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The Role of the Hydrogen Bonding in Cycloadditions of Benzonitrile Oxide with Cyanophenols.

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Abstract: The reactivity of aromatic nitriles in cycloadditions with benzonitrile oxide is remarkably enhanced by the *ortho*-hydroxy substituent. Semiempirical PM3 calculations are in agreement with a hydrogen bonding effect.

The hydrogen bonding has proved to play an important role in nitrile oxide cycloadditions. The reactivity,[1] as well as the sito-,[2-4] regio- and stereo-selectivity,[5-11] of dipolarophiles containing a XH group in a suitable position can be controlled by the occurrence of favourable hydrogen bonding effects. Particularly, in the case of cyclic dipolarophiles there are several examples of allylic alcohols[5-9] and secondary amides,[10,11] which show an expected dipolarophilic reactivity and/or a regio- and stereo-selectivity. This has been rationalised in terms of an accelerative and/or directing hydrogen bonding model, in which the energy of the transition state deriving from an interaction of a hydrogen of the dipolarophile with the oxygen of the 1,3-dipole is reduced relative to the energies of transition states, which do not involve a coordination of the hydrogen of the dipolarophile.[10] However, in the case of acyclic allylic alcohols[12] and secondary amides,[11,13] the hydroxyl and amide groups determine only modest effects, which appear to be unable of determining the outcome of nitrile oxide cycloadditions.

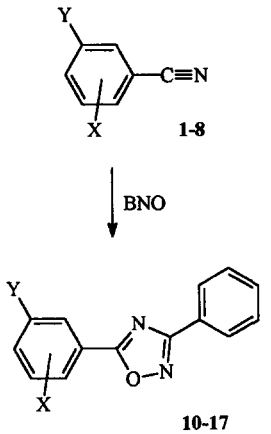
As part of our going interest in the synthetic application of the 1,3-dipolar cycloaddition chemistry[14] we have investigated the reactivity of cyanophenols toward benzonitrile oxide (BNO) with the aim at showing the importance of hydrogen bonding in controlling the reactivity of the C≡N triple bond. Recently, we showed that the dipolarophile activity of the nitrile function of 2-cyanoaniline **1** is enhanced by hydrogen bonding effects.[1] Such enhancement parallels the acidity of the aniline. Thus a change of the yield from 10 to 32-41% has been observed by passing from **1** to its acetyl, benzoyl and tosyl derivatives.

Seeking to support the accelerative model of hydrogen bonding and particularly to verify the prediction of a higher activation because of a higher acidity of the dipolarophile, we have examined the reactivity of 2-cyanophenol **2** towards BNO and we have compared it with that of its 3- and 4-isomer, **3** and **4**, *O*-methyl derivative **5**, the least (4-methoxy-) or most (4-nitro-) acidic derivatives **6** and **7** by means of competitive experiments. These were extended to the benzonitrile **8**, nitrogen and sulfur analogues of **2**, **1** and **9**. Finally we have performed a study of the solvent effect on the competitive experiment of **2** and **5** with BNO, since the hydrogen bond is sensitive to the change of the solvent.

In this paper we report and comment upon the results of this work.

RESULTS AND DISCUSSION

Reactions were performed by adding the BNO, separately generated following the method of the oxidation of benzaldoxime with hypochlorite,[15] to nitriles. In this way, beside the dimerization products of BNO and the excess of the starting nitrile, BNO adds only to the C≡N triple bond of **1-8**.[16] All new oxadiazoles were identified by means of their elemental and spectral data (see Experimental).



10-17

	X	Y
1, 10	2-NH_2	H
2, 11	2-OH	H
3, 12	3-OH	H
4, 13	4-OH	H
5, 14	2-OCH_3	H
6, 15	2-OH	5-OCH_3
7, 16	2-OH	5-NO_2
8, 17	H	H

According to our expectations based on the activation of the cyano group because of a favourable hydrogen bonding between the oxygen of the 1,3-dipole and the phenolic hydrogen, **2** proved to be the most reactive among its 3- and 4-isomers, **3** and **4**, and its *O*-methyl derivative **5**, since it affords a 78% yield of the 3-phenyl-5-(2-hydroxyphenyl)-1,2,4-oxadiazole against 21-25% yield of the corresponding oxadiazoles under the same reaction time. These indications were confirmed by the results of competitive experiments (Table 1) conducted between **2** and the other derivatives.

As Table 1 shows, in dichloromethane the reactivity of 2-cyanophenol **2** is the highest one among those of its isomers **3**, **4** and its *O*-methyl derivative **5**, for which a maximum factor of 14-15 is reached.

