Articles

On the Alternation Effect in Substituted Indolizines and Their Aza-analogs

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The SINDO1 method is used to calculate charge distribution and total energies in the series of isomeric nitro- and methoxy-substituted indolizines, azaindolizines, and *N*-methylazaindolizinium cations. The influence of donor and acceptor substituents on the total energy and charges may be treated according to the simple alternation rule. In the series of isomers (substituted or azaindolizines) the lower energies are observed for those molecules, where acceptor substituents are arranged consonant to the polarity of the chain $N-C_5-C_6-C_7-C_8-C_9-C_1-C_2-C_3$ of the indolizine. The results are used to treat known peculiarities of ring opening/transformation of indolizine and its aza-derivatives. It is proved that the energies of C_3 and C_5 adducts of isomeric azaindolizines with hydroxyl anion follow the same alternation pattern.

1. Introduction

The chemistry of indolizines is well reviewed.[1] For many years indolizine has been considered as the typical π-excessive heterocycle that can easily undergo electrophilic substitution at positions 3 and/or 1. Indolizine can also be isomerized to indole; this ANRORC-type reaction however occurs only for indolizines with strong electron withdrawing groups, namely 6- and 8-nitroindolizines,[2−5] (Scheme 1). The unique ability of 6(8)-indolizines to react with nucleophiles has still attracted very little attention. There are only few works devoted to the influence of substituents on the reactivity of indolizines performed by Hückel,[6] PPP,[7] and semiempirical CNDO[3] and MNDO[8] methods.

The indolizine nucleus may serve as the prototype molecule for the large class of azoloazines with a bridgehead nitrogen atom, in particular, azaindolizines. A specific feature of this class (see reviews[9,10]) is the ability of easy ring cleavage (either azole or azine) and variety of ring transformations and recyclizations. As in the case of indolizine, the general analysis of substituents influence on the reactivity of azaindolizines is poorly developed, although some calculations of their electronic structure have been performed.[11−13]

The general trends of the ring opening reactions of bridgehead azoloazines and the observed influence of substituents on the selectivity of these reactions have been very recently reviewed.[14] As it was proved, the major number of azaindolizine derivatives undergo ring opening with the cleavage of either C_5-N bond of the azine fragment or C_3-N bond of the azole ring, and some selected examples are shown on Scheme 1. The numbering we use here and below corresponds to the conventional numbering of atoms in the prototype indolizine ring.

The question arises whether it is possible to estimate qualitatively the influence of polar substituents on the general reactivity of the entire class of (aza)indolizines and particularly on the direction of their ring opening reactions.

The goal of this communication is to present quantum chemical calculations for the series of substituted indolizines and their aza-analogs in order to provide simple qualitative rules that connect the influence of polar groups in (aza)indolizines with their charge distribution, relative stability of isomers, and selectivity of ring opening.

2. Objects and Methods of Investigation

To understand the influence of polar substituents on the electronic structure of indolizine ring we performed

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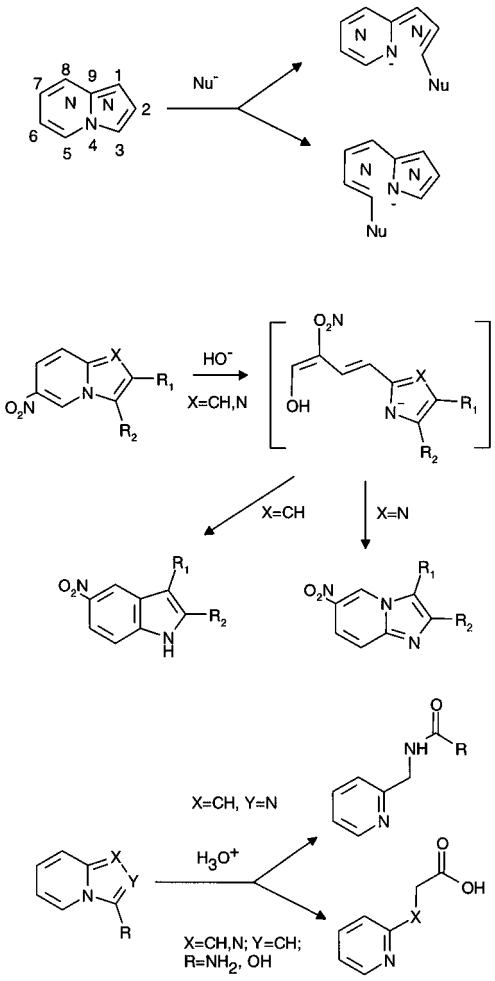
Scheme 1. General Scheme and Selected Examples of C_5-N and C_3-N Bond Cleavage in substituted (Aza)indolizines (nitrogen atom in the ring symbolized aza-substitution of one and/or another ring)



