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Imidazole and Benzimidazole Addition to Quinones. Formation of *meso* and *d,l* Isomers and Crystal Structure of the *d,l* Isomer of 2,3-Bis(benzimidazol-1'-yl)-1,4-Dihydroxybenzene

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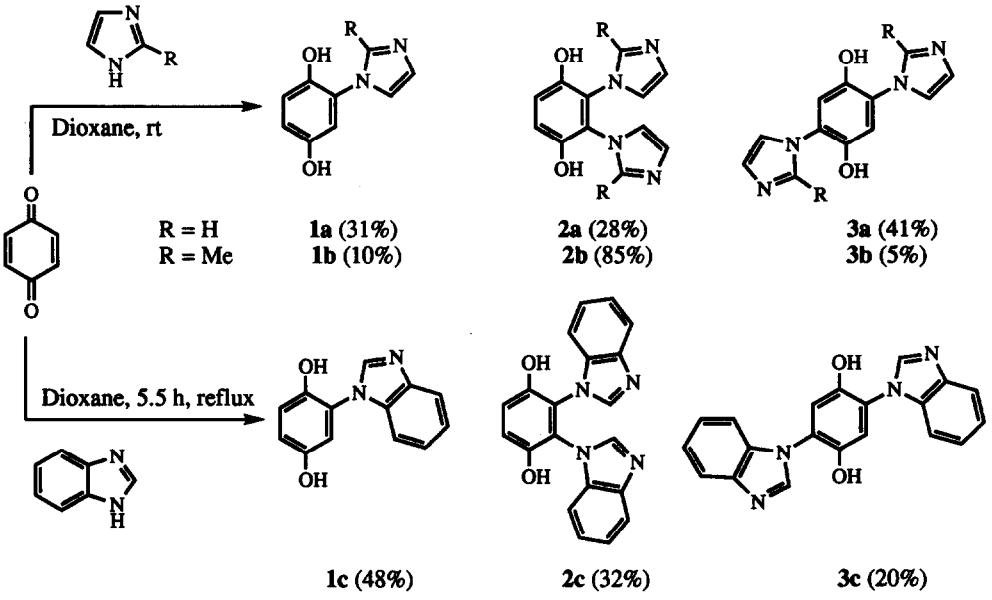
Abstract: The hydroquinones obtained by addition of imidazole, 2-methylimidazole and benzimidazole to 1,4-benzoquinone and 1,4-naphthoquinone have been isolated and identified. In the case of 1,4-benzoquinone they are monosubstituted hydroquinones **1a** - **1c**, *o*-disubstituted hydroquinones **2a** - **2c**, and *p*-disubstituted derivatives **3a** - **3c** while in the case of 1,4-naphthoquinone, only disubstituted derivatives **5a** and **5c** have been isolated. In solution, 2,3-bis(2'-methylimidazol-1'-yl)-1,4-dihydroxybenzene (**2b**), 2,3-bis (benzimidazol-1'-yl)-1,4-dihydroxybenzene (**2c**) and 2,3-bis(benzimidazol-1'-yl)-1,4-dihydroxynaphthalene (**5c**) exist as mixtures of *meso* and *d,l* isomers. NMR spectroscopy (n.O.e. experiments in ^{1}H NMR and solid-state ^{13}C CPMAS spectra) and AM1 semiempirical calculations have been used to establish the structure of the isomers both in the solid state and in solution as well as their interconversion pathways. Compound **2c-d,l** crystallizes with two methanol solvate molecules as guests and it has a crystallographic twofold axis through the middle. The host molecules are linked together by means of the methanol molecules through O-H···O/N hydrogen bonds giving rise to chains along the c axis centrosymmetrically related.

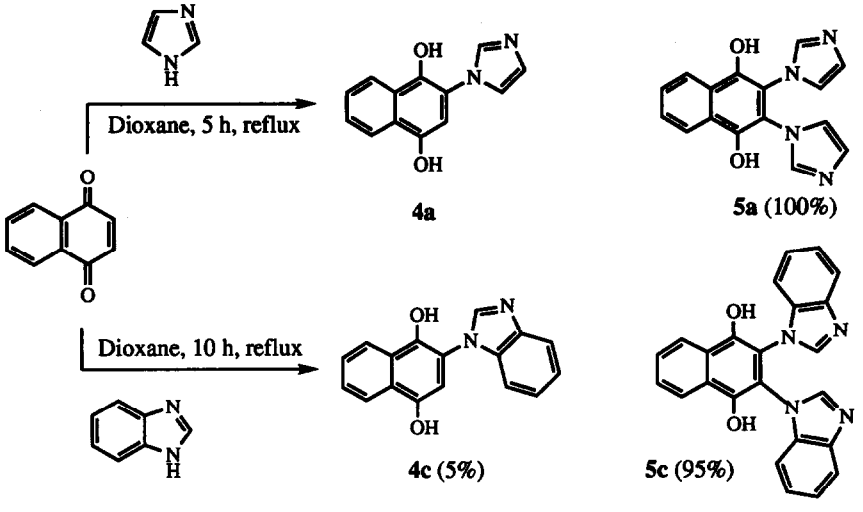
Introduction

We have recently studied the addition reaction of pyrazoles to 1,4-benzoquinone.[1,2] As an extension of our work, we report now the reactions of imidazole, 2-methylimidazole and benzimidazole with 1,4-benzoquinone and of imidazole and benzimidazole with 1,4-naphthoquinone.

