for Ib (Table II).

Migration Step Rate Determination. We have seen that the pinacol rearrangement of IIa and IIb yields 4% of Ia and 30% of Ib via ion V. The fragmentation of IIIa and IIIb yields no detectable amount of Ia and Ib. If we consider the sensitivity of product detection (0.1%),[26] we can conclude that the reversibility of step V → VI cannot be greater than $(100 \times 0.1)/4 = 2.5\%$ for Va and $(100 \times 0.1)/30 = 0.3\%$ for Vb. This allows us to neglect this reversibility, at least as a first approximation.

The stationary state principle, as applied to ion V, gives the following equation:

$$k_{\mathrm{expt}} = k_t(1 - k_{-1}/(k_{-t} + k_2))$$

where k_{expt} is the experimental rate constant for the disappearance of ketone I.

In this equation the ratio $k_{-1}/(k_{-1} + k_2)$ may be estimated from the amounts of I, III, and X, formed after 30 s of reaction via ion V from the pinacol rearrangement of glycols II and is thus equal to $H(100/A)$. These ratios are equal to 0.04 for IIa and 0.3 for IIb. From the above equation it is possible to calculate the constant k_1 and to deduce the partial rate migration constant $k_p{}^{\mathrm{Rm}}$ of groups which migrate during step IV → V.

Calculation of $k_p{}^{\mathrm{Rm}}$. For dissymmetric ketones several groups (R, R′) migrate in competition. In this case the metathetical transposition evolves through several pathways. A pinacol rearrangement corresponds to each one of these pathways. If B represents the relative importance of the different reaction pathways of the metathetical transposition and if A_{R} and $A_{\mathrm{R'}}$ represent, for each pinacol rearrangement, the percentage of the pathways passing via ions V, then the partial rate constant ($k_p{}^{\mathrm{Rm}}$) for the migration of a group Rm may be calculated from the following general equation:

$$k_p{}^{\mathrm{Rm}} = \frac{k_{\mathrm{expt}}}{(1 - k_{-t}/(k_{-t} + k_2))P}\frac{B}{100} = \frac{k_{\mathrm{expt}}}{(1 - (100H/A))P}\frac{B}{100}$$

in which P is a statistical factor equal to the number of identical groups giving rise to the same product by migration.

The partial rate constant for the migration (Table II) of a methyl group in Ia is $775 \times 10^{-8}\ s^{-1}$ and for that of an ethyl group in Ib it is $8 \times 10^{-8}\ s^{-1}$.

Conclusion

Thus the mechanistic study of the metathetical transposition, the pinacol rearrangement, and the fragmentation of ketones indicates that these three reactions constitute a model system for calculating rate constants $k_p{}^{\mathrm{Rm}}$ specific to migration. In a forthcoming article, the analysis of the influence of

Table II. Calculation of Constants k_p^{Rm} for the Ethyl and Methyl Groups

Compd	$10^8\,k_{expt}$,[a] s^{-1}	% of I formed from II[b] and III[c]	H[d]	A[e]	$\frac{k_{-1}}{k_{-1}+k_2}$[f]	P[g]	B[h]	$10^8 k_p^{Rm}$,[i] s^{-1}	log k_p^{Rm} + 8
Ia	4450					6	100	775	2.89
Ib	33					6	100	8	0.9
IIa	$>10^5$	4	0.04	100	0.04				
IIb	$>10^7$	28	0.28	93	0.30				
IIIa		$\leqslant 2.5$							
IIIb		$\leqslant 0.3$							

[a] The disappearance rate constant of ketone I and glycols II in the medium. For the ketones the standard deviation is about 2%. [b] The percentages of ketone I formed in 30 s by the pinacol rearrangement from glycols II. Values are at ±0.5%. [c] The maximum percentage of ketone I which could be formed from III. [d] The molar ratio between I and the sum of the products (I + III + X) formed in 30 s by the pinacol rearrangement of II. Values are at ±0.005. [e] In the pinacol rearrangement leading to products I, III, and X, A represents the percentage, determined by mass spectroscopy, of the pathway passing via ion V. Values are at ±0.5. [f] $H(100/A)$. [g] The statistical factor equal to the number of R or R′ groups, whose migration leads to the same product in the metathetical transposition of I. [h] The percentage, identified according to the nature of the formed products of the metathetical transposition reaction pathways. Since the six groups which can migrate in Ia and Ib are identical, the six pathways of the metathetical transposition yield the same product. Under these conditions $B = 100$. [i] Since these values are obtained from k_{expt}, from percentages of I formed from II and from values of A, then the estimated error is about ±3%.

environments $\mathscr{C}_{Co}$ and $\mathscr{C}_{Ct}$ of the origin and terminal carbons on constant k_p^{Rm} will be examined for a family of bis-*tert*-alkyl ketones where Ia and Ib constitute the structural limits.

