

## Reduction and Radical Addition: A Theoretical Study on Chlorobenzonitriles

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The three isomers of chlorobenzonitrile (CBN) and the corresponding radical anions are investigated by semiempirical methods in order to study the regioselectivity of solvated hydrogen and hydroxy radical attacks. Additional negative charge is distributed upon reduction at the chlorine and cyano subunits and in *para*-position to the cyano group. Most of the negative charge (about 70%) is located in the aromatic ring. The different protonation sites for the negatively charged radical and neutral species are explained by distinctly different electro-negativities. The observed position of a hydroxy radical attack on 2-chlorobenzonitrile is correlated to the relative stabilities of the six possible addition products. The electron density contribution of 2-CBN as calculated by the Mulliken population analysis method is in excellent agreement with the experimentally observed formation of different products: The 2-chloro-5-hydroxybenzonitrile is the preferentially created species, with both the 4- and 6-hydroxy isomers as important sideproducts.

*Key words:* chlorobenzonitriles, radical addition, reduction, semiempirical study

### INTRODUCTION

The reaction of haloarenes with solvated electrons has been subject to intensive experimental studies. A reduction reaction is followed by an intra-

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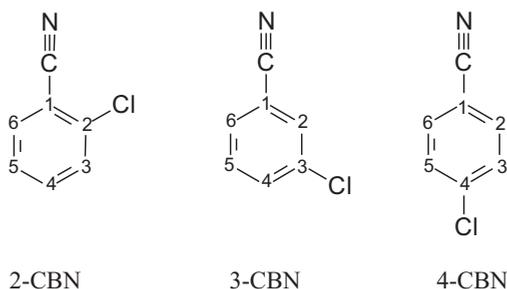


Figure 1. Molecular structures and enumeration of 2-chlorobenzonitrile (2-CBN), 3-chlorobenzonitrile (3-CBN), and 4-chlorobenzonitrile (4-CBN).

molecular electron transfer leading to dehalogenated products.<sup>1-3</sup> The reduction of chlorobenzonitriles (see Figure 1) is an intensively studied reaction,<sup>4-6</sup> as the presence of an additional electron withdrawing group stabilizes the radical anion intermediate. The introduction of a negative charge completely changes the electronic properties of the molecule, thus resulting in different sites of radical attack. Both the protonation of a solvated hydrogen atom and the attack of a solvated hydroxy group is of major interest. In the neutral species, addition of the hydrated proton takes place at the aromatic ring carbon atoms,<sup>5</sup> whereas the negatively charged chlorobenzonitrile radical is selectively protonated at the nitrogen of the cyano group.<sup>6</sup> According to the estimated electron density of the radical anion, the solvated H radical should attack both at the 2- and 4- positions, which cannot be observed in experiment. No satisfactory explanation could be given for this result.<sup>6</sup> In this semiempirical study we present an investigation of the electron density for both the 2-, 3-, and 4-chlorobenzonitriles (2-CBN, 3-CBN, and 4-CBN, see Figure 1) and their radical anions. These investigations yield an insight into regioselectivity of the protonation of chlorobenzonitriles radical anions.

The addition of a hydroxy group represents the second radical reaction investigated. After an attack of hydroxy radicals<sup>5,6</sup> to chlorobenzonitrile, various isomers of chloro-hydroxy-benzonitriles can be formed. This reaction of OH radicals is of special interest due to the regioselectivity of the possible products. The question whether the chloro or cyano unit determines the position of the hydroxy attack remains still unsettled. Mesomeric effects of both the chloro and cyano group favor the OH to attack in *ortho* and *para* position to the chloro atom, and *meta* position relative to the cyano group. Experimentally, the following order is found for preferred sites of OH radical attacks on 2-CBN:  $5 > 3 > 4 \gg 6$ .<sup>5</sup> The attack of OH is thus highly regioselective. The presented theoretical investigation of the stability of vari-

ous OH radical adducts on the chlorobenzonitriles gives a closer insight in the regioselectivity of the OH attack presented at the example of 2-CBN.

