

Quantum-chemical studies of the nitration of benzazoles

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Dedicated to Professor José Elguero on the occasion of his 70th birthday

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Abstract

The *H*-tautomers of benzotriazole, benzimidazole, and their *N*-methyl- derivatives, as well as of their cations have been investigated by using the MP2/cc-pVDZ treatment. The atomic reactivity indices for electrophilic reactions (nitration) in the optimized geometries of the compounds under study have been evaluated as the electron density of the highest occupied molecular orbital. Both the benzotriazoles and their protonated cations prefer nitration in the 4- and/or 7-positions in agreement with experimental data. Only the more stable tautomers of 1*H*-benzimidazole nitrated in the 6-position, and the 3*H*-protonated cations of 1,3-*H*-benzimidazolium and 1-methyl-3*H*-benzimidazolium nitrated in the 5- and 6-positions, in full agreement with experiment. The results imply the importance of the protonated benzdiazolium cations for the nitration.

Keywords: Nitration, benzotriazole, benzimidazole, *N*-methylbenzotriazole, 1-methylbenzimidazole

Introduction

Benzimidazole and benzotriazole are isoelectronic tautomeric heterocyclic systems which are frequently exploited in organic synthesis, having applications in many areas of life, especially owing to their biological activity.¹⁻³ Nitro- derivatives are very important in organic synthesis, mainly owing to the enormous quantity of intermediates prepared by reduction,⁴ but also to their interesting types of reactions.⁵

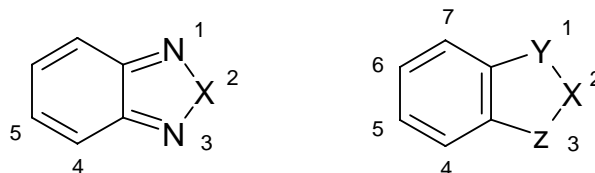
Many derivatives bearing a nitro group play an important role because of their bioactivity, such as the antibiotic chloramphenicol⁶ or the antifungal pyrrolnitrin.⁷ Nitro- heterocycles such as the 2-nitroimidazoles (*e.g.*, misonidazole) were originally developed as radio-sensitizers⁸ or

hypoxia-selective anti-tumor agents.⁹ Some 2-phenylbenzotriazoles have been found to be applicable as fluorescent hydrophobic probes.^{10,11}

A short survey of the nitration of selected benzazoles is given in Table 1 (for the numbering of the benzazole ring see Scheme 1). It was described in the literature a long time ago that the nitration of benzotriazole gives 4- or 7- nitrobenzotriazole, whereas the nitration of benzimidazole occurs at the 5- or 6- position. This discrepancy is especially striking since we are considering two isoelectronic systems.

Nitrations of benzazoles are generally effected using concentrated (65 %) to fuming (100 %) nitric acid, generally at temperatures between 0 – 5 °C. In the nitration of the benzoxazole the azole ring is opened during the reaction.¹² In the nitration of 2,1,3-benzthiadiazole the structure of product was originally assigned wrongly; the results were reinvestigated and the correct structure confirmed using straightforward unambiguous synthesis.¹⁴

Recent *ab initio* quantum-chemical studies of simple benzotriazole and benzimidazole molecules^{15–37} focus on their optimal geometries, the relative stability of the *H*-tautomers, electronic structures, and spectroscopic properties. Unfortunately, their reactivity remains outside the main research direction in this field. The generalized reactivity studies (such as the pioneering work of Brown and Heffernan)³⁸ have not been repeated at the *ab initio* level of theory (with some exceptions such as the study on the nitration of nitro-1*H*-benzotriazole derivatives containing electron withdrawing substituents in the positions *ortho*- and *meta*- to the nitro-group)³⁹ despite new reactivity concepts having been developed by theoretical chemists. The frontier electron density (FED) treatment of Fukui⁴⁰ is based on the evaluation of reactivity indices based on the electron density of the highest occupied molecular orbitals (HOMO) for the electrophilic attacking reagents whereas its formal analogue for the (vacant) lowest unoccupied molecular orbitals (LUMO) is used for the nucleophilic attacking reagents. This treatment has been used widely in semi-empirical methods of quantum chemistry but is also valid at more sophisticated levels of theory. Nevertheless, the simpler (but more time-consuming) treatment based on the geometry optimization of possible reaction products and their energy comparison is preferred nowadays, as the more powerful computers are available. It must be mentioned that Fukui's treatment⁴⁰ supposes the determining role of the first reaction step in the reaction as a whole. Another shortcoming of this treatment is that the use of unbalanced basis sets (with large numbers of polarization and/or diffusion functions such as in the 6-31++G** one) may bring unreliable results (owing to the non-physical origin of the augmented functions). This might be the main reason why the less experienced scientists prefer the alternative treatments.