Experimental Section

General. Gas chromatographic analyses were run on a Varian Aerograph Model 1200 (equipped with a flame ionization detector and electronic integrator, Varian Model 475) using a 10 ft × 0.125 in. column with, respectively, 10% SE-30 and 15% DEGS.

Preparative separations were carried out on a Varian Aerograph Model 1440 (equipped for micropreparative) using a 10 ft × 0.250 in. column with 10% SE-30.

Infrared spectra were measured on a Perkin-Elmer 225 spectrophotometer; NMR spectra were measured on a Jeol C-60-HL spectrometer; mass spectra were taken on a Thomson 208 HL mass spectrometer equipped with a line molecular injector accessory.

2,2,4,4-Tetramethyl-3-pentanone (Ia). Under an argon atmosphere, 500 ml of a 1 M solution of *tert*-butylmagnesium chloride were added to an equimolecular mixture (0.45 mol) of pivaloyl chloride and cuprous chloride in 100 ml of dried ether at −5 °C.[33] The medium was poured onto ice, acidified with HCl, and filtered to separate copper. After neutralization with $NaHCO_3$, three extractions with ether, and drying over $MgSO_4$–K_2CO_3, the distillation yielded 51 g (80%) of 99.5% pure ketone: bp 69.5 °C (48 mm); n^{25}D 1.4170; ir 1686.5 cm^{-1} (C=O) (lit. bp 152 °C (760 mm); n^{25}D 1.4171).

3,3,5,5-Tetraethyl-4-heptanone (Ib). This ketone was prepared by condensation of 1,1-diethylpropylmagnesium chloride at 0.5 M with 2,2-diethylbutanoyl chloride (obtained by carboxylation of 1,1-diethylpropylmagnesium chloride), under the same conditions as used for Ia. The yield of 99% pure product was 30%: bp 115 °C (3 mm); mp 44–45 °C; ir 1678 cm^{-1} (C=O).

3,3,4,4-Tetramethyl-2-pentanone (IIIa). This ketone was obtained by the metathetical transposition of 2,2,4,4-tetramethyl-3-pentanone (1 M of Ia) in 96% H_2SO_4. Ia (35.5 g) and 250 ml of H_2SO_4 were placed in a thermostat at 25 °C. After 7 h, the mixture was poured onto ice, extracted three times with pentane, and dried over $MgSO_4$–K_2CO_3. Distillation gave 24.8 g (0.175 mol) of 3,3,4,4-tetramethyl-2-pentanone whose purity is 99%: bp 80 °C (62 mm); mp 63 °C; ir 1700.4 cm^{-1} (C=O) (lit.[34] bp 164–167 °C; mp 54–60 °C (impure product containing 15% Ia)).

4,4,5,5-Tetraethyl-3-heptanone (IIIb). This ketone was obtained by the pinacol rearrangement of 3,4,5,5-tetraethyl-3,4-heptanediol in 50/50 H_2SO_4–acetic acid (5:1). 3,4,5,5-Tetraethyl-3,4-heptanediol (0.001 mol) was placed in a small tube and vigorously stirred with 1.4 ml of an H_2SO_4–acetic acid mixture for 4 or 5 min at room temperature. An equal volume of cold water was added. The mixture was extracted three times with pentane, dried over $MgSO_4$–K_2CO_3, and concentrated; the yield of pure product was 10%. 4,4,5,5-Tetraethyl-3-heptanone was separated by preparative GLC (10 ft × 0.250 in. column with 10% SE-30 at 175 °C). Consistent ir and NMR spectra were obtained for this ketone: ir 1694 cm^{-1} (C=O).

2,3,4,4-Tetramethyl-2,3 pentanediol (IIa). (1) Potassium permanganate oxidation in aqueous NaOH at room temperature of 7 g of pinacolone, followed by esterification in concentrated H_2SO_4, yielded 5.8 g of methyl 3,3-dimethyl-2-oxo-butanoate: bp 60 °C (19 mm).