## COMPUTATIONAL METHODS

The ground state geometries of all compounds (neutral and radical) are optimized using the AM1 (Ref. 7) Hamiltonian with an unrestricted Hartree-Fock (UHF) method, as implemented in the VAMP program package, version 6.1.<sup>8</sup> For the optimization, Baker's eigenvector following algorithm was used as described in Ref. 9. The radical anions are defined within the unrestricted formalism by a negative charge equivalent of one electron. The addition of a hydroxy radical to the closed shell molecule results in an uncharged radical with 26 alpha and 25 beta electrons, which is also treated with an UHF approach. The charge distributions are calculated by multipole analysis of the distribution of electronic charge density for the given system derived from point charges. The charge densities result as a sum of molecular orbital densities, each the square of the orbital wavefunction, with the charges of the hydrogen atoms summed up into the heavy atoms. The Mulliken population analysis as used throughout the work assigns all charge to the nuclei. We point out, that the absolute values are less meaningful than differences between similar molecules. The main emphasis is put on the comparison of charge distribution between the similar CBN isomers, indicating trends in charge distributions.<sup>10</sup> The Mulliken population analysis is also applied to obtain the relative ratio for the location of the negative charge. The point charges for all six aromatic carbon and attached hydrogen atoms are summarized and compared to the net point charges for both the chlorine and cyano subunits.

## RESULTS AND DISCUSSION

The calculated partial charges are compared for possible addition sites of both the neutral and the radical anion systems (see Figure 2).

In the neutral forms of 2-, 3-, and 4-CBN (see Figure 2, left), the highest electron densities of approximately  $-0.13$  electrons is found both at the cyano group and the unsubstituted 3-position. The benzene carbon atom next to the cyano group bears no negative charge independent from the position of the chlorine atom. The negative charge of the cyano group is mainly located at the carbon atom. The negative charge at the chlorine is neglectable, the electron density of the carbon atom directly connected to it is significantly reduced. A different situation is found for the three corresponding radical anions in contrast to the neutral isomers (see Figure 2, right). The

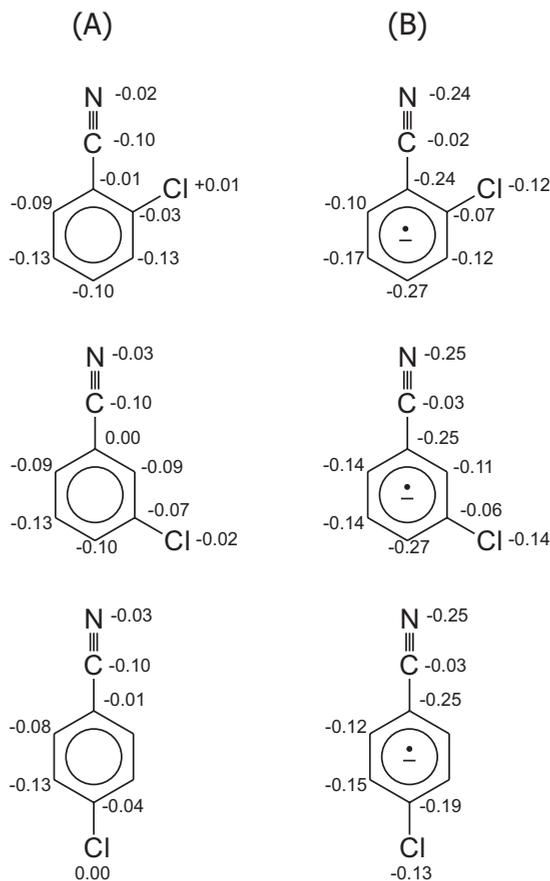


Figure 2. Negative charge distribution in 2-CBN (top), 3-CBN (middle), and 4-CBN (bottom) for the neutral state (A) and the corresponding radical anions (B).

negative charge at the cyano group ( $-0.27$ ) has a much larger value compared to that of the neutral compounds, and the main part of the negative charge is located on the nitrogen atom. The negative charge of the chlorine atom is increased to *ca.*  $-0.13$ , and a negative charge of  $-0.27$  is found at the 4-position for both 2- and 3-CBN.

