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INTERMEDIATES IN NUCLEOPHILIC AROMATIC SUBSTITUTION. PART V (1).

KINETIC VERSUS THERMODYNAMIC CONTROL IN THE REACTIONS OF METHOXIDE ION WITH NITROCYANOANISOLES; REARRANGEMENTS OF 1,3- TO 1,1-DIMETHOXYCYCLOHEXADIENYLIDES

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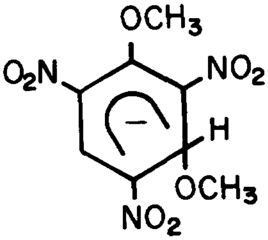
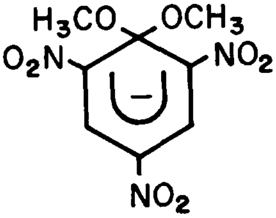
Servis (3) has shown that the reaction of methyl picrate with methoxide ion in DMSO initially yields the 1,3-dimethoxycyclohexadienylide I; complex I undergoes a rapid conversion to the thermodynamically more stable product II. This observation has been considered to be unique in the literature of Meisenheimer complex chemistry (4). Although the reactions of a number of other nitroaryl [2,4- (4,5) and 2,6-dinitrophenyl (4), 2,4-dinitronaphthyl (6)] ethers with alkoxide ions have been examined, no evidence for the formation of complexes analogous to I has been reported. In each of these systems, attack of alkoxide ion is either specific at the substituted ring position to yield the 1,1-dialkoxycyclohexadienylides or the 1,3-complexes, if formed by attack at the 3-positions, rearrange too rapidly to be detected.



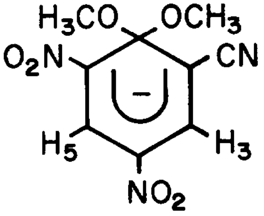
I



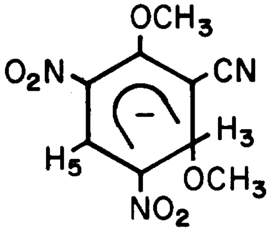
II

Crampton and Gold (7) have suggested that II is a less strained structure than methyl picrate, but that the transition state leading to its formation has a greater strain and therefore the initial attack of methoxide ion gives the thermodynamically less stable I. On this basis, the failure to observe 1,3-complexes as intermediates in the reactions leading to the formation of the 2,6-dinitrophenyl (III) and 2,4-dinitronaphthyl (IV) analogs of II is unexpected. Consequently, the overall free energy for the equilibrium of the system including I and II and their analogs must be delicately balanced between the relative abilities of the ring substituents to carry the negative charge and specific solvent and steric requirements. Equilibrium constants for the formation of II, IV and the 2-cyano-4,6-dinitro (V), 4-cyano-2,6-dinitro (VI) and 2,4-dicyano-6-nitro (VII) analogs of II in methanol at 25.00° have recently become available: K_{II} = 17,000 (8), K_{IV} = 230 (6), K_V = 2,600 (8), K_{VI} = 280 (8), K_{VII} = 210 (8). It was thought that a possible correlation might exist between complex stabilities in methanol and the equilibrium between 1,1- and 1,3-complexes.

As a test of this postulate, the course of the reaction of 2-cyano-4,6-dinitroanisole (VIII) with methoxide ion has been followed by PMR spectroscopy. This reaction has been shown to result in the formation of the 1,1 complex V (9);



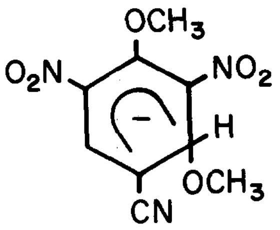
V



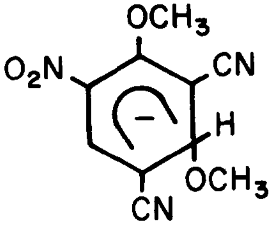
IX

the stability of V in methanol is less than that of II, but of the same order of magnitude. Addition of methanolic postassium methoxide to a solution of VIII (τ_{Me} = 5.73, $\tau_3 = \tau_5$ = 0.93 ppm) in DMSO-d_6 at 25° results in an immediate reduction in the intensity of the 0.93 and 5.73 ppm signals and the development of methoxyl singlets at τ = 6.23, 6.92 and 7.03 ppm; a somewhat slower development of weak singlets at τ = 1.47 and 4.50 ppm occurs. With time, the intensities of the 1.47, 4.50, 6.23 and 6.92 ppm signals decrease, while the intensity of the 7.03 ppm signal increases and doublets appear at 1.28 and 2.10 ppm. Ultimately the former set of signals disappear and the latter set undergoes a further increase in intensity. The sequence is repeated on the addition of further methoxide ion. After the addition of one equivalent of methoxide ion, the stable spectrum consists of an AB system (1.28, 2.10 ppm, J = 2.8 Hz)and a singlet (7.03 ppm). These signals are due to H-5, H-3 and the methoxyl of V; similar parameters are reported (9) for V and are obtained for a solution of the isolated crystalline complex. The transient signals at 1.47, 4.50, 6.23 and 6.92 ppm are assigned to H-5, H-3 and the 1- and 3-methoxyls, respectively, of the 1,3-complex IX. The assignments are made on the basis of the chemical shifts observed for I (3) and for complexes X and XI; in all cases, the integrated intensities of the signals supported the assignments. The approximate half-life of IX is one hour. The formation of the kinetically controlled product IX in this reaction supports the contention that the formation of 1,3-complexes reflects the stability of the system.

Similar observations were also made in studies of the reactions of methoxide ion with 4-cyano-2,6-dinitroanisole (XII) and 2,4-dicyano-6-nitroanisole (XIII). The 1,3-complexes X and XI are formed initially and undergo conversion with time to the isomeric 1,1-complexes VI (10) and VII, respectively. These results are somewhat surprising since the stabilities of VI and VII in methanol are appreciably less than that of V. The equilibrium constant for the formation of VI in methanol is almost identical to that for IV; in the reaction leading to the formation of IV, no evidence was obtained for an initial attack at the 3-position (6). The formation of complexes X and XI indicates that neither complex stability nor steric considerations can provide a full rationalization for the occurrence of kinetic control in reactions leading to the formation of 1,3-complexes. Further work is in progress



X



XI

in this area.

Ring positions 3 and 5 of VIII and XIII are not equivalent and, consequently, the formation of two isomeric 1,3-complexes could occur in the reactions of each of these ethers with methoxide ion. However, 1,3-complex formation was apparently specific to yield IX and XI; no evidence was obtained from PMR studies for the formation of the isomeric complexes. The preferred isomers IX and XI are those formed by attack of nucleophile *para* to a nitro rather than a cyano group. This selectivity parallels the stabilities of the isomeric 1,1-complexes V and VI; in the more stable V, the entering methoxyl is *para* to a nitro group. Previous studies have shown nitro groups to possess a greater stabilizing effect on Meisenheimer complexes than is shown by cyano groups (9,11). *Acknowledgement.* This study was supported in part by the U. S. Atomic Energy Commission. A portion of the PMR studies utilized instrumentation provided by a grant (FR 00292-02) from the National Institutes of Health.

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