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QUANTUM CHEMICAL INVESTIGATION OF THE MECHANISM OF THE REACTION OF PYRIDINES WITH TRICHLOROMETHYLARENES

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Models of the major end products and intermediate products, previously detected in a study of the mechanism of the interaction of trichloromethylarenes with pyridines, were calculated by a semiempirical quantum chemical MNDO method. Models of some putative unstable intermediates of the key redox step of the process under consideration — the aromatization of 4-chloro- or 4-pyridino-substituted 1-(α,α-dichloroarylmethyl)-1,4-dihydropyridines with transfer of hydrogen from the 4-position of the dihydropyridine ring to the benzyl dichloromethylene group and the formation of N-(α-chloroarylmethyl)-4-chloropyridinium chlorides of N-(α-chloroarylmethyl)-4-pyridinopyridinium dichlorides, were also calculated.

Recently a previously unknown reductive condensation reaction, proceeding in the interaction of trichloromethylarenes $ArCCl_3$ (I) with hydroxylamine or hydrazines in pyridine and leading to a number of products that may be considered as derivatives of the corresponding aldehydes ArCHO, was discovered; it was suggested that the hydroxylamine and hydrazines are the reducing agents in this reaction [1, 2]. It was later shown [3-6] that the role of the reducing agent is actually played by pyridine or its 3-substituted derivatives (II), the interaction of which with trichloromethylarenes leads to the corresponding 1-(α-chlorobenzyl)-4-chloropyridinium (III) or 1-(α-chlorobenzyl)-4,1′-bipyridinium (IV) salts, substituted in the benzene ring. The salts III and IV, when hydrolyzed, are readily converted to the aldehydes (V) and 4-chloropyridines (VI) or N-(4-pyridyl)pyridinium salts (VII), respectively. The conversions indicated above are represented by scheme 1 [5, 6]. Derivatives (oximes, azines, hydrazones) of the aromatic aldehydes V are formed when the latter or salts III and IV are reacted with hydroxylamine or hydrazines in a step that does not involve reduction or oxidation.

The first step on this scheme is the formation of an unstable monopyridinium salt (VIII), which can be further converted to a bispyridinium salt (IX). Both these steps can be considered as reversible. When the reaction of sterically unhindered trichloromethylarenes Ia-c with pyridine is conducted in inert solvents such as chloroform or methylene dichloride, the salts IX can be isolated with high yields (they precipitate when diethyl ether is added); in the case of o,o′-disubstituted compounds Id-f, however, the products are 1-(α-chlorobenzyl)-4,1′-bipyridinium salts IV, insoluble in chloroform and methylene chloride [6].

Salt IV may be formed either through the substituted 1-(α,α-dichlorobenzyl)-4-chloro-1,4-dihydropyridines (X) from 4-chloropyridinium salts III (pathway *a*) or in the interaction of the chlorodihydropyridine X with pyridines (pathway b) or in the reaction of the monopyridinium salt VIII with pyridines (pathway c); realization of the last two possibilities presupposes the formation of a dihydropyridylpyridinium intermediate (XI). All the compounds depicted on the scheme, with the exception of the intermediate XI, were isolated or identified in the reaction products [5, 6], in view of which pathway *a* seems more probable.