Scheme 1. Numbering of benzoazoles.

Table 1. Nitrations of benzazoles

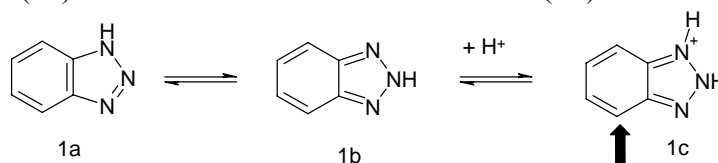
Starting compound	X, or - Y - X - Z -	Product(s)	%	Conditions; Temperatures / °C	Ref.
Benzimidazole	- NH - CH = N -	5(6)-Nitrobenzimidazole	NG	65% HNO ₃ , 96% H ₂ SO ₄ , 30°	43, 44
1-Methyl benzimidazole	- - NMe - CH = N -	5-Nitro-1-methylbenzimidazole	43	65% HNO ₃ , 96% H ₂ SO ₄ , 0–	45
		6-Nitro-1-methylbenzimidazole	44	10°	
Benzotriazole	- NH - N = N -	4(7)-Nitrobenzotriazole	NG	65% HNO ₃ , 96% H ₂ SO ₄ , 30°	46
1-Methylbenzotriazole	-NMe - CH = N -	4-Nitro-1-methylbenzotriazole	NG	65% HNO ₃ , 96% H ₂ SO ₄ , 0–	46
		7-Nitro-1-methylbenzotriazole	NG	100°	
Benzoxazole	- O - CH = N -	4-Nitro-2-formylaminophenol	25	NG	12
		5-Nitro-2-formylaminophenol	75		
	- O - CPh - N -	6-Nitro-2-phenylbenzoxazole	NG	100% HNO ₃ , LT	47
Benzthiazole	- S - CH = N -	All four nitration products, see ref.	NG	100% HNO ₃ , 96% H ₂ SO ₄ , 10–35°	48
2,1,3-Benzthiadiazole	S	4-Nitro-2,1,3-benzthiadiazole	95	65% HNO ₃ , 96% H ₂ SO ₄ , 0–	14
		5-Nitro-2,1,3-benzthiadiazole	90–	20°	13
			93	65% HNO ₃ , 96% H ₂ SO ₄ , 0–	20°
2,1,3-Benzselenadiazole	Se	4-Nitro-2,1,3-benzselenadiazole	90–	65% HNO ₃ , 96% H ₂ SO ₄ , 0–	49
			95	0–10°, 30'	
2-Methylbenzotriazole	NMe	5-Nitro-2-methylbenzotriazole	32	22% HNO ₃ , 60h 100°	50
		4-Nitro-2-methylbenzotriazole,	39	65% HNO ₃ , 96% H ₂ SO ₄ , 0–	51
		5-Nitro-2-methylbenzotriazole	19	to 100°	
		4-Nitro-2-methylbenzotriazole	12		51
		5-Nitro-2-methylbenzotriazole	20	22% HNO ₃ , 60h, 100°	
2-Benzimidazolone	- NH - CO - NH -	5(6)-Nitro-2-benzimidazolone	91	65% HNO ₃ , AcOH, Ac ₂ O	52

NG – not given; LT – laboratory temperature.

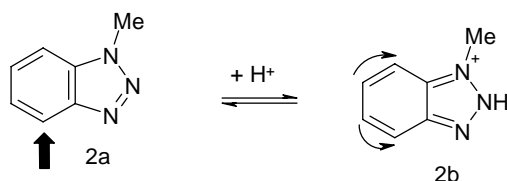
The aim of our study is a theoretical explanation of the experimental results obtained during nitrations of the benzimidazole and benzotriazole as well as of their 1- and 2-methyl-derivatives in concentrated sulfuric acid as a reaction medium (Table 1). The results obtained by quantum-chemical calculations will be compared with the traditional chemical picture of the tautomeric or non-tautomeric parent unsubstituted benzazoles with the benzenoid or *o*-quinonoid structure of the benzene nucleus.