Table 1. Molar per cent and ratio of cycloadducts from competitive experiments between **2** and **1**, **3-8** with BNO in dichloromethane.[a]

Competitive experiments	Cycloadducts yield (%)[b]		Molar ratio
	11	**10, 12-17**	**11 : 10, 12-17**
2 : 1	61.3	8.5	7.2
2 : 3	66.1	9.8	6.7
2 : 4	60.0	7.2	8.3
2 : 5	66.2	4.6	14.4
2 : 6	28.0	39.9	0.7
2 : 7	41.9	32.1	1.3
2 : 8	61.9	8.6	7.2

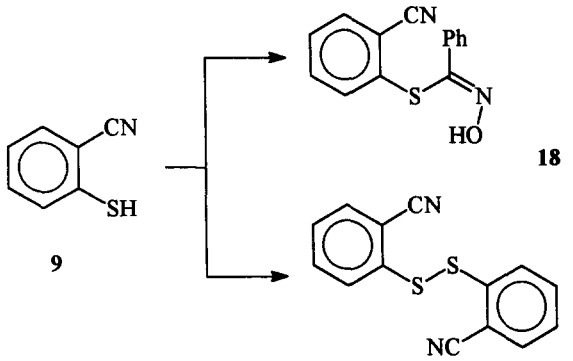
[a]The unreacted BNO was recovered as 3,4-diphenylfuroxane accompanied by minor amounts of 3,5-diphenyl-1,2,4-oxadiazole. [b]The maximum deviation from the average of triplicate runs was ± 2.

The 2-methoxybenzonitrile **5** shows the lowest reactivity probably because the steric hindrance that BNO meets in the addition to the C≡N triple bond. The effect of substituents in the phenyl ring of **2** is in line with the acidity of 4-methoxy- and 4-nitro-2-cyanophenol **6** and **7**, but it is very modest in comparison with the effect of electron-donor and -withdrawn substituents on the acidity of phenol.[17]

By passing to the comparison with benzonitrile **8** and 2-cyanoaniline **1**, which latter still maintains the dipolarophilic activity of the C≡N triple bond and does not afford any trace of 1,3-addition product, the reactivity of **2** remains in the order of that of its isomers **3** and **4**.

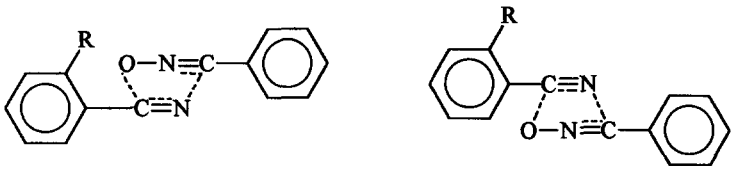
The reactivity of **8**, however, is lower since the dimerization of BNO also contributes to the formation of 3,5-diphenyl-1,2,4-oxadiazole. In an experiment without the dipolarophile, BNO dimerizes giving furoxan and oxadiazole in 79.2 and 20.8% yield, respectively.

In agreement with the incapability of sulfur to form efficient hydrogen bondings because of its rather large size, diffuse orbitals and highest acidity of the sulfydryl group, **9** reacts with BNO under the same conditions used for **2** to give *S*-(2-cyanophenyl) benzothiohydroximate **18**, its 1,3-addition product, along with bis(2-cyanophenyl)disulfide **19**, its oxidation product.



9 **18** **19**

In order to rationalise the observed order of reactivity, calculations were carried out on compounds **1-8** and BNO by means of the semiempirical PM3 method.[18] The results obtained from competitive experiments are not in agreement with the simple theoretical treatment of the substituent effect based on a frontier orbital method,[19] where the interaction between the LUMO-dipolarophile and the HOMO-1,3-dipole dominates in the case of 4-substituted benzonitriles.[20] Moreover starting from different geometries several attempts were made for localising the transition state using the NLLSQ routine according to the procedure followed by Annunziata,[21] but all of them were unsuccessful. Finally, our PM3 results do not evidence sufficient charge density variations on passing from benzonitrile **8** to its 2-substituted derivatives **1-7** to account for the reactivity changes on the basis of the electronic effects (q_C is -0,096 in **2** and **8**, -0.088 in **1** and -0.084 in **5**; q_N ranges from a minimum of -0.062 in **8** to a maximum of -0.075 in **5**). An alternative way was then adopted. Since we think that a possible hydrogen bonding (or favourable electrostatic interactions) between the BNO and **2** can favour the reaction, we tried to insert BNO in the space between the C≡N and the 2-substituent of the 2-substituted benzonitriles (path a) and to approach BNO to the opposite or orthogonal site of the cyano group (path b).



path a path b

Table 2 shows the most important geometric and energetic parameters of structures (X-BNO) in the minimum energy for **1**, **2** and **5** with BNO for path a and path b, obtained from such calculations after full optimisation.