quantum chemical SINDO1 calculations[15] of the indolizine molecule and 28 substituted analogs: isomeric series of nitroindolizines, methoxyindolizines, monoazaindolizines, and isomeric *N*-methyl cations of monoazaindolizines. The SINDO1 method has been frequently used for studies of heteroaromatic rings containing nitrogen[16−18] with success. The bicyclic framework of indolizine and its aza-analogs was considered to be planar; the nitro group was also postulated to lie within the plane of heterocycle. All other parameters were fully optimized in SINDO1. The calculated distribution of charges is presented in the Tables 1−4 and the resulted total energies are in the Table 5.

With the goal to clarify the selectivity of ring opening (azole versus azine fragment) in the family of azaindolizines, two types of isomeric adducts with hydroxyl anion were considered: the 5-OH and the 3-OH anionic adducts. The full energies of these adducts for all seven isomeric azaindolizines are presented in the Table 6.

3. Results and Discussion

The Direct and Reversed Alternation Chains in the Indolizine Nucleus. According to X-ray data,[19] the geometry of indolizine ring can be approximated by a tetraene fragment with three carbon atoms being attached to the same (bridgehead) nitrogen atom. Hence, one can separate in the indolizine bicycle three types of chains A, B, and C (as shown on the Scheme 2). These chains are obtained by formal removal of two (from three) CN-bonds. One may assume that the nitrogen atom adjacent to the carbon tetraene fragment induces an alternation of the donor (d) and acceptor (a) centers along the chain. The notation used on the Scheme 2 is the same as previously discussed by Seebach in his reactivity umpolung model.[20]

The arrangement of donor and acceptor atoms in the chains A and C match each other, and this clockwise alternation will be called *the direct alternation chain*. The arrangement of polarities in the chain B is opposite to the cases A and C, and this counter-clockwise alternation will be called *the reversed alternation chain*. Of course, these artificial patterns are a rather crude approximation of the interaction of the bridgehead atom with the carbon framework. They serve, however, as useful models for the understanding of the qualitative picture of substituent influence on the indolizines charge distribution.

One may assume that any polar substituent attached to the indolizine bicycle (heteroatom or exo-group) according to its own polarity should intensify one or another alternation chain. Thus, the direct alternation chain is intensified by heteroatoms and exo-acceptor groups in positions 6, 8, 1, 3 and exo-donor groups in positions 5, 7, 2. In contrast, the reverse alternation chain is picked out by heteroatoms and exo-acceptor groups in positions 5, 7, 2 and exo-donor groups in positions 6, 8, 1, 3.

Influence of Substituents on the Charge Distribution: The Alternation Effect. The actual SINDO1 charges for the indolizine are shown in Scheme 2. It is obvious that due to its higher electronegativity the nitrogen atom induces positive charges on all three adjacent atoms C_5, C_9, and C_3. The positive sign of charge on the atom C_5 is in the good agreement with the experimentally observed π-deficiency of this center (cf. high C−H acidity of methyl groups in 5-methylindolizines displayed in their reactions with carbonyl compounds[21] or nucleophilic addition reactions at position 5 observed for 6(8)-nitroindolizines[2,3]). However, the observed positive charge on the atom C_3 is in dramatic conflict with known chemical behavior of indolizines: most known electrophilic addition and substitution reactions occur just at the position 3 of the indolizine ring.[1] The problem of correspondence between the charge on C_3 and its experimentally observed π-excessive character has a very long history starting from simple Hückel calculations[22,23] and continuing with the development of semiempirical[24] and ab initio[25] methods, and the discussion is frequently revisited.