The relative amounts of mono- (Compounds **1** or **4**), 2,3-bis-adducts (Compounds **2** or **5**) and 2,5-bis-adducts (Compounds **3**) depicted in Schemes 1 and 2, can be explained through a mechanism in which the nucleophilic character of the azole as well as the oxidation potentials of the mono-adducts are decisive factors in the process.[3] However, formation of a charge-transfer complex prior to the nucleophilic addition could also be considered. As in the case of pyrazoles,[1,2] preferential formation of 2,3-bis derivatives *vs.* 2,5-bis derivatives occurs with hindered imidazoles. Gauss *et al.*[4] reported in the experimental part without any additional



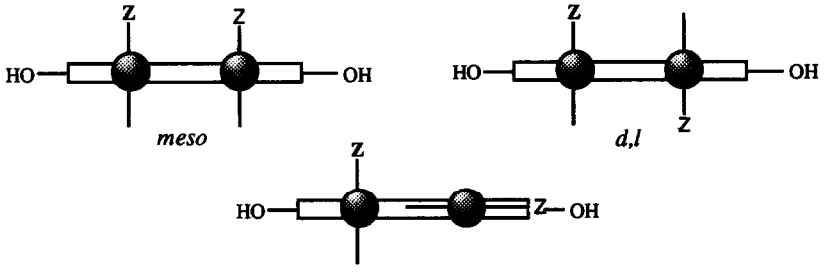
Scheme 1



Scheme 2

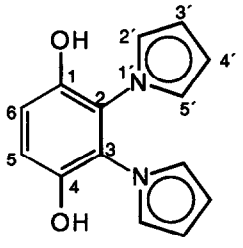
explanation throughout the article that the compound obtained by reaction of 2-methylimidazole with 2-methoxy-1,4-naphthoquinone (**5b**), should be a 38:62 mixture of rotational isomers to explain the signals observed in the ^1H NMR in D_2O/DCl at 60 MHz.

Provided that there is no free rotation about the N-C bonds, the 2,3-(azol-1′-yl)-1,4-dihydroxybenzene derivatives **2b** and **2c** [and also the 2,3-(azol-1′-yl)-1,4-dihydroxynaphthalene **5c**] exist in two forms: the *meso* form (the two substituents, methyl or benzo ring on the same side, i.e. *cisoid*) and the *d,l* form (the substituents on opposite sides, i.e. *transoid*). Since the barrier lies in the planar conformation of one of the heterocyclic rings (the other remaining orthogonal) and since the orthogonal barriers (with regard to conformation slightly apart from the orthogonality) are too low to interfere, we will simplify the representation of both forms using an orthogonal conformation (later on for the calculations of n.O.e effects an optimized geometry with torsion angles different from 90° will be used). Although several cases of atropoisomerism in *ortho*-triaryls have been cited in the literature,[5] we have not found studies in the case of two heteroaryl rings placed mutually *ortho* on a benzene ring.



Transition state

The usual method to distinguish these forms uses chiral LSR.[6] In the presence of such a chiral reagent two coupled protons remain an A_2 system in the case of the *meso* and become an AB system in the case of the *d,l* isomer. However, in the present case, these ought to be the aromatic protons (H_5, H_6 for **2**, and H_5, H_6, H_7, H_8 for **5**) which are too far apart from the chiral part of the molecule.



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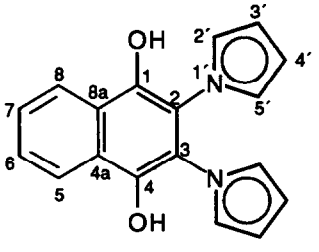

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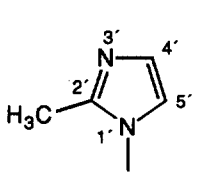
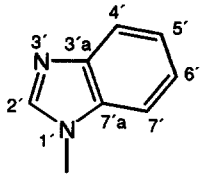
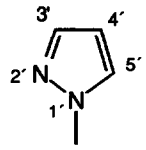
For this reason, we have selected another approach based on n.O.e. effects between both azol-1′-yl residues; for obvious symmetry reasons, no n.O.e. effects can be observed on the *meso* isomer, but in the case of the *d,l* isomer an n.O.e. effect between both heterocycles should be observed. We have studied two substituents: 2′-methylimidazol-1′-yl **b**, benzimidazol-1′-yl **c** and we will briefly summarize the results already described concerning the structure of related compounds pyrazol-1'-yl **d** and 3′,5′-dimethylpyrazol-1′-yl **e**.[1,2]



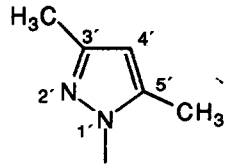
b
(mim)



c
(bzim)



d
(pz)



e
(dmpz)

Results and Discussion

2′-Methylimidazole derivative 2b

In this case the substituent at positions 2 and 3 are a 2′-methylimidazol-1′-yl. A freshly prepared solution presents the following signals in ^1H NMR spectroscopy at 500 MHz:

Table 1. ^1H NMR signals of a recently prepared solution of **2b** in [$^2H_6$]DMSO

δ	intensity	multiplicity	assignment
1.956	77	s	Me
2.133	428	s	Me
6.527	78	d	imidazole
6.595	72	d	imidazole
6.663	14	d	imidazole
7.002	14	d	imidazole
7.020	158	s	aromatic (H_5, H_6)

The signals corresponding to both forms are clearly observed (only the aromatic protons at 7.020 ppm are not split) one of them (signals at 2.133, 6.527 and 6.595) being more abundant than the other (signals at 1.956, 6.663 and 7.002). From the reported intensities the mixture corresponds to 85%-15%. A few hours later, the populations became nearly the same: 56%-44% (Table 2).

Table 2. ^1H NMR signals of an equilibrated solution of **2b** in [$^2H_6$]DMSO

δ	intensity	multiplicity	assignment
1.956	89	s	Me
2.134	125	s	Me
6.516	39	d	imidazole
6.600	34	d	imidazole
6.670	28	d	imidazole
6.970	31	d	imidazole
7.020	74	s	aromatic (H_5, H_6)

The first conclusion is that **2b** in the solid state is almost certainly a unique form and that after dissolution an equilibrium of the two forms (the original one remaining slightly predominant) is attained. The barrier to the racemization should be between 15 and 25 kcal mol^{-1} in order to observe both separate signals in NMR and an isomerization process taking between minutes and hours to reach the equilibrium.

An hmqc experiment correlates the ^{1}H and the ^{13}C spectra (protonated carbon atoms) of the equilibrium mixture (Table 3).

Table 3. Results of the hmqc experiment

$\delta^{1}H$	6.52	6.60	6.67	6.97	7.02
$\delta^{13}C$	119.6	126.7	126.1	121.4	116.8

The geometries of both forms have been optimized using the semi-empirical method AM1:[7] a list of relevant distances between protons in the two imidazole substituents is reported in Table 4 [(2) and (3) represent the imidazole rings at positions 2 and 3 of the 1,4-dihydroxybenzene].