(2) Ketoester (5.8 g, 0.04 mol) in 40 ml of dried ether was added slowly at room temperature to 0.24 mol of methyllithium (prepared under argon, from 6 g (0.85 mol) of lithium and 42.5 g (0.3 mol) of methyl iodide in 270 ml of dried ether).[35] After hydrolysis, the mixture was extracted with ether. The extract was washed with water, dried over $MgSO_4$, and the solvent evaporated.

After purification by preparative GLC (10 ft × 0.250 in. column with 10% SE-30 at 150 °C) a 70% yield of the resulting product was obtained: purity 99%; n^{25}D 1.4542. The glycol was identified by the ir and NMR spectra, as well as by oxidation with lead tetraacetate.

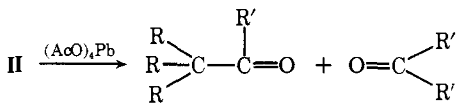
3,4,5,5-Tetraethyl-3,4-heptanediol (IIb). (1) Preparation of 3,3-Diethyl-2-pentanone. 1,1-Diethylpropylmagnesium chloride (750 ml, 0.4 M; prepared by reaction of 0.45 mol of 1,1-diethylpropyl chloride on 0.45 mol of bisublimed magnesium in boiling ether, under an argon atmosphere) was added over 5 h to an equimolecular mixture (0.25 mol) of acetyl chloride and cuprous iodide[35] in 100 ml of dried ether at −15 °C. Distillation gave 20 g (0.14 mol) of 3,3-diethyl-2-pentanone: bp 88 °C (45 mm); 60% yield.

(2) Preparation of Methyl 3,3-Diethyl-2-oxopentanoate. This ketoester was prepared in the same way as the methyl 3,3-dimethyl-2-oxobutanoate: bp 92 °C (10 mm); 75% yield.

(3) The 3,4,5,5-tetraethyl-3,4-heptanediol was synthesized by condensation of ethyllithium on the above ketoester in pentane. Ethyllithium (0.2 mol, 1 M) was prepared by reaction of 27.2 g (0.25 mol) of ethyl bromide on 4.9 g (0.7 mol) of lithium in 180 ml of dried pentane under argon at room temperature. Methyl 3,3-diethyl-2-oxopentanoate (6 g, 0.032 mol) in 50 ml of dried pentane was added over 3 h.[35]

Afterwards, the mixture was cooled in an acetone bath at 0 °C and water was added. The mixture was extracted with pentane, dried over $MgSO_4$, and concentrated. The glycol was separated by preparative GLC (10 ft × 0.250 in. column with 10% SE-30 at 195 °C): white solid, mp 66.5 °C; 10% yield of 99% pure product. The glycol was identified by the ir and NMR spectra, as well as by oxidation with lead tetraacetate.

Glycol Identification with Lead Tetraacetate. The structure of IIa and IIb was determined by oxidation with lead tetraacetate and identification of the resulting ketones. Glycol (3 × 10^{-4} mol) and 3.5



$$\mathrm{II} \xrightarrow{(\mathrm{AcO})_4\mathrm{Pb}} \mathrm{R_3C{-}C(R'){=}O} + \mathrm{O{=}CR'_2}$$

$\times 10^{-4}$ mol of lead tetraacetate (humidified with about 10–15 acetic acid) were placed in 250 μl of dried benzene in a quickfit flask with stirring. The medium was refluxed over a 1-h period in an 85–90 °C bath. After cooling the solution was decanted and neutralized with K_2CO_3. The two resulting ketones were identified by GLC with two different columns (10 ft × 0.125 in. with 10% SE-30 and 15% Carbowax 20M, respectively) by verification of their retention times with those obtained from authentic samples.

2,3,4,4-Tetramethyl-2,3-pentanediol (IIa) yielded the acetone and the pinacolone. 3,4,5,5-Tetraethyl-3,4-heptanediol (IIb) yielded 3-pentanone and 4,4-diethyl-3-hexanone. No trace of other products nor glycols was found again.