However, the complicated picture of charge distribution in indolizine may be also qualitatively described in terms

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Table 1. Charge Distributions (10^{-4}) of N-Substituted Indolizines

subst/atom	N (4)	5	6	7	8	9	1	2	3
5-N	−0524	−0501	+1514	−0256	+0315	+0915	−0620	−0245	+0751
6-N	−1895	+3578	−2458	+1863	−1094	+1774	−0952	−0063	+0962
7-N	−1093	+1011	+0652	−1488	+1678	+0641	−0417	−0343	+1039
8-N	−1728	+2334	−1592	+2502	−2130	+2491	−1305	+0044	+0814
1-N	−1634	+1971	−0935	+0966	−0948	+2891	−2399	+1039	+0269
2-N	−1793	+1838	−0665	+0568	−0138	+0913	+0383	−1956	+2701
3-N	−0711	+1671	−0787	+0819	−0567	+1738	−1687	+1746	−1116

Table 2. Charge Distributions (10^{-4}) of NMe^+-Substituted Indolizines

subst/atom	N (4)	5	6	7	8	9	1	2	3
5-NMe^+	−0572	+0164	+2529	−0564	+1121	+1030	+0210	−0046	+1287
6-NMe^+	−1818	+4418	−1778	+1914	−0457	+1814	−0149	+0299	+1337
7-NMe^+	−0849	+1408	+0964	−0935	+2695	+0058	+0902	−0436	+2007
8-NMe^+	−1545	+3334	−1893	+3374	−1518	+2702	−0813	+0414	+1193
1-NMe^+	−1099	+2201	−0478	+1567	−0910	+3309	−1428	+1257	+0819
2-NMe^+	−1333	+1668	+0033	+0828	+0027	+1452	+0652	−1106	+3362
3-NMe^+	−0441	+1962	−0340	+1391	−0488	+2342	−0759	+1687	−0084

Table 3. Charge distributions (10^{-4}) of NO_2-substituted indolizines.

subst/atom	N (4)	5	6	7	8	9	1	2	3
5-NO_2	−1335	+1263	−01315	+0469	−0112	+1345	−0629	−0216	+1026
6-NO_2	−1404	+2068	−1009	+0669	−0326	+1534	−0739	−0085	+0981
7-NO_2	−1329	+1843	−0680	+0319	−0103	+1357	−0614	−0194	+1035
8-NO_2	−1384	+2126	−0842	+0893	−0639	+1460	−0696	−0121	+0971
1-NO_2	−1260	+1816	−0655	+0793	−0437	+1774	−1204	+0013	+0874
2-NO_2	−1300	+1732	−0553	+0626	−0257	+1453	−0676	−0483	+1206
3-NO_2	−1177	+1735	−0608	+0733	−0423	+1710	−1002	+0365	+0211

Table 4. Charge Distributions (10^{-4}) of MeO-Substituted Indolizines

subst/atom	N (4)	5	6	7	8	9	1	2	3
5-MeO	−1960	+4165	−2155	+1155	−0884	+1710	−0918	−0147	+1006
6-MeO	−1051	+0436	+1858	−0372	+0161	+1090	−0653	−0281	+0917
7-MeO	−1605	+2205	−1564	+3155	−1904	+1949	−1109	−0020	+0819
8-MeO	−1125	+1239	−0146	−0755	+2217	+0506	−0436	−0366	+1026
1-MeO	−1357	+1671	−0543	+0344	+0097	+0142	+1820	−1177	+1398
2-MeO	−1233	+1870	−0831	+0772	−0549	+1847	−1910	+2371	−0367
3-MeO	−1943	+1870	−0719	+0551	−0219	+1148	−0342	−1518	+3368