Table 4. Distances, in Å, between protons of the *d,l* isomer in **2b**

H_5-(2)-CH_3(3) = H_5-(3)-CH_3(2)	4.18, 4.35, 2.80
H_4-(2)-CH_3(3) = H_4-(3)-CH_3(2)	6.70, 6.83, 5.44

The n.O.e. experiments yield the following results: irradiation of the methyl signal at 1.965 ppm produces no effect while irradiation of the methyl signal at 2.134 ppm produces an n.O.e. efect on the proton at 6.52 ppm. From these experiments the following conclusions can be deduced:

i) The signals at 1.956 and 2.133 ppm belong to the *meso* and *d,l* forms respectively.

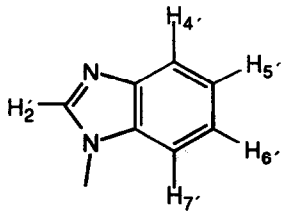
ii) The signal at 6.52 ppm is the imidazole H_5 proton of the *d,l* form.

iii) The most abundant isomer is the *d,l* (2.133, 6.527 and 6.595 ppm) and the minor one is the *meso* (1.956, 6.663 and 7.002 ppm).

iv) In the solid state only the *d,l* form is present.

Benzimidazole derivative 2c

The ^{1}H-NMR spectrum of compound **2c** in [$^{2}H_6$]DMSO (500 MHz) shows two groups of signals, corresponding to the *meso* and *d,l* isomers, of almost the same intensity. The relative intensities do not change with time. Moreover, raising the temperature does not produce any broadening of these signals.



The assignment of the two ABCD systems corresponding to $H_{4'}$, $H_{5'}$, $H_{6'}$ and $H_{7'}$ protons of benzimidazole rings was carried out through a COSY experiment. The following coupling paths were found corresponding to $^3J_{ortho}$ couplings:

7.46(d) ⇔ 7.10(t) ⇔ 7.13(t) ⇔ 7.27(d)
7.45(d) ⇔ 7.02(m) ⇔ 6.97(t) ⇔ 7.00(m)

This experiment does not allow:
i) to determine the sequence order, i.e. which is $H_{4'}$ and which $H_{7'}$;
ii) to assign $H_{2'}$ signals;
iii) to identify the *meso* and *d,l* isomers.

All these problems can be solved simultaneously with n.O.e. experiments. According to its AM1 optimized geometry, the *d,l* isomer has an axis of symmetry, thus the distances (2)-(3) and (3)-(2) are the same. The shortest distance between protons of both benzimidazole substituents (see Table 5) is $H_{2'}(2)$-$H_{7'}(3)$[$H_{2'}(3)$-$H_{7'}(2)$]=3.80 Å.

Table 5. Distances, in Å, between protons of the *d,l* isomer in **2c**

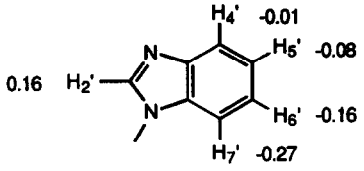
$H_{2'}(2)$-$H_{4'}(3)$/$H_{2'}(3)$-$H_{4'}(2)$	5.56
$H_{2'}(2)$-$H_{5'}(3)$/$H_{2'}(3)$-$H_{5'}(2)$	5.98
$H_{2'}(2)$-$H_{6'}(3)$/$H_{2'}(3)$-$H_{6'}(2)$	5.27
$H_{2'}(2)$-$H_{7'}(3)$/$H_{2'}(3)$-$H_{7'}(2)$	3.80

Irradiation of the proton at 8.174 ppm does not produce any observable n.O.e. effect, thus it can be assigned to proton $H_{2'}$ of the *meso* isomer. On the other hand, irradiation of the 8.013 ppm signals produces a weak n.O.e. effect on the signal at 7.27 ppm. Consequently, these last signals belong to protons $H_{2'}$ and $H_{7'}$ of the *d,l* isomer. We only have to make the hypothesis that the ABCD sequences of both isomers are the same to have the complete assignment of Table 6.

Table 6. Complete assignment of *meso* and *d,l* isomers of compound **2c**

Protons	*meso*	*d,l*
$H_{2'}$	8.174	8.013
$H_{4'}$	7.45	7.46
$H_{5'}$	7.02	7.10
$H_{6'}$	6.97	7.13
$H_{7'}$	7.00	7.27

The differences, $\Delta\delta = \delta_{meso} - \delta_{d,l}$, are represented below:



These differences, positive for $H_{2'}$ and negative for the ABCD system, correspond to the shielding effects of the benzene ring.

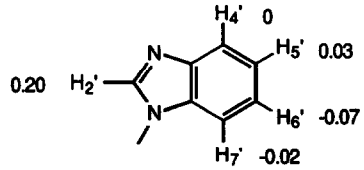
We have calculated the Johnson-Bovey coordinates,[8,9] of the *meso* and *d,l* aromatic protons with regard to the center of the benzene of the opposite benzimidazole ring (Table 7):

Table 7. Coordinates (in Å)[a] of the aromatic protons of *meso* and *d,l* isomers of compound **2c** with regard to the center of the benzene ring

	meso		*d,l*	
Protons	*z*	*p*	*z*	*p*
$H_{2'}$	3.28	4.41	3.26	2.98
$H_{4'}$	6.20	0.64	5.98	2.90
$H_{5'}$	5.69	2.68	5.40	5.33
$H_{6'}$	3.76	3.97	3.56	6.41
$H_{7'}$	2.22	3.59	2.18	5.59

[a]These values must be divided by 1.39 before using them in Appendix B of reference 9 where the definitions of *z* and *p* are reported.