Table 2. Energetic and geometrical parameters of structures (X-BNO) in the minimum energy of **1**, **2**, and **5** with BNO.

	path a			path b		
compound	$r_{C\cdots O}$[a]	$r_{C\cdots N}$[a]	Energy[b] gain	$r_{C\cdots O}$[a]	$r_{C\cdots N}$[a]	Energy[b] gain
1	3.570	3.790	0.639	3.852	4.031	1.619
2	3.420	3.761	2.760	3.748	4.337	0.895
5	4.314	3.840	0.631	3.699	4.162	0.951

[a]Distance in Å. [b]Energies in Kcal mol^{-1}

The main result is that in all cases the linear geometry of the cyano group and nitrile oxide is maintained and that the total energy of structures is lower than the sum of the energies of the two separated molecules. Such energy gain is 2.76 Kcal mol^{-1} for **2**-BNO, 0.64 and 0.63 Kcal mol^{-1} for **1**- and **5**-BNO, respectively. Moreover, the O...O distance (2.71 Å) for **2**-BNO is shorter than the sum of the van der Waals radii of oxygen (3.0 Å), so that it can be argued that a hydrogen bonding is present. For **1**- and **5**-BNO the distances do not agree with a possible hydrogen bond formation and the above energy gain is attributable only to favourable electrostatic interactions.

When the BNO is approached to the opposite or orthogonal site (path b), i. e. distant from the 2-substituent, the energy gain is lower than the previous case for **2**-BNO and higher for **1**- and **5**-BNO. The ΔE value of 2.76 Kcal mol^{-1}, found in path a, agrees with the highest reactivity of **2**-BNO. On the same ground **1**- and **5**-BNO would have reactivity lower than **2**-BNO and comparable to each other, but this is in contrast with experimental findings. However, if the distances (Table 2) separating the atoms between which the bonds of a giving final product must be formed, are considered, the path a remains the most favoured and the best distances are those of **2**-BNO, followed by those of **1**-BNO and finally those of **5**-BNO, in good agreement with the observed reactivity order.

Since it is known that hydrogen bonding is sensitive to the nature of the solvent, to ascertain its involvement in the case of **2**, we have repeated some competitive experiments in solvents different from dichloromethane, like benzene, dimethyl formamide and dimethyl sulfoxide and the results are shown in Table 3.

As Table 3 shows, the reactivity of cyano group observed in dichloromethane is kept in benzene, which is

a nonhydrogen bonding solvent, but it is remarkably reduced in strongly acceptor solvents of hydrogen bonds, like dimethyl formamide and dimethyl sulfoxide.[22] These latter form stronger hydrogen bonds with the hydroxyl of **2** and thus the reactivity of **2** is depressed to values similar to that shown by the *O*-methyl derivative **5**, and no 1,3-addition products are formed.

Table 3. Solvent influence on the molar per cent and ratio of cycloadducts from competitive experiments of **2** and **5** with BNO.[a]

solvent	Cycloadducts yield (%)[b]		Molar ratio
	11	**14**	**11 : 14**
CH_2Cl_2	66.2	4.6	14.4
PhH	64.2	5.7	11.2
DMF	35.0	11.5	3.0
DMSO	33.9	19.5	1.7

[a]The unreacted BNO was recovered as 3,4-diphenylfuroxane accompanied by minor amounts of 3,5-diphenyl-1,2,4-oxadiazole. [b]The maximum deviation from the average of triplicate runs was ±2.

In conclusion we here report the first evidence of enhancement of the reactivity of a nitrile function by hydrogen bonding effects deriving from the participation of the phenolic *ortho*-hydroxyl.

EXPERIMENTAL

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. ^{1}H NMR spectra were recorded on a Bruker WP 80 FT spectrometer using tetramethylsilane as internal standard and deuterochloform, unless otherwise stated. IR spectra (potassium bromide) were recorded on a Perkin Elmer 281 spectrophotometer, and mass spectra on a VG ZAB-2SE spectrometer operating at 70 eV. Analytical thin layer chromatographic separations were performed on aluminium plates pre-coated with Merck silica gel 60-F_{254}. Preparative chromatographic separations of reaction mixtures were performed by means of flash chromatography using Merck silica gel 60. Mixtures of cyclohexane-ethyl acetate were used as eluents. Gas-chromatographic analyses were performed on a HP-5890 instrument equipped with a fused silica gel capillary (20 m × 0.53 mm × 2.65 μm) column and a flame-ionisation detector using helium as a carrier gas.