Table 5. Total Energy *E* (Hartree[a]) of Some Substituted Indolizines

place of substitution	*E* of N-substituted indolizines	*E* of NMe^+-substituted indolizines	*E* of NO_2-substituted indolizines	*E* of MeO-substituted indolizines
5	−64.012	−71.307	−101.801	−83.071
6	−64.003	−71.315	−101.804	−83.051
7	−63.990	−71.297	−101.803	−83.061
8	−64.002	−71.310	−101.803	−83.051
1	−64.011	−71.349	−101.813	−83.053
2	−64.004	−71.334	−101.810	−83.058
3	−64.025	−71.360	−101.812	−83.069

Table 6. Comparison of Energies *E* (Hartree[a]) and Heats of Formation (kcal/mol) of the 5-OH and the 3-OH σ-Complexes for Isomeric Azaindolizines

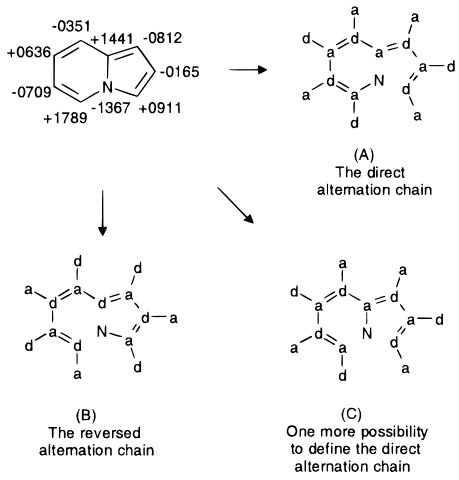
Place of aza-substituent	*E* of 5-OH σ-complex	heat of formation of 5-OH σ-complex	*E* of 3-OH σ-complex	heat of formation of 3-OH σ-complex	difference in heats of formation between 5-OH and 3-OH σ−complexes
indolizine	−76.851	−69.4	−76.845	−66.0	−3.4
5-N	−80.819	−46.2	−80.8546	−68.8	+22.56
6-N	−80.874	−86.8	−80.848	−70.4	−16.4
7-N	−80.827	−64.8	−80.839	−72.6	+7.8
8-N	−80.857	−76.3	−80.851	−72.5	−3.8
1-N	−80.861	−73.5	−80.850	−66.3	−7.2
2-N	−80.843	−66.6	−80.862	−78.4	+11.8
3-N	−80.866	−67.2	−80.813	−33.8	−33.4

[a] 1 Hartree = 627.5 kcal/mol.

of direct and reverse alternation chains. Thus, the charge distribution in the fragment $N-C_5-C_6-C_7-C_8-C_9-C_1$ corresponds to the direct alternation chain, whereas the distribution along the fragment $N-C_2-C_3$ corresponds to the reversed alternation chain. The electronic structure of indolizine may, therefore, be approximated as superposition of these two chains, from which one is the α-picolyl-like fragment and another is the enamine.

Comparison of charges in each structure of a substituted (aza)indolizine with charges in the parent indolizine displays remarkable peculiarity of charge distribution. Consider the case of isomeric azaindolizines (Table

Scheme 2. SINDO1 Charges (10^{-4}) in the Indolizine, and Approximation of Its Polar Structure by Open-Chain Fragments



1, Figures 1a,b). As it is evident from the figures, an introduction of an aza-substituent causes pronounced decrease of charge in the odd positions to the inserted nitrogen atom along the carbon framework. On the contrary, the increase of charges is observed in the even positions to the aza-group.

