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Electric Hindrance and Dipole Moments in 2-Aminopyridine Nitration

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Abstract The different isomer yields observed in many aromatic electrophilic substitution reactions can be explained by steric hindrance. However, this is not the case when there are drastic differences in the reaction yields of the isomeric products obtained. This is generally due to the presence of other factors, for instance, electric rejection between two positive charges in the reaction stage. Thus, a very important point to bear in mind is electric hindrance, a new theoretical concept. We have taken as an example 2-aminopyridine nitration. We provide an extended theory on this subject, which is in accord with the observed regiochemistry and with the reaction yields of the isomeric products obtained. Dipole moments were also taken into account. We discuss too the 2-nitraminopyridine rearrangement in acidic medium. The theoretical discussion is also in accord with reported trans-nitration experimental results. Our proposals were contrasted too with the findings from thermolysis and photolysis experiments carried out with 2-nitraminopyridine.

Keywords Electric hindrance, Nitration, Reaction mechanisms, Reactive intermediates, Regioisomers

1. Introduction

Electric Hindrance is a new concept in Organic Chemistry. It has been introduced by us and recognized by the American Chemical Society [1]. In this communication, this theoretical concept has been used to explain the remarkable differences shown in the regioisomers yields obtained in 2-aminopyridine nitration. Other theoretical concepts were also employed. A causal relationship was found on this subject after a careful analysis of the electronic and electric effects present both in the substrate as well on the reaction intermediates in 2-aminopyridine nitration.

The rearrangement of 2-nitraminopyridine to amino-nitropyridines has also been studied. Our proposal on the rearrangement type is in accord with trans-nitration experiments carried out by other authors, as will be discussed later.

2. Theoretical Part

There are several reviews on aminopyridines [2-6]. An interesting reaction is 2-aminopyridine nitration due to the contrasts observed in its regiochemistry.

When Tchitchibabin nitrated 2-aminopyridine [7, 8], obtained as main product 2-amino-5-nitropyridine, 1, and 2-amino-3-nitropyridine, 2, as by-product (Figure 1). Since the Tchitchibabin papers are written in Russian and the published English and French abstracts are short, there are later communications, English [9] and American [10], on 2-aminopyridine nitration. These are detailed procedures based on the original experiments.

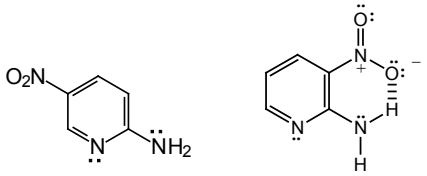

Figure 1. Dissimilar reaction products from 2-aminopyridine nitration

2-Amino-3-nitropyridine, 2, can be separated by steam distillation. As has been explained afterwards, this is due to intramolecular hydrogen bond formation between the ortho amino and nitro groups [11], forming a secondary six-member ring (Figure 1). This chelate hinders intermolecular hydrogen bond formation, as in the case of 2-amino-5-nitropyridine, which is not volatile. The obtained regioisomers are in a 9:1 relationship, by weight. The two amino-nitropyridines can be separated by sublimation [11, 12], besides the original separations by crystallization and by steam distillation.

Since there is no theoretical explanation of the 5-nitro-isomer preponderance, i.e., the remarkable disproportion of the reaction yields, we propose a theory in order to explain the especial regiochemistry found in this

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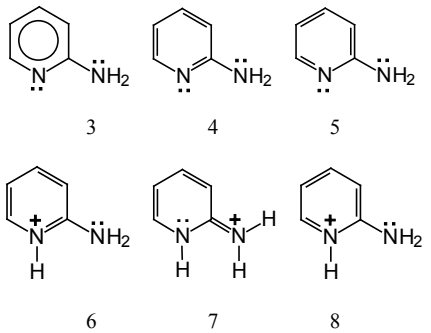
reaction.

The electron-ring formula of 2-aminopyridine molecule, 3, Figure 2, is inadequate since there is no equal reactivity at the C atoms, but regioselectivity. Using Kekule structures, 4 and 5, the first does not permit to explain the electrophilic substitution reactions, since in acidic medium, the protonated endocyclic nitrogen atom forms an iminium-enamine grouping, 6. This turns into structure 7, with no free electrons in the NH_2 group at C-2, and precluding the electronic contribution to the ortho and para positions. However, 2-aminopyridine presents a higher reactivity than pyridine [7]. Thus, structures 5 and 8 are favourable to explain 2-aminopyridine reactivity.

