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BASE-CATALYSED POLYALKYLATION OF ALIPHATIC KETONES. II. REACTION GRAPH FOR THE POLYMETHYLATION OF METHYLNEOHEXYL KETONE.

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We wish to present results, related to the continuous polyalkylation of aliphatic ketones, which illustrate the utility of the reaction graph method described in our previous communication (1).

Reaction in ether at 35° of a large excess (6 to 10-fold) of MeI with methylneohexylketone (2) previously enolized by means of $NaNH_2$ gives, of the possible eleven ketones, only six(denoted in order of increasing retention time : A, B, C, D, E and F). Products were purified by preparative glpc, and were checked by analytical glpc.

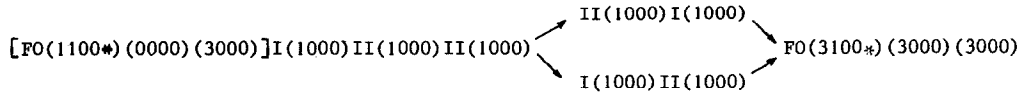
Reaction graph and product identification : Since certain of the likely products (2,1, 3,1, 2,2, 2,3 ...) (3) have not been described, identification by direct comparison with reference compounds necessitates complex syntheses. Furthermore, the nmr spectra of these ketones are rather similar and not readily analysed. Nor can topology-information correlations of the u.v. (4) and i.r. (5) spectral frequencies of aliphatic ketones be used since they have yet to be extended to compounds of the degree of elaboration encountered here. Therefore, the products were characterised indirectly by a combination of three techniques :

(a) elemental analysis is used to situate the product at its correct alkylation level ;
(b) glpc study of product evolution with reaction duration shows that each ketone must be derived at least partially from the parent identified at the preceding methylation level ;
(c) a proton signal readily identifiable by its chemical shift, strength and multiplicity is selected in order to distinguish the two remaining structures.

Consider ketone A : there are two isomers which can be formed by monomethylation of methylneohexylketone (neoPe)CH_2-CO-CH_3, that is (2,0) and (1,1). In the nmr spectrum is found only the α-methyl absorption of (2,0) and not that of the α-methylene hydrogens of (1,1). Furthermore, since the dimethylated ketone B has A as its parent, it cannot be (1,2). Similarly, the trimethylated ketone C cannot be (1,3). Partial analysis of the spectra of B and C showed that they were (2,1) and (2,2) respectively. The two tetramethylated products can only be (2,3)

and (3,2), and complete analysis of the nmr spectrum showed that the major product (70%) was (2,3).

The total reaction graph is thus given by Fig.1 ; the significant nmr signals (the relevant group is underlined) are indicated in the Table. It is seen that there is at first only one reaction path which, however, divides into two for the 4th methylation ; this result can be expressed (1) in the following manner :