According to this trend the family of seven isomeric azaindolizines falls into two groups. The first group corresponds to 1-, 3-, 6-, and 8-azaindolizines (see Figure 1a). The local changes of the charges within this family (compared to the parent indolizine) match the same pattern: the charge is decreased at positions 5, 7, 9, and 2 and is increased at positions 1, 3, 6, and 8. Another family is the 2-, 5-, and 7-azaindolizines (Figure 1b), where the changes of charges are reversed to the previous case.

Qualitatively the same picture is observed in the series of seven isomeric nitroindolizines and seven *N*-methylazaindolizinium cations. In all cases (aza-, nitro-, and NMe^+-substitution) the substituted (aza)indolizines may be separated into two classes according to the location of substituent in either 1, 3, 6, and 8 position or, respectively, 2, 5, and 7.

In contrast to the discussed influence of the electron-withdrawing groups, the insertion of the electron-donating methoxy group causes the expected opposite effect on the changes of charge distribution. Indeed, the observed trend in the family of isomeric methoxyindolizines is fully reversed: the increase of charges is observed in the odd positions to MeO-group, whereas the charge is decreased in the even positions. As one might expect, a substituent in all cases exerts the strongest influence on the most closed atoms of the chain, whereas in the cases of terminal atoms of the chain (e.g. for atom 3 in the 5-azaindolizine and for atom 5 in the 3-substituted ones) the difference in charges is negligibly small.

One may conclude that the result of pronounced oscillation in charge differences may be treated in terms of a very simple alternation rule, namely, the effect is the same as if a donor/acceptor group would be attached to a polyenic chain. However, the actual chains that we can separate in the indolizine belong either to the direct or to the reverse alternation pattern. Therefore, one can conclude, that insertion of any polar group (depending on the polar nature of the group) should intensify either one or another polarity pattern. Thus, two types of charge changes observed in Figure 1, parts a and b, correspond just to the increase of either direct or reverse alternation chains. From this viewpoint it is easy to treat qualitatively the actual charges in the substituted (aza)-indolizines. Indeed, sometimes (as e.g. in the case of azaindolizinium cations) the strengthening of the direct polarity pattern reinforces globally the initial charge distribution of indolizines and causes appearance of a positive charge at position 2. (The charge on the atom C_3 remains, however, positive in most cases.) More frequently the strengthening of one or another alternation chain results only in local (1−2 neighboring atoms) charge alternation.

The Alternation Effect and the Energy of Isomers. One peculiarity of systems with charge alternation is their higher thermodynamic stability than for isomers without alternation. This feature, first mentioned by Benson for small molecules[26] was later proved for delocalized carbanions and heterosubstituted organic structures;[27] many references are collected in the book[28] and review.[29] It was, however, unclear how to apply this rule for comparison of isomeric systems without any alternation.

According to Gimarc[30] heteroatomic molecules are stabilized when more electronegative atoms are placed in those positions where the atoms of the reference hydrocarbon frame have the highest electron charge. This principle, known as the topological charge stabilization principle, has been widely applied to the analysis of energies of isomers for quite different prototype systems, in particular, to nonalternant delocalized hydrocarbons, adamantane-like structures, and boron hydrides.[31−33] The charges have been calculated by different methods (particularly, by the extended Hückel method and ab initio[32]), and the general validity of the principle was proved.

There were a few reasons to apply this principle to the discussed series of substituted indolizines. First, it is worth analyzing the validity of the principle for the initial reference structure indolizine, which is not a hydrocarbon. Second, the effect of substitution by an exo-group (like a nitro- or methoxy-group) seems to be out of the scope of the principle. Finally, the clear energy trends among the isomers (if they exist) would better clarify the picture of real charge distribution in the indolizine.