2,3,4,4-Tetramethyl-2,3-pentanediol-*3-*^{13}*C* and 3,4,5,5-Tetraethyl-3,4-heptanediol-*4-*^{13}*C*. These two glycols were obtained from commercial sodium acetate·$3H_2O$ labeled on the carbonyl with 56–57% ^{13}C (Centre d'Energie Atomique de Saclay, France). The sodium acetate was dehydrated by heat in a nickel crucible, then transformed into acetyl chloride by reaction with thionyl chloride: 72% yield.

3,3-Diethyl-2-pentanone-*2-*^{13}*C* was obtained as described above for the unmarked ketone. For 3,3-dimethyl-2-butanone-*2-*^{13}*C* an analogous procedure was used (cuprous chloride instead of cuprous iodide): 56% yield.

The same procedures as those used for 2,3,4,4-tetramethyl-2,3-pentanediol and 3,4,5,5-tetraethyl-3,4-heptanediol were followed to obtain 2,3,4,4-tetramethyl-2,3-pentanediol-*3-*^{13}*C* and 3,4,5,5-tetraethyl-3,4-heptanediol-*4-*^{13}*C*.

Kinetic Procedure of Ketones. In a hemolysis tube, 0.6 ml of H_2SO_4 (96 wt %) and 6×10^{-4} mol of ketone were mixed and placed in a thermostat at 25 °C. At a time *t*, the mixture was poured onto ice. THF (10–12 drops) and 2 drops of heliantin were added. The solution was cooled in an ice bath and neutralized by 20% NaOH. At room temperature, the solution was salted out with sodium chloride and extracted two more times with THF. The THF extracts were rapidly dried over Na_2SO_4. Eight to ten assays were measured for each ketone.

The percentages of different compounds were determined by GLC[36] (10 ft × 0.125 in. column with 15% DEGS; programming temperature 4 °C/min; limit temperatures according to boiling points of ketones composing the fraction) using specific calibration factors for peak area measurements.[37] The GLC retention times and the ir and NMR spectra obtained for each of the fragmented ketones (separated by preparative GLC) were identical with those obtained from authentic samples.

Kinetic Procedure for 2,3,4,4-Tetramethyl-2,3-pentanediol (IIa) and 3,4,5,5-Tetraethyl-3,4-heptanediol (IIb). In a hemolysis tube, 0.6 ml of H_2SO_4 (96 wt %) and 6×10^{-4} mol of glycol were rapidly mixed (time <30 s) and immediately poured onto ice. The extraction, identification of different components, and calculation were the same as for the ketones.

NMR Study on 3,3,5,5-Tetraethyl-4-heptanone (Ib) and 4,4,5,5-Tetraethyl-3-heptanone (IIIb) in D_2SO_4. The experiment was carried out in 96% D_2SO_4 (Fluka commercial product), deuteration >99%, with dioxane as the internal standard (1 mol ketone/liter of D_2SO_4). In a small flask, under argon, 6 ml of D_2SO_4 was mixed with 0.6 ml of dioxane. The medium (0.5 ml) was added to the NMR tube labeled "1", containing 0.103 g of 3,3,5,5-tetraethyl-4-heptanone (Ib), and 0.055 ml in a microcell kit, labeled "2", containing 0.011 g of 4,4,5,5-tetraethyl-3-heptanone (IIIb).

The integration was carried out after 20 minutes at room temperature and compared with a tube containing only 0.5 ml of the medium. Immediately after, integrations "1" and "2" were hydrolyzed, then extracted as for the ketones.

Analysis (GLC) on 10 ft × 0.125 in. column with 15% DEGS at 100–160 °C gave 0.6% for "1" and 100% for "2" of 4-ethyl-3-hexanone (Xb).

Acknowledgments. We express our thanks to Dr. J. A. MacPhee and Mrs. O. Bruno for their advice on preparation of the manuscript and to Mrs. S. Briand for her technical assistance.

References and Notes

(1) For preliminary communications on this topic see: J. E. Dubois and P. Bauer, *J. Am. Chem. Soc.*, **90**, 4510, 4511 (1968).

(2) Throughout this article we will use the term "migratory aptitude" in a broad sense: the ability of a group to migrate.