Starting materials. Benzaldoxime, 2-cyanoaniline **1**, 2-, 3- and 4-cyanophenol **2-4** and benzonitrile **8** are commercial compounds and have been purchased from the Aldrich Co. *O*-Methylcyanophenol[23] **5**, 4-methoxy and 4-nitro-2-cyanophenol,[24] **6** and **7**, are known compounds. The former was prepared by methylation of the corresponding phenoxide ion with iodomethane in refluxing methanol for 1h. The latter two phenols were obtained as acetals from the corresponding aldehydes through the oximes, which were dehydrated by acetic anhydride. The hydrolysis of the acetates with 5% sodium hydroxide at the temperature of the vapour bath for 10 min., followed by neutralisation with diluted hydrochloric acid, yielded phenols **6** and **7** in 60-72% yield. 2-Cyanothiophenol[25] **9**, bis(2-cyanophenyl)disulfide[25] **19**, 3,5-diphenyl-1,2,4-oxadiazole[26] and 3-phenyl-5-(2-aminophenyl)-1,2,4-oxadiazole[1] **10** were prepared following literature procedures.

Eluents used in chromatography were reagent grade. Solvents for competitive experiments were dried

following literature procedures.[27] The identification of samples deriving from different experiments was secured by superimposable IR spectra.

General procedure for reactions of BNO with 1-9. To a solution of the nitrile **1-9** (20 mmol) in dichloromethane (30 ml) a solution of BNO, freshly prepared from benzaldoxime (1.2 mg, 10 mmol) and 11% aqueous sodium hypochlorite (10 ml, 17 mmol), was added at O °C and the mixture was allowed to reach the room temperature. After 24 h the solvent was removed and the residue was subjected to flash chromatography.

In the case of cyanophenols **1-8** the order of elution was 3,4-diphenylfuroxan accompanied by minor amounts of 3,5-diphenyl-1,2,4-oxdiazoles, expected oxadiazoles and unreacted nitriles.

3-phenyl-5-(2-hydroxyphenyl)-1,2,4-oxadiazole **11**: colourless crystals (78%), mp 140-142 °C from cyclohexane/ethyl acetate (Found: C, 70.63; H, 4.26; N, 11.92. $C_{14}H_{10}N_2O_2$ requires: C, 70.58; H, 4.23; N, 11.76); IR (KBr): vbr 3200 cm^{-1}; ^1H NMR ($CDCl_3$) 6.98-7.12 (2H, m, phenyl H); 7.42-7.51 (4H, m, phenyl H); 7.90-8.09 (3H, m, phenyl H); 10.55 (1H, s, hydroxyl H).

3-phenyl-5-(3-hydroxyphenyl)-1,2,4-oxadiazole **12**: colourless crystals (24%), mp 190-192 °C from cyclohexane/ethyl acetate (Found: C, 70.68; H, 4.28; N, 11.62. $C_{14}H_{10}N_2O_2$ requires: C, 70.58; H, 4.23; N, 11.76); IR (KBr): br 3310 cm^{-1}; ^1H NMR ($CDCl_3$) 7.01-7.13 (1H, m, phenyl H); 7.41-7.62 (6H, m, phenyl H); 8.06-8.11 (2H, m, phenyl H); 10.50 (1H, s, hydroxyl H).

3-phenyl-5-(4-hydroxyphenyl)-1,2,4-oxadiazole **13**: colourless crystals (21%), mp 169-171 °C from cyclohexane/ethyl acetate (Found: C, 70.81, H, 4.33; N, 11.70. $C_{14}H_{10}N_2O_2$ requires: C, 70.58; H, 4.23; N, 11.76); IR (KBr): br 3300 cm^{-1}; ^1H NMR ($CDCl_3$) 6.99 (2H, d, J = 8 Hz, phenyl H); 7.52 (3H, m, phenyl H); 8.07 (2H, d, J = 8 Hz, phenyl H); 8.13 (2H, m, phenyl H).

3-phenyl-5-(2-methoxyphenyl)-1,2,4-oxadiazole **14**: colourless crystals (25%), mp 87-89 °C from cyclohexane/ethyl acetate (Found: C, 71.49; H, 4.85; N, 10.82. $C_{15}H_{12}N_2O_2$ requires: C, 71.42; H, 4.79; N, 11.10); IR (KBr): 1610 cm^{-1}; ^1H NMR ($CDCl_3$) 3.97 (3H, s, methoxy H); 7.03-7.12 (2H, m, phenyl H); 7.45-7.52 (4H, m, phenyl H); 8.11-8.20 (3H, m, phenyl H).