Comparison of the charges (Tables 1−4) and the energies of isomers (Table 5) gives a qualitatively consistent picture. The acceptor groups arranged consonantly to the direct alternation chain cause a more significant decrease in energy than the same groups that are consonant to the reverse alternation chain. In particular, indolizines with acceptors (aza-, NMe^+-, or nitro-group) at positions 6 and 8 (with negative charge at the parent indolizine) have significantly lower energy than their 5- and 7-isomers (with initially positive charges in the parent indolizine). The most remarkable fact is that both 1- and 3-substituted structures have the lowest energies within each series. The opposite picture is observed for methoxyindolizines: here the lowest

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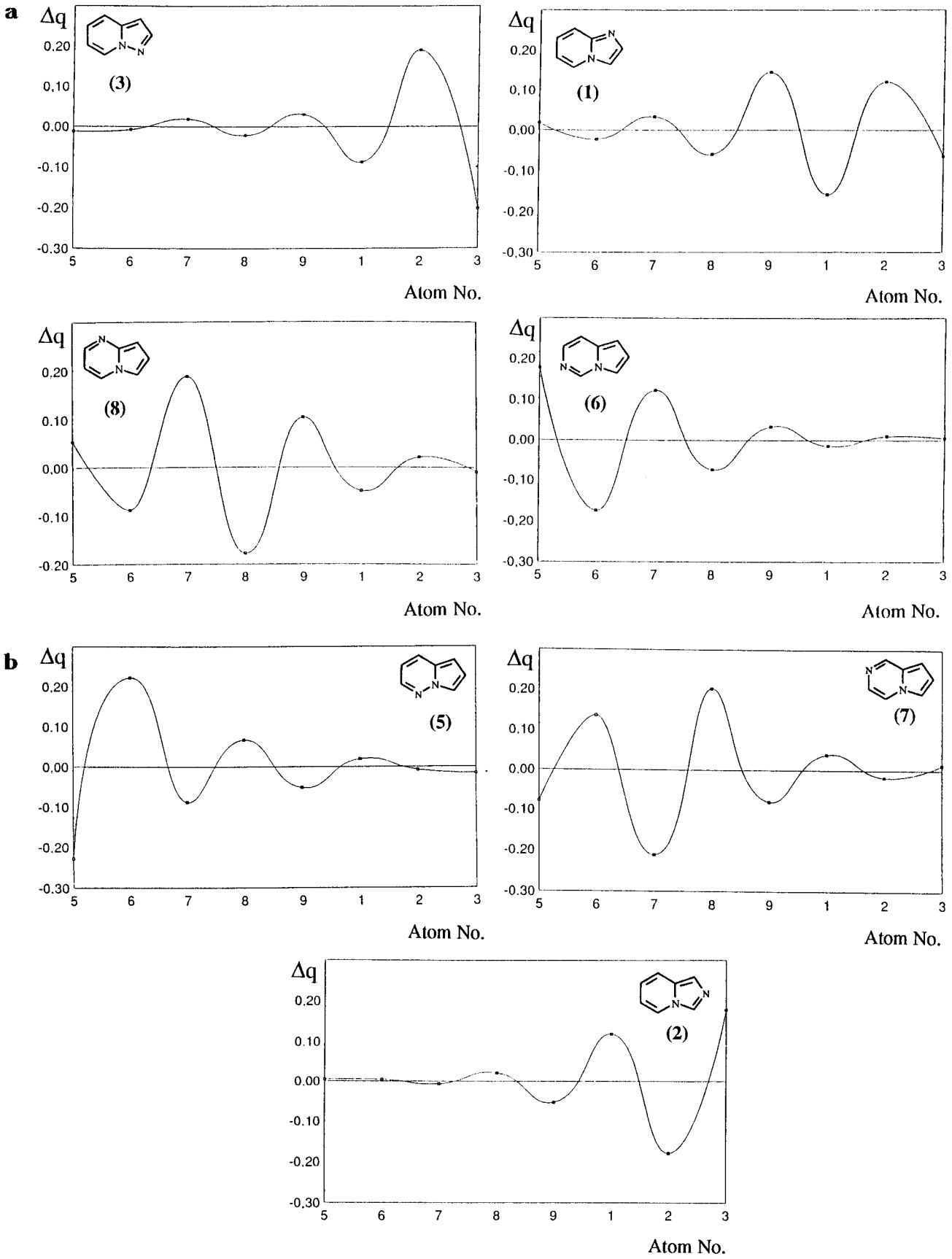
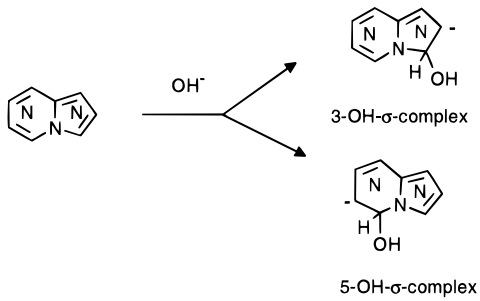