Results and Discussion

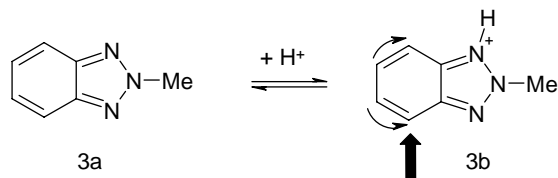
The recent classical chemical picture of benzotriazole- and benzimidazole- nitration consists in the tautomerism of these two systems. Benzotriazole itself could exist in two tautomeric forms, the 1*H*-benzotriazole (**1a**) and the less basic 2*H*-benzotriazole (**1b**):



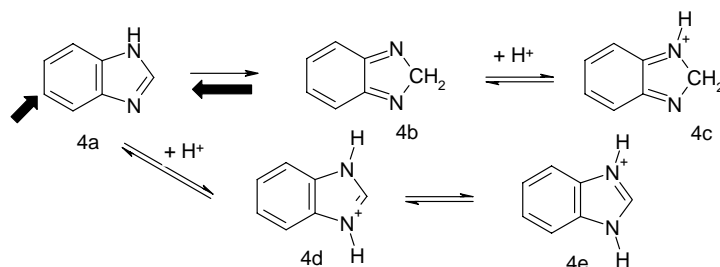
The second of these has a non-aromatic, *o*-quinonoid structure which could also be found in 2,1,3-benzoselenadiazole or 2,1,3-benzothiadiazole. These two heterocycles are nitrated regioselectively in the 4-position, *i.e.*, to the position *ortho*- to the protonated heterocyclic ring. There is a conjugated diene π -system of non-heterocyclic part of the molecule. It is polarized by the protonated azole ring and therefore the nitration produces *ortho*-nitro- derivatives to the benzazole ring, *i.e.*, to the 4-positions. The tautomerism of 1-methylbenzotriazole (**2**) is restricted by the presence of the methyl group in the 1-position, but the protonation produces the isoelectronic non-aromatic *o*-quinonoid species **1c**, **2b** and **3b**, respectively:



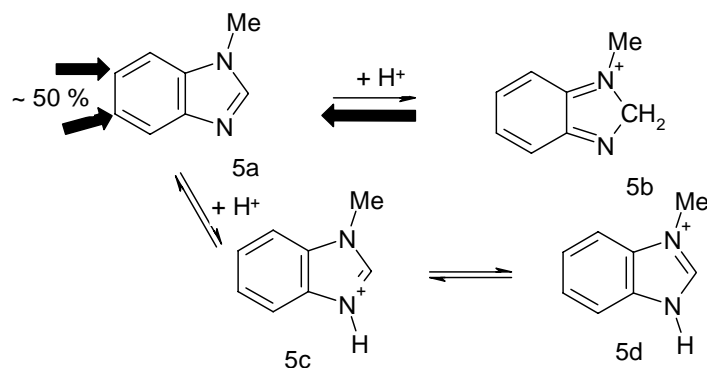
3b is produced by the protonation of the isomeric 2-methylbenzotriazole, which is nitrated to give a mixture of 4- and 5- isomers or only the 5-isomer for the case of the use of diluted nitric acid without concentrated sulfuric acid. This fact could be explained by the lower basicity of 2-methylbenzotriazole derivatives:⁴¹



Benzimidazole (**1**) could also exist like the 1*H*- (**4a**) or 2*H*- (**4b**) tautomer, but the equilibrium is predominantly shifted to the 1*H*-tautomer. Therefore, *o*-quinonoid non-aromatic species **4b** and its protonated analogue **4c** are not present. The protonated tautomer 1*H*- produces a species **4d** (= **4e**) with an aromatic benzene ring:



The protonated imidazole ring is not so strong an electron acceptor as in the case of the triazole ring, and the aromaticity of the benzene ring is not violated. Thus, the formation of a 5(6)-nitro- isomer only may be explained formally as due to the imidazole ring's acting as a *meta*- orienting substituent. The same situation occurs in the case of the nitration of 1-methylbenzotriazole:



An equimolar mixture of 5- and 6-nitro-1-methylbenzimidazoles is formed. Similar nitration products are given when 2-methyl- or 2-alkyl- benzimidazole,⁴² 2-amino-1-methylbenzimidazole, or 2-phenylbenzimidazole is nitrated. In the case of nitration of the last substrate, the phenyl ring is not nitrated.