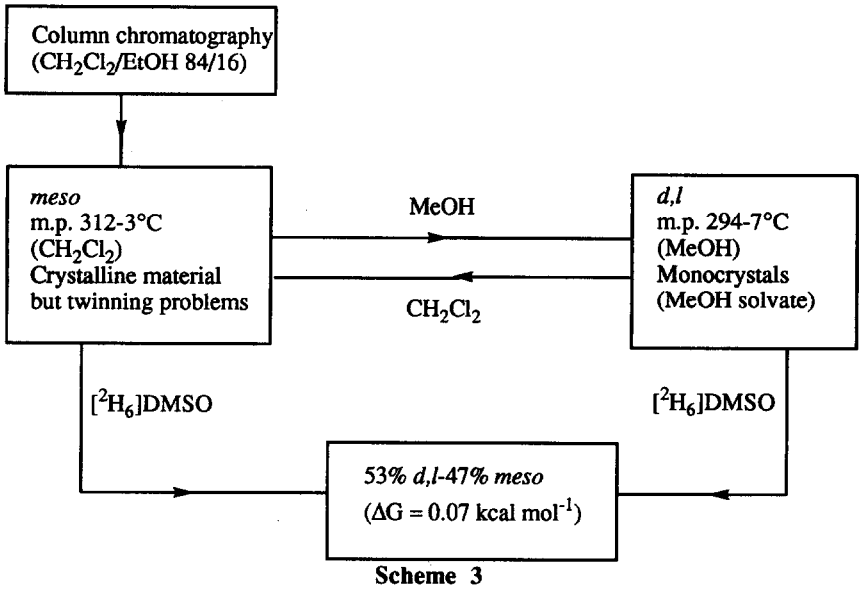
With these coordinates and the table of reference 9, the shielding values in ppm can be calculated. The differences, $\Delta\delta = \delta_{meso} - \delta_{d,l}$, are represented below:



Taking into account the simplifications we have used (neglecting the anisotropy of the imidazole ring, for instance) the agreement is acceptable and can be considered a supplementary proof of the correct assignment of the *meso* and *d,l* isomers.

Once having identified both isomers of compound **2c** in solution, we can come back to the structure in the solid state. In this case only, we have succeeded (by a combination of column chromatography and solvents of crystallization) in isolating both isomers in the solid state, which constitutes a case of conformational polymorphism. These pure isomers when their ^{1}H-NMR spectra are recorded in [$^2H_6$]DMSO or in [$^2H_4$]methanol, immediately after the solution was prepared and using only a few scans, show that the

corresponding signals represent more than 80% of the mixture. Rapidly both mixtures (80% *meso*-20% *d,l* and 80% *d,l*-20% *meso*) evolve to the equilibrium mixture formed by 53% *d,l*-47% *meso*. The following scheme summarizes the experiments we have carried out on **2c** polymorphs.



Scheme 3

Pyrazole derivative 2d

The structure of this compound has been determined by X-ray crystal analysis:[1] the compound exists in the solid state as the *d,l* isomer. It shows in ^1H and ^{13}C NMR in solution only one series of peaks which must correspond to this isomer or to a rapid (on the NMR time scale) equilibrating mixture of *meso* and *d,l* isomers.[1]

3',5'-Dimethylpyrazole derivative 2e

The *d,l* structure of this compound has also been determined by crystallography.[1] It shows in ^1H and ^{13}C NMR spectroscopy in solution only one series of peaks which must correspond to the *d,l* isomer or to a rapid (on the NMR time scale) equilibrating mixture of *meso* and *d,l* isomers.[1] We have now determined that a solution of **2e** in $CDCl_3$ does not present any new peak one month afterwards (the same result is obtained after 24 h at 60°C in $CDCl_3$ as well as after one week at 135°C in [$^2H_{10}$]-*p*-xylene, but heating at 150°C in DMSO produces the decomposition of the sample).

Solid State ^{13}C CPMAS NMR Results

The solid state ^{13}C NMR chemical shifts of compounds **2b**, **2c** (*meso* and *d,l* isomers), **2e** and **5c** have been obtained using the CPMAS technique (see experimental part). The spectra corresponding to compounds **2b** and **2e** present very narrow well-resolved signals proving that nothing dynamic is taking place; there is one signal per carbon atom, thus neither disorder nor a mixture of isomers are present. The following signals were

observed, for compound **2b:** 147.3 (C_1,C_4), 121.9 (C_2,C_3), 117.1 (C_5,C_6), 147.3 ($C_{2'}$), 124.9 ($C_{4'}$), 121.9 ($C_{5'}$), 11.8 ppm (CH_3) and for compound **2e**: 147.6 (C_1,C_4), 124.2 (C_2,C_3), 121.1 (C_5,C_6), 149.0 ($C_{3'}$), 104.6 ($C_{4'}$), 144.0 ($C_{5'}$), 13.1 (CH_3-3), 11.6 ppm (CH_3-5).

By comparison with the values in solution (*d,l* isomer, Table 11) for **2b** and ref. 1 for **2e**, the $\Delta\delta = \delta_{solid} - \delta_{solution}$, can be calculated.The largest effects are observed for carbons $C_{2'}$ (+2.6 ppm) and $C_{5'}$ (+2.5 ppm) of **2b** and for carbons $C_{3'}$ (+2.5 ppm) and $C_{5'}$ (+2.6 ppm) of **2e**. For the 2-methylimidazole derivative **2b** we have used the values corresponding to the *d,l* isomer, but the differences between both isomers, *d,l* and *meso*, are very small (less than 1 ppm except for carbon $C_{5'}$ where the difference amounts to 2.0 ppm, Table 11). Thus, although the ^{13}C solid state chemical shifts are consistent with the fact that both are *d,l* isomers (see the consistency of the $\Delta\delta$ values for heterocyclic carbons α to nitrogen atoms), solution ^{13}C NMR chemical shifts cannot be used for establishing the isomeric structure in the solid state of this kind of atropisomerism.

The ^{13}C CPMAS NMR spectra of compound **5c** shows the following signals: 144.6 (C_1,C_4), 110.0 (C_2,C_3), 126.7 and 127.8 (C_{4a},C_{8a}), 123.9 (C_5,C_8), 129.0 (C_6,C_7), 144.6 ($C_{2'}$), 140.2 ($C_{3'a}$), 117.0 ($C_{4'}$), 123.9 ($C_{5'}$), 123.9 ($C_{6'}$), 110.0 ($C_{7'}$) and 134.2 ppm ($C_{7'a}$). Carbon atoms C_{4a} and C_{8a}, related by symmetry in the isolated molecule, are split. We tentatively assign this splitting (two signals of the same intensity) to a decrease in the symmetry in the solid state compared to the solution.