Figure 1. Charge shift (Δq) in 1-, 3-, 6-, and 8-azaindolizines compared to parent indolizine in dependence of the atom no. in the skeleton. (Numbers in brackets correspond to the position of aza-group.) (b) Charge shift (Δq) in 2-, 5-, and 7-azaindolizines compared to parent indolizine in dependence of the atom no. in the skeleton. (Numbers in brackets correspond to the position of aza-group.)

Scheme 3. Intermediate Formation of Anionic σ-Complexes as the First Step of Ring Cleavage



energy is observed for 5- and 7-methoxy derivatives (with direct alternation chain), while the highest is for 6- and 8-isomers. Although there are a few exceptions from this trend, the result may be treated in such a manner that the direct alternation chain is the best approximation of the charge distribution in the parent indolizine nucleus.

Analysis of Selectivity of the Ring-Opening in Azaindolizines. The initial step of the ring-opening reactions of (aza)indolizines (see Scheme 1) requires a nucleophilic attack on either the C_3 or the C_5 atom,forming an anionic σ-complex. An example of this reaction for a typical nucleophile (hydroxyl-anion) is presented in Scheme 3.

The above discussed qualitative trends of the substituent influence on the charge distribution in the (aza)indolizine may serve for explaining the experimentally observed trends. According to ref 14, p 1275, the reviewed trends are as follows:

(i) The C_5-N bond cleavage is promoted by the donating nature (aza substitution, the presence of an external acceptor) of positions 6, 8, 1, and 3 in the bicycle and by the accepting nature (the presence of external donating and oxo substituents at positions 5, 7, and 2). The chain atoms closest to the opening assembly (primarily 5 and 6 and then 7 and 8 and so forth) have the greatest effect. Quaternization at positions 1 and 3 also promotes this bond cleavage.

(ii) Cleavage of the C_3-N bond is observed more rarely. It occurs in the structures with donating groups at positions 2, 5, and 7 and the accepting nature of atoms 3, 1, 8, and 6. As in the previous case the polarity of the centers closest to the opening assembly (i.e. of atoms in the five-membered ring) is most significant.

One may conclude that the observed trends can be quite clearly explained in the terms of direct and reversed alternation chains proposed above. Namely, the substituents that emphasize the direct alternation chain promote C_5-N bond cleavage, whereas the substituents that increase the reverse alternation chain assist C_3-N bond cleavage.

The final confirmation of this simple rule follows from the analysis of the energies for 3-OH and 5-OH anionic σ-complexes calculated by SINDO1 for seven isomeric azaindolizines (see Table 6). The lowest energy among isomeric 5-OH-adducts is observed for 6-azaindolizine, whereas the most favorable 3-OH-adduct is formed by 2-aza- and 5-azaindolizines. (As one might have expected, the highest energy of adducts and lowest heat of reaction in all cases correspond to the addition of the OH-group to the nitrogen atom.) The highest heat of reaction is in the cases of 5-OH-6-aza- and 3-OH-7-aza adducts. The data shown in Table 6 for other isomers display the same principle: the azaindolizines with a nitrogen atom at positions 6, 8, 3, 1 (increase of direct alternation chain) prefer to form the 5-OH-adducts, whereas those aza-substituted at positions 2, 5, 7 (increase of reverse alternation chain) favor to form the 3-OH-adducts.

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