The contribution of the negative charge between the aromatic, cyano, and chloro moiety of the molecule is presented in Figure 3. The major part of the negative charge is located at the benzene moiety with minor contributions divided equally between the cyano and the chloro group (14% and 19%). In all cases, a slightly larger negative charge is found at the cyano group, indicating its stronger electron withdrawing property. A detailed investigation of the charge distribution within the aromatic subunit shows a

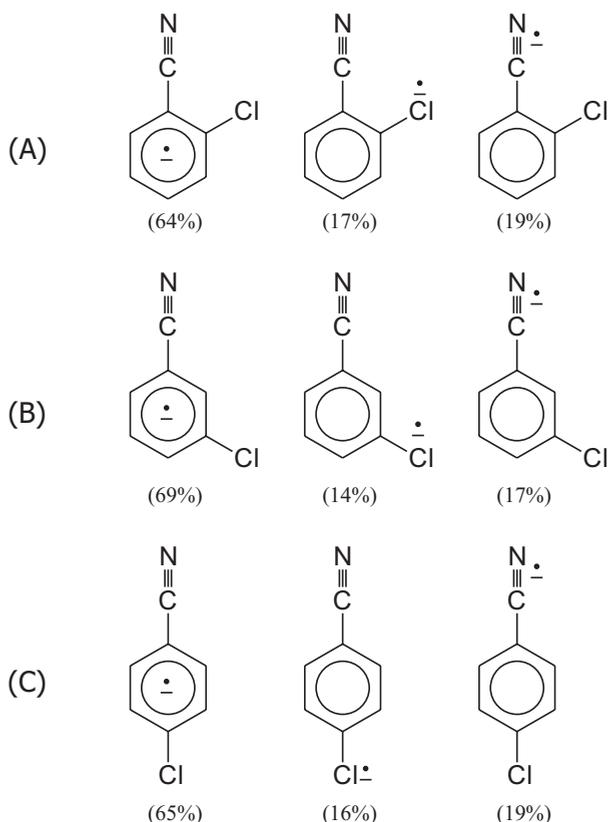


Figure 3. Positions of the negative charge distribution in 2-CBN (A), 3-CBN (B), and 4-CBN (C) radical anion.

distinct preferred reaction position for this compound. More than 70% of the negative charge are located at the 1- and the 4-positions within the benzene moiety. This clearly demonstrates the dominating electronic effect of the cyano group compared to the chloro subunit, where no such directing effects can be observed. The preferences of protonation sites are thus determined for both the neutral systems and radical anions. In the three neutral CBN molecules, the major part of the electron density is located in the aromatic ring moiety, favoring a protonation at the aromatic ring carbon atoms.<sup>5</sup> In contrast, the addition of an electron shifts the negative charge from the ring towards the cyano group, and within this moiety to the nitrogen atom. In agreement with experiment,<sup>6</sup> we find a protonation at the cyano group as the preferred reaction.

The regioselectivity for the addition of the OH radical to the three CBN systems is mainly related to three aspects: 1) directing influences of the

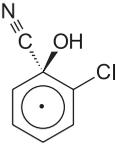
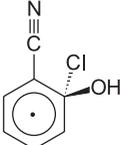
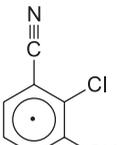
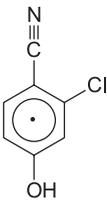
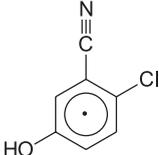
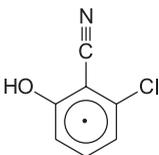
		$\Delta H$ [kJ/mol]
		98.4
		81.0
		69.0
		63.2
		62.6
		63.5