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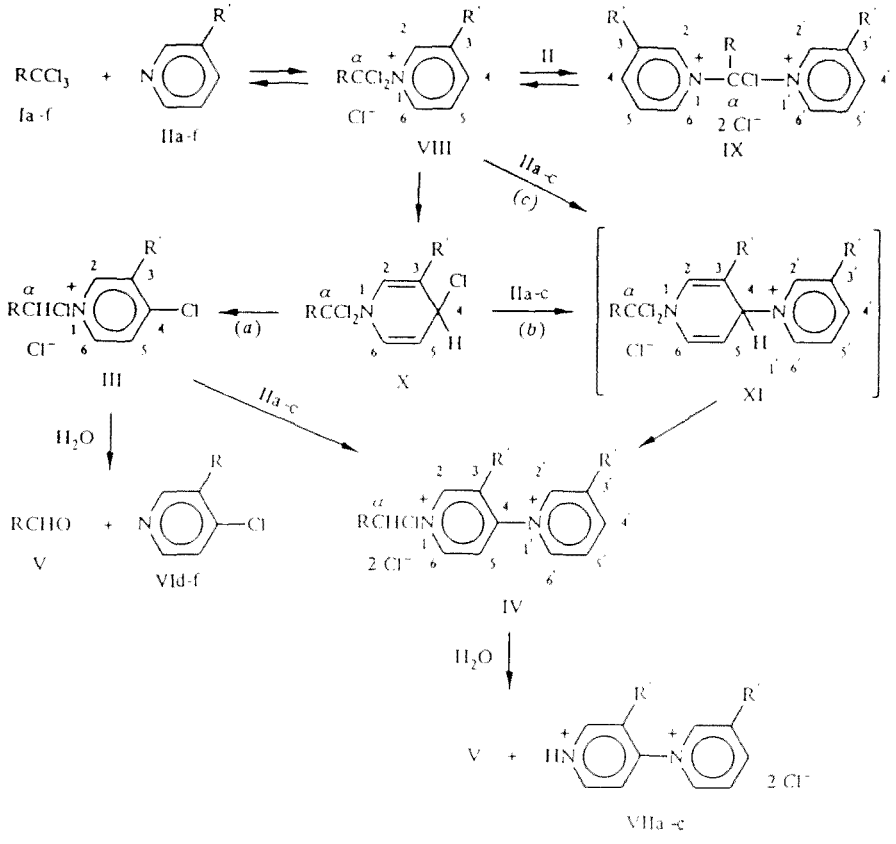
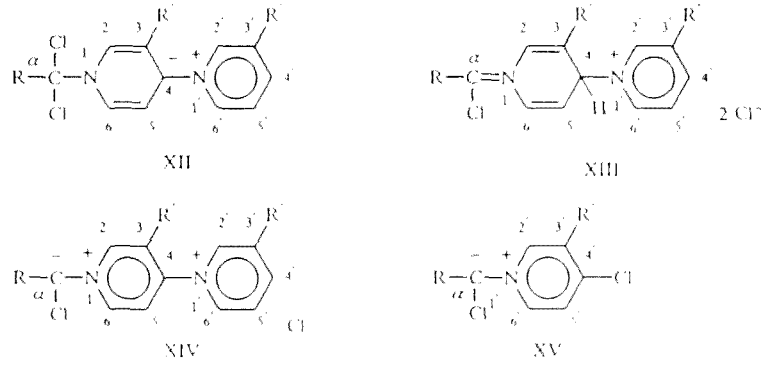
Scheme 1



I, III—V, VIII—XI a R′ = Ph, b R′ = 2,4-$Me_2C_6H_3$, c R′ = 2,4,5-$Me_3C_6H_2$, d R′ = 2,4,6-$Me_3C_6H_2$, e R′ = 2,3,4,6-Me_4C_6H, f R′ = 2,3,5,6-Me_4C_6H II—IV, VI—XI a R′ = H, b R′ = 3-Me, c R′ = 3-OH, d R′ = 3-$CONH_2$, e R′ = 3-COOEt, f R′ = 3-Br

In this work, for a quantum chemical investigation of the mechanism of individual steps of the reductive condensation process described in [5, 6], models of the basic end products (III, IV) and intermediate products (VIII-IX), shown in Scheme 1 (see Table 1), as well as models of some putative unstable intermediates (XII-XV) and the pyridine molecule (see Table 2), were calculated by the standard semiempirical MNDO method [7].



For simplification, the calculations were performed for R = Me and R′ = H. There is no doubt of the justification of the latter condition, since all the conversions under consideration have been most fully studied precisely using unsubstituted pyridine (II, R′ = H). To verify the permissibility of replacement of the aryl group by methyl in the models selected, two structures were calculated (III and XV, R = Ph), and it was shown that the distributions of electron densities in their pyridine rings are very close to those found for analyses with methyl groups.