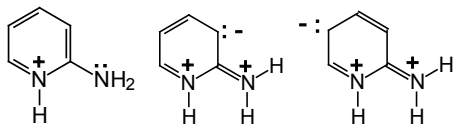


3 4 5 6 7 8

Figure 2. Non equivalent 2-aminopyridine representations due to its reactivity, plus derived cations

Protonation of the exocyclic nitrogen has not been taken into account because there is experimental evidence that the amino group at C-2 enhances nitration, thus ammonium salt formation must be reversible.

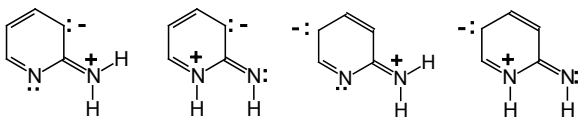
We consider now the resonance structures derived from 8 (Figure 3). In structure 9 there is a 1, 3-dipole arising from the amino group. Whereas in the semiquinone structure 10 there is a 1, 5-dipole. In both structures, 9 and 10, there is another 1, 3-dipole between the two positive charged nitrogen atoms. This electric repulsion can be eliminated by deprotonation.



8 9 10

Figure 3. High energy resonance structures of 2-aminopyridinium cation

Deprotonation of the pyridinium cations 9 and 10 leads to structures 11-14 (Figure 4).



11 12 13 14

Figure 4. Neutral dipole structures as reactive intermediates

Structures 12 and 14 show 1, 3-dipoles, thus they must have similar reactivities. On the other hand, isomers 11 and 13 show 1, 3- and 1, 5-dipoles, respectively. These would have very different reactivities. Structures 11 and 13 are derived directly from neutral 2-aminopyridine and indicate that the reactivity is directed by the kind of dipole formed from the amino group.

The nitronium ion reacts with the existing carbanions in 11 and 13. In the first case there is some steric hindrance due to the iminium group, but the major effect is the electric repulsion due to the nitrogen positive-charge at C-2 (electric hindrance). In the other hand, in structure13 there is no electric hindrance. Thus, 5-nitro-2-aminopyridine is the main product, and 3-nitro-2-aminopyridine results the by-product. Besides, in intermediate 11 the dipole moment is smaller than in 13. The latter is of higher content, more unstable, and by the same more reactive. Another consideration to be taken into account is that the C-5 carbanion (13), which is farther from the positive charge, is isolated (nude carbanion). Thus, this carbanion is more reactive than the C-3 carbanion (11). These considerations are in accord with experimental results [13, 14], pointing out that higher temperature favours the 5-nitro-2-aminopyridine yield, i.e., the formation of the higher-energy intermediate, 13, is enhanced.

Tchitchibabin also reported [13, 14] that when nitric acid was added to a chilled 10% solution of 2-aminopyridine in concentrated sulphuric acid, 2-nitraminopyridine, 15, was obtained (Figure 5).

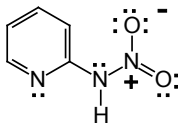


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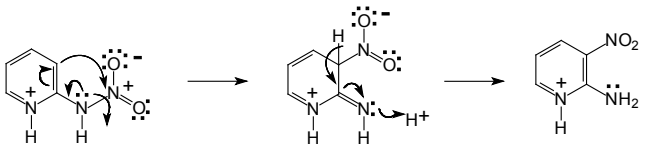
Figure 5. 2-Nitraminopyridine, kinetic product in 2-aminopyridine nitration

This amphoteric compound is soluble in mineral acids and in dilute alkaline solutions. In concentrated alkaline solutions, the alkaline nitramine salts are precipitated (nitronates). Sodium carbonate solution dissolves 2-nitraminopyridine with evolution of carbon dioxide.

The theoretical explanation of 2-nitraminopyridine formation is as follows: the low temperature, under 40°C, hinders the electronic contribution from the exocyclic nitrogen, in structure 5, to the aromatic ring. Thus, aromaticity is not disturbed and the nitronium ion reacts at the exocyclic nitrogen atom. Then 2-nitraminopyridine is formed after deprotonation. So, the kinetic product results, not the thermodynamic ones, as is the case when the temperature is above 40°C.

2-Nitraminopyridine, dissolved in sulphuric acid and heated to 50°C or higher, is transformed into 2-amino-3-nitro- and 2-amino-5-nitropyridine [2]. A 1, 3-shift of the nitro group has been suggested in order to form 2-amino-3-nitropyridine [6]. However, this is not possible

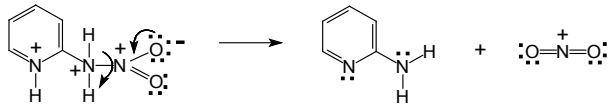
due to theoretical reasons and because it does not agree with experimental results. The proposed shift requires an electron donor effect from the amino group, as shown in Scheme 1.