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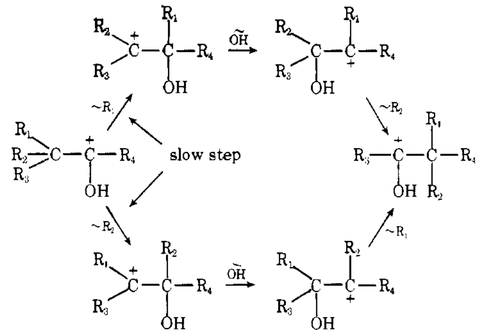
(7) In the transposition of ketones in acidic medium, in addition to the difficulties already mentioned, a mechanism by oxygen migration had been ascertained in certain cases (K. Bhatia and A. Fry, *J. Org. Chem.*, **34**, 806 (1969)) which prevents any sort of clear correlation between product structure and the nature of the migrating group in the slow step.



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(16) In the series of bis-*tert*-alkyl ketones studied the reference structure will be hexamethylacetone.

(17) Ketone IIIb rapidly gives rise to a fragmentation reaction whose products are capable of an ion exchange with the medium: ion VIII and enol IX. For this reason this ketone was chosen for this study. Furthermore, no trace of Ib has ever been observed during this fragmentation reaction.

(18) Ib, which is not enolizable, cannot exchange isotopes.

(19) These derived products, the enols of ketones IIIb and Xb and carbonium ion VIIIb, can exchange isotopes with the medium.

(20) At this point it is hard to go further into detail about the kinetic phenomena which govern this exchange, since the relative rates of exchange for enols as well as for carbonium ions are unknown.

(21) M. Stiles and R. P. Mayer, *Chem. Ind.* (*London*), 1357 (1957).

(22) We have verified that the disappearance constants of several hexasubstituted ketones remain unchanged whenever the H_2SO_4 concentration is between 95 and 99%. α,α'-bis-*tert*-alkyl ketones: Ia, Ib, and 2,2,4,4-tetramethyl-3-hexanone; α',α,β-tri-*tert*-alkyl ketones: 2,2,4,4,5,5-hexamethyl-3-hexanone and 3,3-diethyl-5,5,6,6-tetramethyl-4-heptanone.

(23) Preequilibrium protonations are known to be rapid reactions. In additions, the lifetime of the glycols II in the medium is less than 30 s. The rate of disappearance of the glycols II in the medium is thus at least 10^5–10^7 times greater than the rate of disappearance of the ketones I.

(24) The standard deviation of these constants is 2%.

(25) The fragmentation products were identified by comparing the ir, NMR, and mass spectra of the ketones X with commercial samples.

(26) The kinetic experiments were followed by GLC analysis using a Varian 1200 chromatograph equipped with a Varian 475 integrator. Traces of products smaller than 0.1% may be detected.

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(29) These percentages result from the average for three measurements which were carried out; the precision of the values was at ±0.5%. It should be noted that the percentage of ^{13}C found on the molecular peak of labeled ketones IIIa and Xb (56%) coincides with the isotopic concentration of the initial product used for the synthesis of IIa and IIb (the "Centre d'Energie Atomique" pointed out an isotope enrichment of 56–57% on the carbonyl of the sodium acetate).

(30) The study of ketone Xb did not require the use of high resolution, since the fragments have distinctly different masses.

(31) Since the compounds are very close to each other, the variation in the width of the peaks is so small that is was possible to deduce the percentages from a comparison of the relative heights of the peaks. We took into account the percentage of natural ^{13}C found in the unlabeled ketone.

(32) These results are valid only if the reversibility of step V → VI is negligible or nil. Now, the fact that the metathetical transposition is not reversible (since I was never obtained from III) shows that one of the two steps, IV → V or V → VI, is not reversible. Furthermore, the pinacol rearrangement yielding I and III from II implies that step IV → V is reversible. Thus, as we

shall show in this article, the reversibility of step V → VI can be discarded.

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(35) Before use the organolithium compound was decanted under argon pressure to eliminate excess lithium.

(36) The accuracy of this method was verified from a standard solution containing the very same products as the reaction. For each product the average of the values found is ±0.5% of the theoretical value.

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Metathetical Transposition of Bis-*tert*-alkyl Ketones. 2. Structural Effects on Alkyl Migration. Existence of Linear Relationship Networks

P. Bauer and J. E. Dubois*

Contribution from the Laboratoire de Chimie Organique Physique de l'Université de Paris VII, associé au C.N.R.S., 75005 Paris, France.