The two polymorphs of compound **2c**, the *meso* and the *d,l*, show quite different ^{13}C CPMAS NMR spectra. Since the differences between both isomers in solution (Table 14) are very small (generally 0.0 or 0.1 ppm; only $C_{6'}$ shows a difference of 0.4 ppm), this proves two things: i) that solid state ^{13}C chemical shifts cannot be used to determine the *meso* or the *d,l* structure of compound **2c**; ii) that the differences between solid state and solution ^{13}C chemical shifts, which can amount 2-3 ppm, are due to crystal effects and not to isomerism:

meso: 148.9 ($\Delta\delta$ = 1.8 ppm) (C_1, C_4), 122.2 ($\Delta\delta$ = 1.2 ppm) (C_2, C_3), 119.9 ($\Delta\delta$ = 1.5 ppm) (C_5, C_6), 147.3 ($\Delta\delta$ = 2.3 ppm) ($C_{2'}$), 140.0 and 141.2 ($\Delta\delta$ = -1,2 and -2.4 ppm) ($C_{3'a}$), 119.9 ($\Delta\delta$ = 0.4 ppm) ($C_{4'}$), 122.2 ($\Delta\delta$ = -0.4 ppm) ($C_{5'}$), 124.2 ($\Delta\delta$ = 0.6 ppm) ($C_{6'}$), 110.4 and 113.5 ($\Delta\delta$ = -0.6 and 2.5 ppm) ($C_{7'}$), 132.6 ($\Delta\delta$ = -1.7 ppm) ($C_{7'a}$).

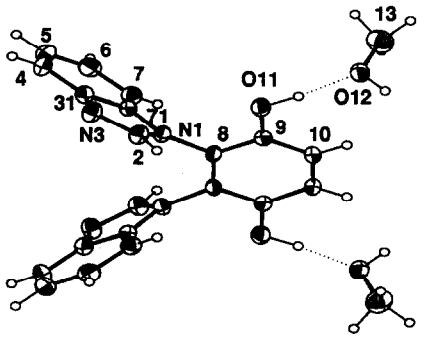
d,l: 146.2 ($\Delta\delta$ = -0.9 ppm) (C_1, C_4), 119.3 ($\Delta\delta$ = -1.7 ppm) (C_2, C_3), 119.3 ($\Delta\delta$ = 0.9 ppm) (C_5, C_6), 146.2 ($\Delta\delta$ = 1.2 ppm) ($C_{2'}$), 140.7 ($\Delta\delta$ = -1,7 ppm) ($C_{3'a}$), 119.3 ($\Delta\delta$ = -0.2 ppm) ($C_{4'}$), 123.2 ($\Delta\delta$ = 0.6 ppm) ($C_{5'}$), 126.5 ($\Delta\delta$ = 2.9 ppm) ($C_{6'}$), 110.2 ($\Delta\delta$ = -0.8 ppm) ($C_{7'}$), 133.1 ($\Delta\delta$ = -1.2 ppm) ($C_{7'a}$). Only the *meso* isomer shows splittings (affecting $C_{3'a}$ and $C_{7'}$) which can be due to a less symmetric structure, for instance, to the fact that the dihedral angles C_2-$C_{1'}$ and C_3-$C_{1'}$ are different. The $\Delta\delta$ values are probably related to differences in hydrogen bonding between the solid state and the solution.

Experimental evidence: X-ray structure determination of compound 2c.

Although the structure of both polymorphs of compound **2c** can be established by recording their ^1H NMR spectra in freshly prepared solutions (see previously), it was decided to determine their X-ray structures. Unfortunately, only the *d,l* isomer yields monocrystals while those of the *meso* isomer proved unsuitable for X-ray diffraction (twining).

Crystals of **2c**-*d,l* were obtained by slow evaporation of a methanolic solution using the compound isolated by column chromatography. The main geometrical parameters are shown in Table 8 according to the numbering scheme shown in Fig. 1a.[10] The molecules correspond to the *d,l* isomer, the torsion of the benzimidazole substituents with regard to the central ring being given by the C(9)-C(8)-N(1)-C(2) angle of

(a)



(b)

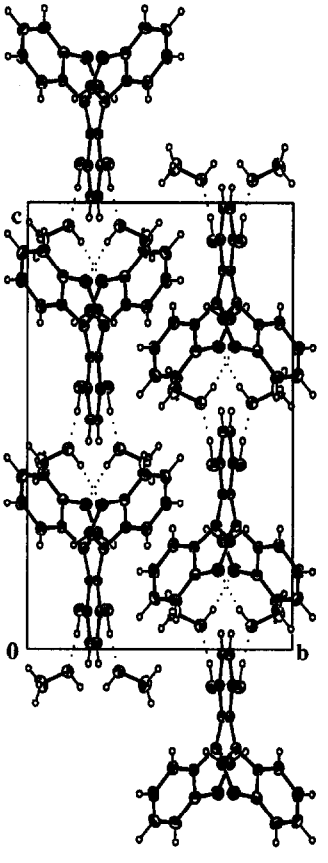


Fig.1. (a) Molecular structure illustrating the numbering system. (b) Packing diagram showing the two centrosymmetrically chains of molecules along the c axis.