Our quantum-chemical treatment is based on the comparison of total energies and HOMO FED reaction indices only because other electronic structure- and geometry characteristics of the compounds under study have been investigated by other authors¹⁵⁻³⁷ and are not necessary for our purposes. The reactivity indices for the carbon atoms in the 3a- and 7a- positions are not presented because the next reaction steps (after the predicted first one) in these positions are highly improbable. If comparing the nitration and protonation at the remaining positions (presented in the Tables), their rates are also modified by the next reaction steps. Thus, the higher probability of nitration than protonation at the benzene ring, and their reverse relation at its azole neighbor may be assumed formally.

The problem of the relative stability of the benzotriazole tautomers in real systems is not fully solved yet. Reasonable arguments for the higher stability of 1*H*-benzotriazole (**1a**)^{18,24,29,32,34} as well as of 2*H*-benzotriazole (**1b**)^{15,16,17,26,30} may be found in the literature. From our point of view, it is important that their total energy difference is so small (*ca* 3 kcal/mol) that they may coexist in the solution (Table 2). Moreover, their HOMO FED reactivity indices

indicate the preferred 4(7)-position for nitration in agreement with experimental data.⁴⁶ The same holds for their protonated form (**1c**). However, our results indicate that the protonation of both benzotriazole tautomers in the 2-position is highly improbable. Thus, the protonated form (**1c**) may be formed from the (**1b**) tautomer by the more probable protonation in the 1(3)- position only.

An analogous situation (Table 3) may be observed in the case of methylbenzotriazoles (**2a**) and (**3a**) as well as their protonated forms (**2b**) and (**3b**). In all cases, the nitration in 4- and 7- positions is preferred (in agreement with experimental data⁴⁶) whereas the protonation in 2- position is highly improbable. Thus the possible existence of 2-methyl-1*H*-benzotriazolium (**3b**) might be explained by its formation from its less stable 1-methyl-analogue (**2b**).

Table 2. The total energy E_{tot} and HOMO FED indices of benzotriazoles

Compound	1 <i>H</i> -Benzotriazole	2 <i>H</i> -Benzotriazole	1,2- <i>H</i> -Benzotriazolium
	1a	1b	1c
E_{tot} (a.u.)	-394.72265	-394.72750	-395.06216
HOMO FED			
1- N	0.248	0.250	0.170
2- N	0.005	0.001	0.002
3- N	0.047	0.250	0.090
4- C	0.356	0.354	0.427
5- C	0.265	0.150	0.290
6- C	0.046	0.150	0.038
7- C	0.392	0.354	0.403

Table 3. The total energy, E_{tot} and HOMO FED indices of methylbenzotriazoles

Compound	1-Methyl- benzotriazole	1-Methyl-2 <i>H</i> - benzotriazolium	2-Methyl- benzotriazole	2-Methyl-1 <i>H</i> - benzotriazolium
	2a	2b	3a	3b
E_{tot} (a.u.)	-433.90402	-434.25087	-433.91027	-434.25434
HOMO FED				
1- N	0.295	0.204	0.252	0.165
2- N	0.004	0.002	0.001	0.002
3- N	0.174	0.112	0.249	0.090
4- C	0.331	0.412	0.352	0.423
5- C	0.248	0.262	0.155	0.282
6- C	0.050	0.050	0.143	0.039
7- C	0.369	0.404	0.354	0.407

The problem of benzimidazoles' nitration (Table 4) is not so simple. The preferred nitration site of the 1*H*-tautomer (**4a**) is the 6-position, in agreement with experimental data,⁴³⁻⁴⁵ whereas the less stable (*ca* 30 kcal/mol) 2*H*-tautomer (**4b**) prefers the 4(7)-position. If the protonated benzimidazolium cations are considered, the less stable (*ca* 40 kcal/mol) 1,2-*H*-tautomer (**4c**) prefers the positions 4, 5 and 7, whereas the more stable 1,3-*H*-benzimidazolium (**4d**) prefers the experimentally confirmed⁴³⁻⁴⁵ 5(6)-position. The problem is in the benzimidazolium cation formation. Whereas the less stable 1,2-*H*-tautomer (**4c**) may arise from both imidazole tautomers, the formation of 1,3-*H*-benzimidazolium (**4d**) is less probable, owing to the very small reactivity index of 1*H*-imidazole (**4a**) at the 3-position (Table 4).