Scheme 1. An erroneous reaction mechanism that has been proposed in order to explain the 2-nitraminopyridine rearrangement

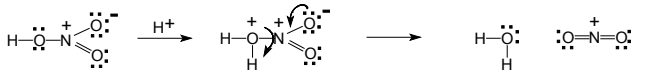
This proposal is very doubtful since this nitrogen atom is bonded to an electron withdrawing group, the nitro group. Thus, a reverse electron effect is expected. Moreover, a 1, 3-shift implies a concerted four-member reaction mechanism, but the preferred ones are the five- or the six-member cyclic mechanisms. Besides, 2-amino-3-nitropyridine would be the main product, or maybe the sole product, since there would be no reason for a nitro-group shift to C-5. However, the experimental results are the same as in direct nitration: the 2-amino-5-nitro-isomer is by far the main product (9:1).

A more feasible alternative than the above reaction mechanism, is protonation of the exocyclic nitrogen, due to the strong acidic medium (H_2SO_4) and higher temperature. The resultant intermediate is a high-energy one due to the existence of two contiguous positive charges. This electric repulsion induces the formation of a nitronium ion and a 2-aminopyridine molecule (Scheme 2).



Scheme 2. Fragmentation mechanism of 2-nitraminopyridine in acidic medium and higher temperature (40-50°C)

This way we have the same reactivity as in direct nitration at 40°C or higher temperature. This explains that the reaction yields are the same in both cases. The proposed dissociation is similar to the one in nitronium ion formation from nitric acid (Scheme 3).



Scheme 3. Molecular fragmentation due to contiguous positive charges, as proposed in Scheme 2

Our theoretical deductions on the type and course of this rearrangement are substantiated by the following experimental results.

Trans-nitration experiments (crossover experiments) [15, 16], with acetanilide as additional compound, are in accord with an intermolecular reaction mechanism. This remove doubts about the rearrangement character, doubts arising from experiments employing $Na^{15}NO_3$ [17]. Since the nitrate ion is not the reactive species, ^{15}N interchange is not the determinant because $^{15}NO_2^+$ must be produced in the reaction conditions, introducing an extra factor.

Experiments with different acid concentrations have been carried. The results indicate that the reaction yields diminish on dilution [18]. This is in accord with the first step of our reaction mechanism of 2-nitraminopyridine rearrangement: a strong acidic medium enhances NH protonation in the nitramino group, inducing acidolysis.

The 2-nitramino rearrangement also occurs by thermolysis and by photolysis. Since in both methods free radicals are involved, instead of ions, the results are indirect, but interesting. In the thermolysis, carried out in chlorobenzene at 132°C, the same regioisomers are obtained, but the reaction yields are inverted [19]. Now the main product is 3-nitro-2-aminopyridine (40%) and the secondary product is 5-nitro-2-aminopyridine (26%). The rearrangement also occurs in anisole and in m-xylene solutions, without crossover nitration. Thus, there is an intramolecular rearrangement, and the yields are the opposite of the observed in acidic medium, via the intermolecular rearrangement that we have proposed.

The irradiation of 2-nitraminopyridine in methanol with a mercury lamp yields both 2-amino-3-nitro- and 2-amino-5-nitropyridine [20]. The isomer ratio is 6.26:1, i.e., it is reversed in respect to that resulting from the acid-catalyzed rearrangement of the nitramine. This outcome also confirms our theory on the type and course of the 2-nitraminopyridine rearrangement in Tchitchibabin's experimental conditions.

3. Conclusions

In order to explain the experimental facts, i.e., the regiochemistry and the reaction yields in 2-aminopyridine nitration, a novel theory has been provided. Our study includes a discussion on the type and course of 2-nitraminopyridine rearrangement. We have deduced reasonable grounds for the studied chemical reactions. Our proposals are in complete agreement with all the available experimental results.

The outstanding points are:

1. Steric hindrance is not the determining factor in the regiochemistry of 2-aminopyridine nitration.
2. Electric hindrance, due to repulsion between two positive charges, is the directing factor in the above reaction.
3. 2-Nitraminopyridine is the kinetic product in 2-aminopyridine nitration.
4. The regioisomers resulting from ring nitration are the thermodynamic reaction-products.
5. 2-Nitraminopyridine rearrangement does not occur via a cyclic reaction mechanism, in a chain sequence, as has been suggested previously.
6. The above mentioned rearrangement proceeds via protonation, dissociation and ring-nitration, i.e., it is an intermolecular pathway.

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