Figure 4. Total energies for the 2-chloro-1-hydroxybenzonitrile to 2-chloro-6-hydroxybenzonitrile addition products.

chloro and cyano groups, 2) electron densities, and 3) steric hindrance. 2-CBN is studied as a representative example due to the previously discussed similarities between all three systems. All six carbon atoms of the aromatic system are considered as possible reactive sites for the addition of the hydroxy radical. The total energies of all six products are presented in Figure 4 along with their molecular structure. The results clearly indicate a preferred addition at the 5-position, yielding the most stable system. Additions at the 4- and 6-position result in slightly less stable conformations ( $\Delta E = 0.8$  kJ/mol). Compared to the product of an addition at the 5-position the addition product in 3-position is destabilized by more than 6.3 kJ/mol. Sterical hindrance causes additions both at the chloro and at the cyano positions resulting in significantly destabilized compounds. According to our calculations, the 5-position is the preferred position of a hydroxy radical group attack, with the chlorine atom as the most effective directing group. The 4- and 6-positions (*i.e. ortho* and *para* to CN) are only slightly destabilized. The *para* addition relative to the cyano unit (4-position) results in a less stable product compared to the *para* addition relative to the Cl atom. It becomes clear thereby, that the chloro atom has stronger directing effects compared to that of the cyano group. The 3-position (*i.e. mesomeric favored ortho* position to chlorine) results in a less stable product, due to strong steric hindrance caused by the large halogen atom. This indicates that the cyano group has electron withdrawing properties of the same magnitude as the chlorine moiety. Sterical hindrance is less important in this case due to the strong stabilization caused by the low energy of the addition product of the reaction at the 6-position.

As an electrophilic species, the hydroxy radical preferably attacks the site with the highest electron density. According to Figure 2, these are the 3- and 5-positions, and to a somewhat smaller degree the 4-position. A comparison of electron densities and stabilities of addition products (see Figure 4) is in good agreement with experimental data,<sup>5</sup> where both the 3- and 5-position are found as the main sites of addition. Both the 4- and 6-adducts are relevant sideproducts.<sup>5</sup> Our calculations of total energies yield the 3- and 5-addition products as the most stable – besides the 4-product – and a corresponding large electron density is found at these positions. A clear disadvantage of the direct addition to the chloro and cyano *ipso* position is observed, which is in agreement with experimental results.<sup>5</sup>

## CONCLUSIONS

The chlorobenzonitriles and their radical anions are investigated by semiempirical methods. The different protonation sites for neutral and reduced CBN are satisfactorily predicted by these quantum mechanical studies

of the prevailing charge densities. The electron densities and the relative stability of various hydroxy radical addition products thus allow the explanation of the experimentally observed products.

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## SAŽETAK

### Redukcija i adicija radikala: Teorijska istraživanja klorbenzonitrila

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Izomeri klorbenzonitrila te njihovi anion-radikali istraživani su semiempirijskim računskim metodama da se dođe do novih saznanja o regioselektivnosti reakcija solvativiranog vodika i hidroksil-radikala. Negativni naboj stvoren tijekom redukcije raspodijeli se između klora, ciano-substituenta i ugljika u *para*-položaju u odnosu na ciano-skupinu. Oko 70% negativnog naboja nalazi se na aromatskom prstenu. Razlika u reaktivnim mjestima negativno nabijenog radikala i neutralne molekule može se objasniti razlikama u elektronegativnosti. U reakciji hidroksil-radikala s 2-klorbenzonitrilom mjesto adicije ovisi o relativnoj stabilnosti šest mogućih produkata. Elektronske gustoće, izračunane Mulliken-ovom populacijskom analizom za 2-klorbenzonitril, vrlo se dobro slažu s dobivenim primarnim i sekundarnim produktima: 2-klor-5-hidroksibenzonitril je primarni produkt, a 4-hidroksi- i 6-hidroksi-izomeri glavni su sekundarni produkti.