TABLE 1. Results of Quantum Chemical Calculations by the MNDO Method of Models of the Major End Products (III, IV) and Intermediates (VIII-XI) of the Reductive Condensation of Trichloromethylarenes with Pyridine

Structure	III* (R = Me)	III* (R = Ph)	IV †	VIII*	IX †	X	XI*
Enthalpy of formation, ΔH_f, kcal/mole	179,7	211,2	453,6	187,7	511,4	6,6	220,4
Ionization potential, I_f, eV	15,3	12,8	17,8	15,2	18,0	9,3	12,6
Difference of orbital energies of LUMO and HOMO, $\Delta E_f \rightarrow \nu$	9,0	6,8	8,4	9,0	8,9	8,9	7,4
Charges on atoms, Q:							
α-C	0,19	0,28	0,18	0,24	0,31	0,33	0,30
α-H	0,08	0,08	0,10	—	—	—	—
α-Cl	-0,10	-0,11	-0,07	-0,07	-0,04	-0,19 (-0,17)	-0,13 (-0,14)
1-N	-0,18	-0,18	-0,15	-0,18	-0,23	-0,32	-0,32
2-C	0,16	0,16	0,17	0,16	0,16	0,12	0,17
6-C	0,15	0,14	0,18	0,15	0,12	0,10	0,16
3-C	-0,08	-0,08	-0,07	-0,09	-0,07	-0,16	-0,25
5-C	-0,08	-0,08	-0,07	-0,09	-0,08	-0,16	-0,25
4-C	0,13	0,12	0,14	0,12	0,14	0,20	0,25
1'-N	—	—	-0,16	—	-0,22	—	-0,16
2'-C	—	—	0,15	—	0,14	—	0,13
6'-C	—	—	0,15	—	0,15	—	0,13
3'-C	—	—	-0,08	—	-0,08	—	-0,09
5'-C	—	—	-0,08	—	-0,08	—	-0,09
4'-C	—	—	0,14	—	0,15	—	-0,08
2,3,5,6-H	-0,14	-0,14	-0,14	-0,13	-0,13	-0,10	-0,10
4-H	—	—	—	0,13	0,13	0,04	0,05
2',3',5',6'-H	—	—	-0,14	—	-0,13	—	-0,12
4'-H	—	—	0,14	—	0,13	—	0,12
4-Cl	0,04	0,03	—	—	—	-0,24	—
C_R	0,00	‡	-0,01	0,01	0,00	0,02	0,01
H_R	-0,04	-0,07	-0,05	-0,05	-0,05	-0,03	-0,05

*Cation.

†Dication.

‡Charges on atoms C_i: −20, C_o: 0.00 (−0.01), C_m: −0.06 (−0.06), C_p: 0.01.

The results of the calculation of the model of the pyridinium salt VIII show that its cation contains four positively charged sites — the carbon atoms in the dichloromethylene group (α-C) and in the 2-, 4-, and 6-positions of the pyridine ring. Precisely these sites may be subjected to the attack of nucleophiles — chloride anions or pyridine molecules.

Nucleophilic substitution of the labile α-Cl atom in analogs of salts of type III or VIII is a well-studied reaction, which proceeds rather readily in the absence of steric hindrances and, as it follows from the literature data [8-11], leads to the conversion of N-(α-haloalkyl)pyridinium salts to bispyridinium salts of the IX type. The formation of monopyridinium salts VIII and conversion of the latter to salts IX have been confirmed experimentally for trichloromethylarenes Ia-c [5, 6]; however, this pathway is hindered in the presence of substituents close to the reaction site, both in trichloromethylarenes (o,o'-disubstituted compounds Ig-f) and in pyridine derivatives (2-methyl-, 2,3-, and 2,6-dimethylpyridines, 8-methylquinoline) [6]. The attack of a chloride anion on the α-C atom of the salt VIII is considered as a stage of nucleophilic substitution of the pyridinium fragment according to the S_n2 reaction type, leading to the original trichloromethylarene I and pyridine II.