3-phenyl-5-(2-hydroxy-4-methoxyphenyl)-1,2,4-oxadiazole **15**: colourless crystals (60%), mp 222-224 °C from cyclohexane/ethyl acetate (Found: C, 67.19; H, 4.54; N, 10.40. $C_{15}H_{12}N_2O_3$ requires: C, 67.16; H, 4.51; N, 10.44); IR (KBr): br 3210 cm^{-1}; ^1H NMR ($CDCl_3$) 4.05 (3H, 3, methoxy H); 7.24-7.64 (3H, m, phenyl H); 7.73-7.81 (3H, m, phenyl H); 8.32-8.37 (2H, m, phenyl H); 10.18 (1H, s, hydroxyl H).

3-phenyl-5-(2-hydroxy-4-nitrophenyl)-1,2,4-oxadiazole **16**: colourless crystals (81%), mp 230-232 °C from cyclohexane/ethyl acetate (Found: C, 59.54; H, 3.22; N, 14.81. $C_{14}H_9N_3O_4$ requires: C, 59.37; H, 3.20; N, 14.84); IR (KBr): br 3130 cm^{-1}; ^1H NMR ($CDCl_3$) 7.28 (2H, d, J = 8 Hz, phenyl H); 7.63-7.79 (3H, m, phenyl H); 8.11-8.15 (2H, m, phenyl H); 8.38-8.42 (2H, m, phenyl H).

In the case of **9** the order of elution was diphenylfuroxane accompanied by minor amounts of 3,5-diphenyl-1,2,4-oxadiazole, bis(2-cyanophenyl)disulphide **19**, *S*-(2-cyanophenyl) benzothiohydroximate **18** and unreacted 2-cyanothiophenol.

Bis(cyanophenyl)disulphide **19**: light yellow crystals (15%), mp 102-103 °C (Literature mp 103-104 °C[24]) from cyclohexane/ethyl acetate (Found: C, 62.30; H, 3.21; N, 10.63; S, 23.48. $C_{14}H_8N_2S_2$ requires: C, 62.66; H, 3.00; N, 10.44; S, 23.89); IR (KBr): 2220, 1580 cm^{-1}; ^1H NMR ($CDCl_3$): 7.34-7.39 (8H, m, aromatic H); ^{13}C NMR ($CDCl_3$): 110.92, 113.16, 116.16, 128.38, 133.55, 133.73, 139.86.

S-(2-cyanophenyl) benzothiohydroximate **18**: colourless crystals (60%), mp 108-109 °C from cyclohexane/ethyl acetate (Found: C, 66.33; H, 3.89; N, 11.25; S, 12.58. $C_{14}H_{10}N_2OS$ requires: C, 66.12; H, 3.96; N, 11.02; S, 12.61); IR (KBr): br 3250, 2220, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) 7.15-7.48 (9H, m, aromatic H); 9.9 (1H, s, oximic H); ^{13}C NMR ($CDCl_3$) 116.59, 117.16, 128.00, 128.47, 128.85, 129.44, 130.10, 132.11,

132.52, 133.38, 134.80, 135.36, 151.95.

Competition experiments. For competitive experiments between **2** and **1**, **3-8**, a solution of BNO in dichloromethane (10 ml) freshly prepared at O °C from benzaldoxime (1.21 mg, 10 mmol) and 11% aqueous sodium hypochlorite (10 ml, 17 mmol), was added to the two nitriles (10 mmol) in the same solvent (30 ml). The reaction mixtures were allowed to stand at room temperature under stirring for 24 hours.

For the solvent effect, a solution of BNO in dichloromethane (6 ml), freshly prepared at O °C from benzaldoxime (1.21 mg, 10 mmol) and 11% aqueous sodium hypochlorite (10 ml, 17 mmol), was divided in 4 portions. Each portion was diluted with the appropriate solvent (8.5 ml) and then added to a solution of the two nitriles (5 mmol) in the same solvent (20 ml) at O °C. The reaction mixtures were allowed to stand at room temperature under stirring for 24 hours.

Yields of the two cycloadducts were determined by GC analysis of three different reaction mixtures following the method of internal standard, and the results are shown in Tables 1 and 3. The maximum deviation from the average of triplicate runs was ±2.

Method of calculations. The calculations were performed by means of the semiempirical PM3 method[18] available in the MOPAC computation package distributed by QCPE (QCPE program nr. 455, version 6.0).

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