-64.9(4)°. They present a two-fold crystallographic axis going through the middle of the molecule which is characteristic of a *d,l* isomer. The two hydroxyl groups have an EE orientation (see **§Semiempirical AM1 calculations**) with respect to the benzimidazole substituents, while compound **2e** was an EZ isomer[1] and compound **2d** was a ZZ isomer,[1] due to hydrogen bonds with the methanol guests. The conformation of the OH groups is given by the torsion angle C(10)-C(9)-O(11)-H(11) = 3(3)°. Bond distances and angles compare well with those of the similar compounds **2d** and **2e**.[1] In the benzimidazoles, the C(2)-N(3) bond has a double bond character and the condensed benzene ring is largely delocalized. The central hydroquinone ring shows a double bond character for the C(10)-C(10') bond [1.375(4) Å]. The molecules are arranged in centrosymmetric chains joined by OH···O/N hydrogen bonding interactions (see Table 8 and Fig. 1b) involving the methanol groups. In this way, the hydroquinone OH groups act as HB donors towards acceptor methanol molecules which are also HB donors towards the benzimidazole N(3) atom of another molecule, resulting in a chain along the **c** axis. If one considers the isolated **2c** molecule as the primary structure, these strong HB linked chains forms the secondary structure. Finally, the tertiary structure, a bunch of chains along the **c** axis, is formed by a series of parallel secondary structures held together by aromatic ring attractive interactions of benzimidazoles (see Table 8 and Fig. 1b).

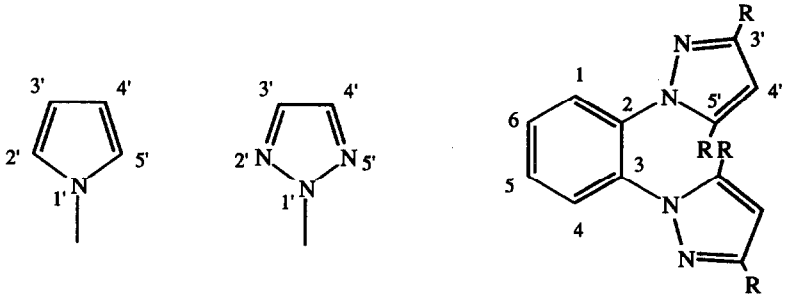
Table 8. Selected geometrical parameters and hydrogen bonds (Å, °). C(31-71) and C(8-10) stand for the centroids of the C(31), C(4),···C(71) and C(8), C(9),···C(8') rings.

N(1)-C(2)	1.362(4)	C(2)-N(3)	1.315(4)	N(1)-C(8)	1.430(3)
C(3)-C(31)	1.391(4)	C(9)-O(11)	1.350(3)	C(31)-C(71)	1.398(4)
C(9)-C(10)	1.395(4)	O(12)-C(13)	1.399(5)		
C(9)-C(8)-N(1)	119.6(2)	C(8)-N(1)-C(2)	128.1(2)	C(2)-N(1)-C(71)	106.6(2)
C(8)-N(1)-C(71)	125.3(2)	N(1)-C(2)-N(3)	113.6(3)	C(2)-N(3)-C(31)	104.7(2)
N(3)-C(31)-C(71)	110.1(2)	C(31)-C(71)-N(1)	105.1(2)		
C(9)-C(8)-N(1)-C(2)		-64.9(4)			
X-H···Y		X-H	X···Y	H···Y	X-H···Y
O(11)-H(11)···O(12)		0.99(5)	2.655(3)	1.67(5)	172(5)
O(12)-H(12)···N(3) (x, 1/2-y,-1/2+z)		0.90(6)	2.844(3)	2.01(6)	153(5)
C(2)-H(2)···C(31-71) (1-x, -1/2-y,1/2-z)		1.01(4)	4.200(3)	3.22(4)	164(3)
C(7)-H(7)···C(31-71) (-1/2+x, 1-y,1/2-z)		0.85(4)	4.184(3)	3.44(4)	147(3)
C(13)-H(133)···C(8-10) (1-x, 1-y,-z)		1.03(9)	4.052(5)	3.39(10)	124(6)

Compound **2c**, after purification by column chromatography, is in the *meso* form. Crystallization in methanol transforms the *meso* isomer into the methanol solvate of the *d,l* form. The crystalline structure of the methanol solvate is stable only in the presence of methanol. Open to air, it becomes a white non-transparent solid which corresponds to the pure **2c** compound (no traces of methanol in the ^{1}H NMR spectrum). If this compound is dissolved in [$^2H_6$]DMSO and the spectrum recorded in less than 2 min time, a mixture containing more than 80% of the *d,l* isomer is observed, then the spectrum evolves towards a 65%-35% mixture of *d,l* and *meso* isomers (3 min later) to finally reach the 53%-47% equilibrium mixture. Thus, when compound **2c** crystallizes in the *d,l* form, the solvent is necessary to maintain the lattice but not to stabilize this form: once formed, the *d,l* isomer is stable in the solid state; loss of methanol solvent destroys the lattice but does not modify the isomeric composition.

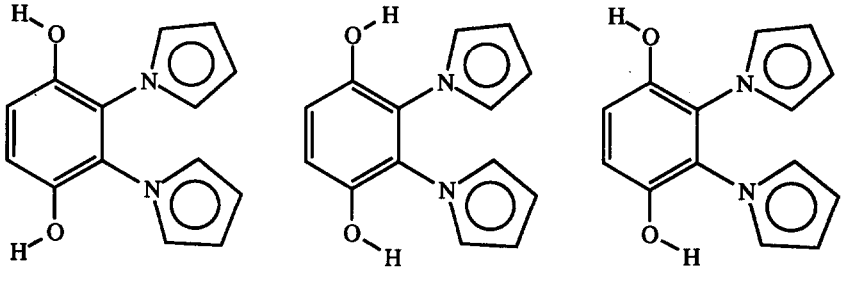
Semiempirical AM1 calculations

To provide some foundations to those empirical observations we have carried out a computational study (using the AM1 Hamiltonian),[7] not only on compounds **2b**, **2c**, **2d** and **2e**, but also on related compounds **2f** (bearing two pyrrole rings) and **2g** (carrying to 2*H*-1,2,3-triazole rings) which are still unknown. To understand the role of the OH groups, pyrazole derivatives, without substituents at positions 1 and 4, **6d** (R = H) and **6e** (R = CH_3) have been calculated.