Nucleophilic attack on the ring of various pyridinium cations has been well studied and is directed to positions 2 (6) and 4 of the heterocycle; the formation of 2- and 6-substituted pyridines and dihydropyridines is usually considered as kinetically controlled, while that of 4-substituted dipyridines is regarded as a thermodynamically controlled process [12]. Considering this, as well as the presence of a voluminous α,α-dichlorobenzyl radical, capable of shielding the 2- and 6-positions of pyridinium, in salts of the type of VIII, nucleophilic attack on position 4 seems the most probable. Such an attack by pyridine should lead to salts of the type of XI, analogs of which were considered earlier as intermediates in the formation of

TABLE 2. Results of Quantum Chemical Calculations by the MNDO Method of Pyridine (II, R′ = H) and Models of Possible Unstable Intermediates (XII-XV) of the Reductive Condensation of Trimethylarenes with Pyridine

Structure	II (R′ = H)	XII	XIII*	XIV†	XV (R = Me)	XV (R = Ph)
Enthalpy of formation, ΔH_f, kcal/mole	28,7	92,1	475,8	245,1	48,2	78,6
Ionziation potential I_f, eV	9,7	6,7	17,4	10,9	7,7	7,6
Difference of orbital energies LUMO and HOMO, $\Delta E_{f \rightarrow \nu}$	9,7	5,9	8,1	5,7	6,9	6,9
Charges on atoms, Q:						
α-C	—	0,34	0,31	-0,01	-0,18	-0,11
α-Cl	—	-0,18 (-0,22)	0,10	-0,03	-0,09	-0,09
1-N	-0,23	-0,31	-0,15	0,05	0,09	0,09
2-C	0,05	0,04	0,05	-0,12	-0,11	-0,12
6-C	0,05	0,07	0,04	-0,11	-0,10	-0,11
3-C	-0,12	-0,05	-0,08	0,08	0,04	0,04
5-C	-0,12	-0,07	-0,08	0,07	0,04	0,04
4-C	-0,01	-0,14	0,18	-0,24	-0,10	-0,11
1′-N	—	0,08	-0,18	-0,05	—	—
2′-C	—	-0,11	0,12	0,14	—	—
6′-C	—	-0,11	0,15	0,14		
3′-C	—	0,01	-0,08	-0,10	—	—
5′-C	—	0,01	-0,08	-0,10		
4′-C	—	-0,15	0,13	0,08	—	—
2,6-H	0,08	-0,08	-0,14	-0,12	-0,10	-0,10
3,5-H	0,08	0,06	-0,14	-0,12	-0,10	-0,10
4-H	0,07	—	-0,14	-0,12	—	—
2′,6′-H	—	0,09	-0,14	-0,12	—	—
3′,5′-H	—	0,07	-0,14	-0,12	—	—
4′-H	—	0,07	-0,14	-0,12	—	—
4-Cl	—	—	—	—	-0,10	-0,10
4′-Cl	—	—	—	—	—	—
C_R	—	+0,02	-0,01	+0,07	+0,11	‡
H_R	—	-0,03	-0,08	-0,03	-0,11	-0,06

*Dication.

†Cation.

‡Charges on atoms C_i: −0.03; C_o: −0.02 (−0.02), C_m: −0.07 (-0.07), C_p: −0.04.

N-(4-pyridyl)pyridinium salts [13-16] (the ClSO residue instead of $RCCl_2$), as well as in reactions of hetarylation by N-acylpyridinium salts [17] (the RCO residue instead of $RCCl_2$).

The interaction of pyridinium salts with halide anions has been less studied than that with other nucleophiles; however, it obeys the general laws [12], so that the conversion VIII → X seems quite natural. We should mention here that the synthesis of pyridylpyridinium salts from 4-halopyridines is known [18], and replacement of halogen in 4-chloropyridinium salts III by pyridine with the formation of pyridylpyridinium salt IV should occur even more readily, just like the interaction of pyridine with "allyl" chloride X, leading to the pyridinium salt XI.