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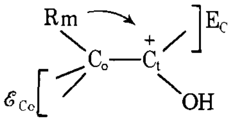
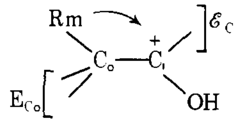
Abstract: Structure-migrating group interactions which are present during 1,2 migrations of alkyl groups Rm (Rm = Me or Et) have been studied as a function of the influence of a variable environment $\mathcal{E}_{C_o}$ of the origin carbon C_o for a fixed environment E_{C_t} of the terminal carbon C_t, and vice versa, on the partial rate constant (k_p^{Rm}) for migration in IV. The constants k_p^{Rm} were determined from a study, in 96% H_2SO_4, of the metathetical transposition of 11 α,α'-bis-*tert*-alkyl ketones ($R_1R_2RmCCORt$ (I)) leading to 24 rearrangement pathways of the following type: I $\rightleftharpoons$ $R_1R_2RmC_oC_t^+OHRt$ (IV) $\rightleftharpoons$ $R_1R_2C^+COHRmRt$ (V) → $R_1R_2RtCC^+OHRm$ (VI). In a first approximation values k_p^{Rm} were calculated while considering the return of step IV $\rightleftharpoons$ V, during which group Rm migrates, as being negligible. This hypothesis was ultimately verified by measuring the return of this step by a study of the pinacol rearrangement of 16 glycols ($R_1R_2COHCOHRmRt$ (II) → V → IV + VI) chosen as constituting the structural limits for the studied environments $\mathcal{E}_{C_o}$ and $\mathcal{E}_{C_t}$. Our results show that the return of step IV $\rightleftharpoons$ V is too small to be the cause of the observed structural effects. The measured values of k_p^{Rm} cover a range of about three powers of ten. Linear relationships have been observed between log k_p^{Rm} and the number of carbon atoms, n_o and n_t, comprising the environments $\mathcal{E}_{C_o}$ and $\mathcal{E}_{C_t}$: $\log k_p^{Rm}(\mathcal{E}_{C_o}, E_{C_t}) = \log k_{op}^{Rm} + an_o$, and $\log k_p^{Rm}(E_{C_o}, \mathcal{E}_{C_t}) = \log k_{op}^{Rm} + bn_t$, in which $a = 0.017$ (Rm = Me) and 0.26 (Rm = Et) for E_{C_t} = *t*-Bu; and $b = -0.63$ (Rm = Me) and -0.66 (Rm = Et) for E_{C_o} = Me, Me. Thus, the environment $\mathcal{E}_{C_t}$ opposes migration, whereas the environment $\mathcal{E}_{C_o}$ assists it. Moreover, the effect of $\mathcal{E}_{C_t}$ is more important than that of $\mathcal{E}_{C_o}$, but it is less sensitive to the nature of Rm. Among the structures studied two types of behavior are observed: a strict additivity of environmental effects as shown by the relationship $\log k_p^{Rm}(\mathcal{E}_{C_o}, \mathcal{E}_{C_t}) = \log k_{op}^{Rm} + an_o + bn_t + i$ (in which $i = 0$) and a partial additivity ($i \neq 0$). Each migrating group is characterized by a network of linear relationships. A comparison of the theoretical network ($i = 0$) with the experimental one shows that "i" is most often independent of the nature of Rm. It is likely that conformational effects and unbonded steric interactions will explain "i".

The migratory aptitude[1] of a group is a complex phenomenon which depends not only on the nature of the group, but also on the interactions between the group and the structure in which it migrates (group-structure interactions).[2] The lack of systematic information regarding these interactions is certainly one of the main reasons for the absence of quantitative data concerning the migratory aptitudes of alkyl groups.[3]

In the preceding article[4] we have shown that the metathetical transposition of α,α'-bis-*tert*-alkyl ketones (Scheme I) was a reaction particularly suited to the obtainment of this kind of information. Reasoning that it is not possible to consider the notion of migratory aptitude without considering these interactions, we propose in this article to use this reaction for a systematic study of group-structure interactions in order to measure their importance and to attempt to specify the nature of the structural parameters responsible for this effect.

The complexity of this kind of interaction has led us to begin by separating arbitrarily the influence of the environments E_{C_o} and E_{C_t} of the origin and terminal carbons, C_o and C_t, of the migration.[5] Thus, we have studied how the rate constant k_p^{Rm} varies as a function of $\mathcal{E}_{C_o}$ when the environment of the terminal carbon is held constant at E_{C_t} and conversely, as a function of $\mathcal{E}_{C_t}$ with E_{C_o} constant. Every variable environment





Scheme I