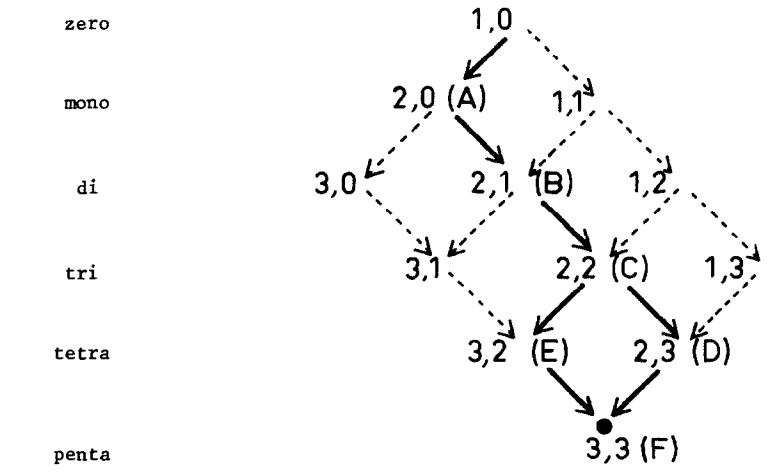


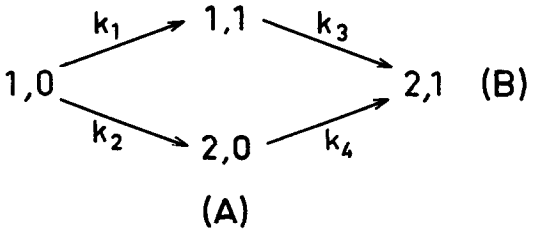
Fig.1 : The Total Reaction Graph

TABLE

Compound	Formula	DEL (6)	Chemical shift
A	(neoPe)(Me)CH-CO-$\underline{CH}_3$	FO(2100*)(0000)(3000)	2.1 ppm
B	(neoPe)(Me)$\underline{CH}$-CO-CH_2(Me)	FO(2100*)(1000)(3000)	2.75 ppm
C	(neoPe)(Me)$\underline{CH}$-CO-CH$(Me)_2$	FO(2100*)(2000)(3000)	2.75 ppm
D	(neoPe)(Me)$\underline{CH}$-CO-C$(Me)_3$	FO(3000)(2100*)(3000)	3.07 ppm
E	(neoPe)$(Me)_2$C-CO-$\underline{CH}(Me)_2$	FO(3100*)(2000)(3000)	3.14 ppm
F	(neoPe)$(Me)_2$C-CO-C$(\underline{Me})_3$	FO(3100*)(3000)(3000)	1.25 ppm

Ketones B, C, D and F are new (7).

Plurality of Reaction Pathways : It is worth noting that, in the absence of a kinetic analysis of all the steps, it is not possible to assert that the observed pathways are the only ones followed. However, our efforts to detect other ketones, such as (1,1), by using a much smaller excess of MeI and stopping the reaction early on, have failed. Initially, only A and B are isolated. In principle, it is possible that most or part of B is formed via (1,1). This would, however, imply $k_3 >> k_1$ and also $k_2 > k_1$ (since A is observed before B) in the scheme below. There is no reason to think that such a disparity of the rate constants is likely in this system. Furthermore, the product filiation studies [see (b) above] show that the methylated ketones must be formed at least partially by the routes indicated by linking the isolated products (7). Experiments to determine whether these routes are the only ones followed are in progress.



Pathways and Orientation Factors : The determination of the reaction graph for the two-step reaction (enolization and alkylation) makes possible a preliminary analysis of the factors governing orientation in this system. It seems reasonable to consider, as a first approximation, that the alkyls α and α' to the carbonyl group do not interact and that the relative ease of methylation is determined by the environments of the α and α' carbon atoms. The stability of enolate anions has been considered to be determined by hyperconjugation (8) and the rate of addition seems likely to be determined largely by steric factors. For the parent ketone, hyperconjugation favours the formation of (2,0) (isolated), whereas steric control would favour (1,1) (not isolated). On the other hand, all subsequent steps are sterically controlled. Methylation of (2,2) gives predominantly the sterically preferred product. However, the difference in reactivity may not be as great as that suggested by the isolated product ratio, since E is probably more rapidly converted to F than is the more hindered ketone D.

Hyperconjugative control of every step would cause the reactions to follow the path indicated in Fig.2 ; steric control would most likely lead to that in Fig.3 .

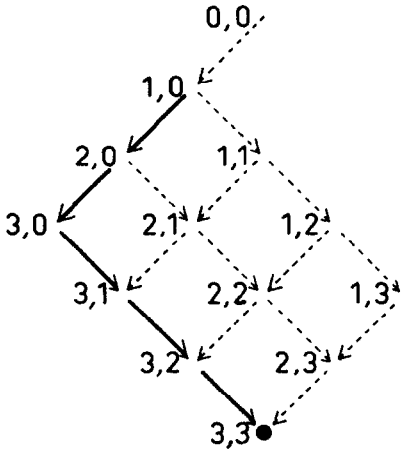


Fig.2 : Hyperconjugative Control

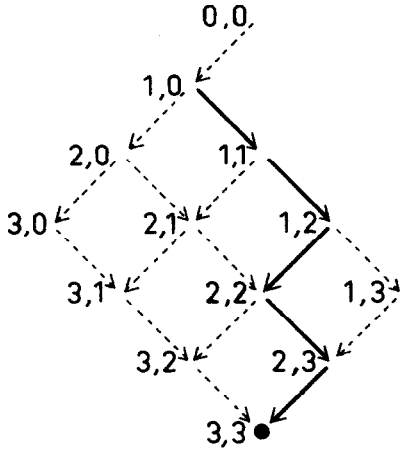


Fig.3 : Steric Control

Application of this approach to the ethylation of methylneohexylketone makes it clear that the steric factor determines in the same way the orientation of the second alkylation. More striking is the result that the product corresponding to (1,1) is formed to the extent of 20%, thus indicating a measure of steric control of even the first alkylation when a larger alkylating agent is involved (1).

Eventually, when more detailed information on the kinetics of these reactions is available, it is proposed to treat the interactions between the alkylating agents and the substituents in terms of the DARC topological system. However, it is evident that complete analysis of the reaction pathway requires the comparison of the graph of continuous polyalkylation with the graphs obtained by assembling, in sequence, the data for the individual alkylations, studied under conditions of either thermodynamic or kinetic control.

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