In 1-methyl-benzimidazole (**5a**) the nitration in the 6-position is preferred (Table 5) whereas nearly equal amounts of 5- and 6-nitro-derivatives are obtained experimentally.⁴⁵

Table 4. The total energy E_{tot} and HOMO FED indices of benzimidazoles

Compound	1 <i>H</i> - Benzimidazole 4a	2 <i>H</i> -Benzimidazole 4b	1,2- <i>H</i> - Benzimidazolium 4c	1,3- <i>H</i> - Benzimidazolium 4d
E_{tot} (a.u.)	-378.73720	-378.68393	-379.04535	-379.11353
HOMO FED				
1- N	0.001	0.248	0.191	0.015
2- C	0.272	0.001	0.001	0.206
3- N	0.098	0.248	0.120	0.016
4- C	0.089	0.305	0.392	0.007
5- C	0.095	0.182	0.340	0.322
6- C	0.361	0.183	0.052	0.322
7- C	0.042	0.305	0.378	0.007

Table 5. The total energy E_{tot} and HOMO FED indices of 1-methylbenzimidazoles

Compound	1-Methyl- benzimidazole 5a	1-Methyl-2 <i>H</i> - benzimidazolium 5b	1-Methyl-3 <i>H</i> - benzimidazolium 5c, 5d
E_{tot} (a.u.)	-417.91505	-418.23042	-418.29709
HOMO FED			
1- N	0.001	0.225	0.015
2- C	0.272	0.000	0.167
3- N	0.104	0.141	0.012
4- C	0.093	0.369	0.006
5- C	0.093	0.311	0.232
6- C	0.360	0.064	0.222
7- C	0.040	0.371	0.004

The nearly equal reaction indices for the nitration in the 5- and 6-positions may be attributed to 1-methyl-3*H*-benzimidazolium (**5c**, **5d**). Its less stable (*ca* 40 kcal/mol) 2*H*-tautomer (**5b**) prefers nitration in the 4-, 5- and 7-positions. It must be mentioned that the 1-methyl-benzimidazole (**5b**) in the 2-position is more probable than in the 3-position. This means that the rate of the less stable 1-methyl-2*H*-benzimidazolium's (**5b**) formation is higher than of its more stable 3*H*-tautomer (**5c**, **5d**). The higher reaction rate corresponds to the lower reaction barrier (and vice versa) and so the concentration equilibrium of both cations in the solution must be obtained by their mutual interconversion. The agreement of experimental data with the reactivity indices of the protonated 1-methyl-3*H*-benzimidazolium (**5c**, **5d**) and not of the neutral 1-methyl-benzimidazole (**5a**) confirms the important role of protonated cations for the nitration of benzazoles.³⁹

Finally, it may be concluded that many principles of the above-mentioned classical picture are confirmed by the results of high-level quantum-chemical calculations. The theoretical predictions based on Fukui reaction indices⁴⁰ of the systems under study are in excellent agreement with experimental data. The predictions for the benzotriazoles are equal for all their tautomers as well as all tautomers of their protonated cations. On the other hand, only the more stable tautomers of 1*H*-benzimidazole nitrated in the 6-position, as well as of 1,3-*H*-benzimidazolium and 1-methyl-3*H*-benzimidazolium cations nitrated in the 5- and 6-positions are in full agreement with experiment. This implies the importance of the protonated benzimidazolium cations for the nitration.

Similar conclusions based on Fukui's rules⁴⁰ also hold for other electrophilic substitutions. Nevertheless, the extrapolation of our results to the similar types of benzodiazoles must be treated very carefully (see Table 1). Further theoretical studies in this field are desirable.

Experimental Section

General Procedures. Using the Gaussian03 program package,⁵³ the optimal geometries of the compounds under study are investigated within the standard MP2 treatment with standard accuracy parameters and Dunning's correlation-consistent cc-pVDZ basis sets.⁵⁴ To compare the reactivity indices for the reaction with electrophilic attacking reagents, the frontier electron densities (FED) for the highest occupied molecular orbitals (HOMO) of individual atoms according to Fukui⁴⁰ were evaluated using the doubled sum of squared LCAO coefficients.

Acknowledgments

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