Table 3 presents MNDO estimates of the heats of individual steps of the reductive condensation process, pertaining to the gas phase or nonpolar solvents. Thus, the reaction VIII + Cl^- → X (1) should be strongly exothermic. On the contrary, the reaction VIII + Py → XI (2), analogous to what was suggested in the literature for describing the mechanism of synthesis of pyridylpyridinium salts [13-16], proves to be slightly endothermic. Of course, the estimated difference of the heats of reactions (1) and (2), even in nonpolar solvents, such as those used in [5, 6], methylene chloride and chloroform, is greatly exaggerated, since the formation of ion pairs was not considered in the calculations in any way: cations and anions contained in the salts depicted on the scheme were considered as isolated ions. It is especially important to keep the indicated peculiarity

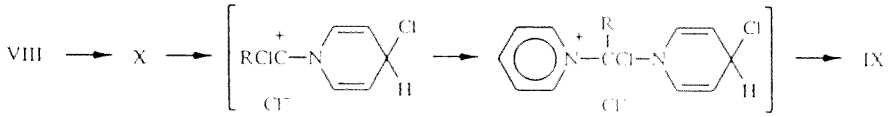
TABLE 3. Results of MNDO Estimates of the Heats of Certain Reactions in the Gas Phase (or a nonpolar solvent), Modeling Possible Stages of the Reductive Condensation of Trichloromethylarenes with Pyridine

Reaction			Heat, kcal/mole
VIII + Cl^-	→ X	(1)	−125
VIII + Py	→ XI	(2)	5
X	→ III + Cl^-	(3)	120
X + Py	→ XI + Cl^-	(4)	130
III + Py	→ IV + Cl^-	(5)	190
XI	→ IV + Cl^-	(6)	180
XI + Cl^-	→ XII + HCl	(7)	−90
XI	→ XIII + Cl^-	(8)	200
XII	→ XIV + Cl^-	(9)	100

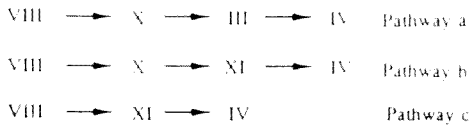
of the calculations in mind in considering the models IV, IX, and XIII, including dications with two counter ions, which leads to extremely high calculated enthalpies of their formation (Tables 1 and 2). And yet, the salts IV and IX, as already mentioned, are readily formed and are isolated with very high yields from nonpolar solvents, which in itself is evidence against the hypothesis that they are systems with isolated ions. We should mention in connection with this that compound X with a covalent bond $C_{(4)}-Cl$ may be considered as a maximally "close" ions pair, corresponding to the salt VIII.

Considering steric hindrances in the attack of pyridine on the α-C atom according to an S_N2 mechanism and the low probability of splitting off of a chloride anion from the cation of the salt VIII, we cannot rule out the possibility of conversion of the monopyridinium salt VIII to a bispyridinium salt IX according to an S_N1 mechanism through a neutral molecule X (Scheme 2). It is evident that in the X molecule the unshared pair of electrons of the nitrogen atom can substantially facilitate the splitting off of a chloride anion from the α-C atom and stabilizing the cation that arises, as indicated by the results of calculation of the similar model XIII.

Scheme 2



The data shown in Table 3 for reactions (1)-(6) permit a qualitative estimation of the probability of realization, at least in nonpolar solvents, of each of the three pathways mentioned above:



Naturally, the summary energy expenditures for each of these pathways, which possess identical starting materials and products, are the same (~ 185 kcal/mole). Nonetheless, the last of them (pathway c), while the shortest, should be considered

the least probable, since it includes only endothermic steps. Among the rest, pathway *a* seems more probable, since its first two steps are slightly exothermic (−5 kcal/mole), whereas for pathway b they are slightly endothermic (5 kcal/mole).