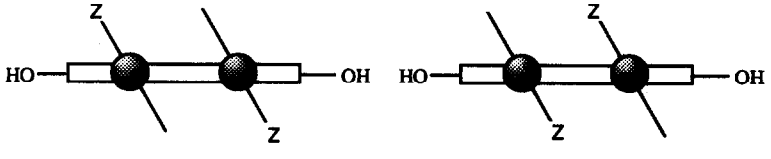
f (pyr) **g** (trz) **6**

Although in the case of derivatives **6** only the *meso* and *d,l* isomers are possible, for hydroquinones **2** the two hydroxy groups introduce another problem of isomerism: depending on their orientation with regard to the azole rings there are three isomers which we have called EE, ZZ and EZ:



EE ZZ EZ

Ground state heats of formation. We have reported in Table 9 the energies of the different minima.The convention for what we have named *d,l*-outside and *d,l*-inside are represented below.



d,l-outside *d,l*-inside

Table 9. Heats of formation (in kcal mol^{-1}) of the minima corresponding to *meso* and *d,l* isomers of compounds **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **6d** and **6e** (after complete geometry optimization). In brackets, the dipole moment (in D)

Compound	*meso*			*d,l*		
	EE	ZZ	EZ	EE	ZZ	EZ
2b	63.14 [8.35]	59.08 [3.80]	61.04 [6.10]	62.49 [8.13][b]	58.46 [3.42][b]	60.39 [5.78][b]
				63.69 [8.48][c]	59.54 [3.73][c]	61.53 [6.11][c]
2c	110.03 [7.31]	106.76 [3.37]	109.04 [5.46]	110.39 [7.74][c]	105.81 [2.87][c]	107.76 [5.29][c]
2d	109.34 [4.85]	105.68 [2.20]	108.25 [3.08]	109.03 [3.46][b]	104.53 [1.09][b]	106.67 [1.27][b]
				107.50 [4.82][c]	105.12 [0.38][c]	106.19 [2.57][c]
2e	80.81 [4.93]	76.04 [2.78]	77.97 [3.31]	78.98 [4.42][d]	74.92 [0.79][d]	77.28 [1.59][d]
2f[a]		50.34 [0.60]			50.34 [0.60]	
2g[a]		161.90 [2.24]			161.90 [2.24]	
6d		190.96 [3.68]		189.84 [0.88][b]	190.18 [2.81][c]	
6e		162.40 [4.01]			161.52 [1.77][d]	

[a]In these compounds, due to the C_S symmetry of the azole, the *meso* and *d,l* isomers are identical (only the ZZ conformation was calculated); [b] With the nitrogen atoms (positions 2 or 3) outside; [c] With the nitrogen atoms (positions 2 or 3) inside; [d] In these cases, the azole ring is orthogonal and outside and inside are identical.

The results of Table 9 can be summarized as follows:

i) The *d,l* isomer appears always more stable than the *meso* one, although the differences are quite small. Considering only the most stable conformations, the differences amount to **2b** 0.62, **2c** 0.95, **2d** 1.15, **2e** 1.12, **6d** 1.12 and **6e** 0.88 kcal mol^{-1}. The most stable structures for compounds **2d** and **2e** are in agreement with those found in the solid state by X-ray crystallography.[1] For compound **2c** we have isolated the *meso* isomer by column chromatography and the *d,l* by crystallization (although it contains methanol in the lattice, the loss of methanol by evaporation does not affect the isomerism); the only possible conclusion is that both forms are of similar energy.

ii) The ZZ conformation is always the most stable, the EZ one lies about 2 kcal mol^{-1} higher, and the EE another 2 more kcal mol^{-1} higher. In the solid state (X-ray structures), this conclusion is affected by HBs with the solvent of crystallization. The same problem is probably involved in solution depending on the HB donor or acceptor character of the solvent used.

iii) The relative stabilities of the *d,l*-outside and inside conformations (remember that all the values of Table 9 are true minima) depends on the heterocycle: for **2b** (mim) the outside (lone pairs far away) is the most stable; for **2c** (bzim) only the inside (benzene rings far away) can be calculated, the outside conformation is probably not a minimum; for **2d** (pz) the stability depends on the conformation of the OH groups.

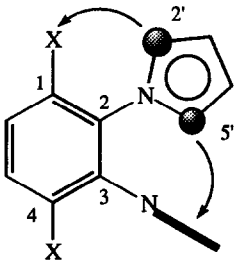
Transition state heats of formation. We have reported in Table 10 the energies associated with those transition states which we have been able to locate. The differences between the transition states and the minimum (the ***d,l*** value of Table 9) correspond to the isomerization barriers. Since most of these heterocycles

lack a C_2 axis, there are two different ways to be coplanar [for instance, for **2b**, methyl group outside (H) and methyl group inside (Me)].

Table 10. Heats of formation (in kcal mol^{-1}) of the transition states corresponding to compounds **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **6d** and **6e** (after complete geometry optimization). In square brackets, the dipole moment (in Debye units)

Compound	Transition state		Difference in kcal mol^{-1} between the transition state and the *d,l* minimum	
2b	77.18 [4.91] (H)	80.12 [5.28] (Me)	18.72 (H)	21.66 (Me)
2c	123.47 [4.81] (H)	------ (Bz)	17.66 (H)	>> 25 (Bz)
2d	109.86 [6.07] (lp)	113.55 [5.58] (H)	5.02 (lp)	9.02 (H)
2e	90.27 [3.07] (lp)	(94.34) (Me)	15.35 (lp)	(19.42) (Me)
2f	58.85 [2.47] (H)		8.51 (H)	
2g	166.21 [2.47] (lp)		4.31 (lp)	
6d	193.32 [3.50] (lp)	195.25 [2.36] (H)	3.48 (lp)	5.41 (H)
6e	167.58 [3.50] (lp)	176.07 [1.75] (Me)	6.06 (lp)	14.55 (Me)

To discuss these barriers and also to verify their internal consistency we have assumed a very simple model: the origin of the barrier is the sum of the interactions between the 'planar' azole (represented only by its position 2' and 5') and the substituent at position 1 (an OH or an H) on one hand and the 'perpendicular' azole on the other. The interactions are, with regard to position 1: H/H, H/lp (lone pair), H/Me, OH/H, OH/lp, OH/Me and OH/Bz; with regard to the 'perpendicular' azole ring: H/Az, lp/Az and Me/Az (the interaction Bz/Az should be much too important to obtain a transition state, for this reason in Table 10 we have added >> 25 kcal mol^{-1}). 2,3-Dipyrrolylbenzene **6f** was taken as reference compound (H/H and H/Az). The results of the multiple regression are: 12 values, 8 variables, $r^2 = 0.992$. Constant = 7.5 (corresponds to **6f**), H/lp = -2.9, H/Me = 1.8, OH/H = 2.6, OH/lp = 1.2, OH/Me = 11.5 and OH/Bz = 10.1; lp/Az = -4.0, Me/Az = 10.7 (all values in kcal mol^{-1}). With this equation the value 19.42 for compound **2e** (isomerization by the methyl group) has been calculated and added between parentheses to Table 10.