The most intriguing reactions presented on the scheme are the redox conversions X → III (3) and XI → IV (6). According to the data of Table 3, the first one possesses an advantage — lower endothermicity. The conversions under discussion are formally reduced to transfer of a hydride ion from the 4-position of the dihydropyridinium fragment (the latter is oxidized in the process) to a dichloromethyl group, which is reduced to chloromethylene, splitting out a chloride ion. However, as it follows from the experimental data of [6] and literature analyses, including those pertaining to very important biochemical reactions involving NADH (see the monograph [19]), the possibility of transfer of a hydrogen ion is extremely doubtful, and the aromatization of various N-substituted 1,4-dihydropyridines actually should include a step of displacement of two electrons and a proton; various sequences of the elementary events of one-electron transfer and displacement of a proton are possible. Such a mechanism is also realized in the case of electrochemical oxidation of 1,4-dihydropyridines [20]: first there is an electron transfer, accompanied by splitting out of a proton from the radical cation formed, and then a second electron is transferred, and an aromatic system arises.

Thus, the conversions X → III and XI → IV evidently include several steps, in which oxidation and reduction most likely occur within a single compound of the type of X or XI. Actually, the appearance of a radical cation, as indicated by the data shown in Table 1, in the case of nonpolar and weakly polar solvents should involve the overcoming of a significant ionization potential (9.3 and 12.6 eV), and therefore should be relatively improbable. Intramolecular displacement of electrons in the indicated compounds, however, can occur comparatively readily (compare the values of $\Delta E_f \rightarrow \nu$ in Tables 1 and 2, correlated with the energies of electronic excitations, taken as a measure of the reactivity in such cases [21]).

On the other hand, the transfer of a proton, judging by the data of [6], may occur intermolecularly, so that its stripping, promoted by some sort of structural transformation, is quite accessible as the first step of the reaction. Such a stripping of H^+ from a cation of the salt XI in nonpolar solvents or solvents of low polarity is evidently exothermic: According to the data of the MNDO method, the enthalpy of the gas-phase process XI + Cl^- → VII + HCl (7) is close to −90 kcal/mole.

The ylide structure of XII depicted on the scheme does not reflect the calculated distribution of electron densities in this intermediate. In particular, the high negative charge on the 1-N atom (Q = −0.32) is noteworthy. We should also emphasize that reaction (8) — the splitting out of a chloride anion from the CCl_2 group in the salt XI with the formation of the dication XIII — as an elementary event of the process, requiring a significantly greater energy consumption than in other cases, is relatively improbable. A similar stripping of a chloride anion from the zwitterion XII (9) is far more preferable energetically, and the dication XIV formed is readily converted to the salt IV by simple addition of a proton at the α-C atom. The analogous intermediate XV may be considered as a precursor of the salt III. It is important to note here that of all the model structures calculated, only XIV and XV have a negatively charged α-C atom, which should promote the addition of a proton at this site.

Thus, our calculations of models of the major end products and intermediate products, as well as some unstable intermediates, the possibility of appearance of which in the new redox system trichloromethylarene–pyridine base was suggested in this work, support the formation of N-substituted 4-chloro-1,2-dihydropyridines X as a stage in the detailed mechanism of the conversions considered (Scheme 1) in nonpolar solvents. Compounds X act as the most probable precursors both of 4-chloropyridinium salts III and 1-(4-pyridyl)pyridinium salts IV (Scheme 1, pathway *a*) and of the bispyridinium salts IX (Scheme 2). The results obtained are in good agreement with the available experimental data, in particular, with the isolation or detection of intermediates III, VIII, and IX [5, 6]. We should also mention that our calculations do not permit a conclusion to be drawn on preference for intramolecular or intermolecular transfer of electrons or a proton in compounds X and XI. Nonetheless, the results obtained are in satisfactory correlation with the experimental data cited earlier [6], which indicate an intermolecular transfer of a proton during the redox conversions X → III or XI → IV.

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