X = H, OH

2' = H, lp, Me, Bz

5' = H, lp, Me

Concerning the interactions with the substituent at position 1, the barrier is lower for H than for OH and the difference increases for bulky Me and Bz (fused benzene ring) groups. Thus, for hydroquinones, a methyl group or a fused benzene ring near the OH contributes significantly to the barrier (about 10 kcal mol^{-1}). The order of bulkiness is: lone pair < H < fused benzene ≤ methyl group. Concerning the other interactions, the order is lone pair (-4 kcal mol^{-1}), H (0 by definition) and methyl group (10.7 kcal mol^{-1}). A hydroquinone with two 2,5-dimethylpyrryl substituents should have a barrier of about 30 kcal mol^{-1} and the *meso* and *d,l* isomers should be separable.

Conclusion. We can summarize the experimental results with regard to the isomerism between the *meso* and *d,l* forms: in the solid state all these *ortho*-substituted hydroquinones exist as pure isomers: *d,l* for compounds **2b**, **2c**, **2d** and **2e**, and additionally *meso* for compound **2c**. When these compounds are dissolved, they evolve towards nearly 50:50 mixtures of *meso* and *d,l* forms. Two situations are possible: i) the barrier is relatively high and the evolution can be followed by NMR (that is the case of benzimidazole **2c**, quite rapid, and of 2-methylimidazole **2b**, more slowly); ii) the barrier is lower and only average signals corresponding to both isomers are observed (case of pyrazole derivatives **2d** and **2e**). Although we have succeeded in obtaining *meso* and *d,l* conformational polymorphs only in the case of **2c**, this does not exclude the existence of similar polymorphs for the other compounds since the differences in energy are always quite small.

We consider that the barriers calculated using the AM1 Hamiltonian are a good approximation of the reality, perhaps not the absolute values, but certainly their relative order: **2d** (5.02) < **2e** (15.35) < **2c** (17.66) < **2b** (18.72).

Compound **2b**. This compound in the solid state has been isolated as the *d,l* isomer. When dissolved, it evolves to an equilibrium mixture of 56% *d,l*-44% *meso* ($\delta\Delta H$ = 0.14 kcal mol^{-1} while the AM1 method lead to $\delta\Delta H$ = 0.62 kcal mol^{-1}). It takes half an hour to reach the equilibrium, that is between 15-20 kcal mol^{-1} of activation energy, which is consistent with the AM1 calculated value (18.7 kcal mol^{-1}, proton inside).

Compound **2c**. This compound in the solid state can be isolated either as a *meso* or a *d,l* isomer, i.e. it shows **conformational polymorphism**. In solution, both isomers evolve rapidly towards a 53:47 mixture of both isomers ($\delta\Delta H$ = 0.07 kcal mol^{-1} while the AM1 method leads to $\delta\Delta H$ = 0.95 kcal mol^{-1}). In both cases, the equilibria are more rapidly attained than in the preceding case, which corresponds to a slight decrease in the calculated barrier (17.7 kcal mol^{-1}).

Compound **2d**. In the solid state, this compound exists as the *d,l* isomer.[1] In solution, the equilibrium should be rapidly attained (calculated $\delta\Delta H$ = 1.15 kcal mol^{-1}) but since the barrier is too low ($\delta\Delta H^{\ddagger}$ = 5.0 kcal mol^{-1}), only averaged signals are observed.

Compound **2e**. This compound has been isolated in the solid state as the *d,l* isomer.[1] We think that the solution ^1H NMR spectrum corresponds to a rapidly equilibrating mixture of both isomers (calculated $\delta\Delta H$ = 1.12 kcal mol^{-1}). However, the calculated activation barrier ($\delta\Delta H^{\ddagger}$ = 15.4 kcal mol^{-1}), seems too high to be consistent with the observation that the signals remain narrow even at 173 K in [$^2H_6$]methanol ($\Delta H^{\ddagger} \leq 10$ kcal mol^{-1}). We cannot exclude that only the *d,l* isomer is present in solution.

Experimental

General. Melting points were determined in a capillary tube and are uncorrected. Column chromatography was performed on silica gel Merck 60 (70-230 mesh). The R_f were measured on tlc aluminium sheets of silicagel 60 F_{254} (layer thickness 0.2 mm) with the eluent indicated in each case.

^1H and ^{13}C NMR Spectroscopy. The ^1H and ^{13}C NMR spectra in solution were recorded on a Bruker AC 200 instrument working at 200.14 and 50.32 MHz. Chemical shifts (δ) are given from internal tetramethylsilane with an accuracy of 0.01 (for ^1H NMR) and 0.1 (for ^{13}C NMR) ppm. Coupling constants (J) are accurate to ± 0.2 and ± 0.6 Hz, respectively. Tables 10 and 11 reports the ^1H and ^{13}C NMR spectra of imidazole derivatives, Tables 12 and 13 reports the ^1H and ^{13}C NMR spectra of benzimidazole derivatives.

The ^1H NMR solution spectra at 499.84 MHz (on a Varian UNITY-500 spectrometer) were collected in 20800 data points over a 5490 Hz spectral width (1.9 s acquisition time) and zero filled to 32 K before Fourier transformation. Homonuclear $^1H\{^1H\}$ n.O.e.s were determined by means of n.O.e. difference technique using an irradiation time of 10 s and 20 Hz of decoupling power. Double-quantum filtered COSY 2D NMR spectra were acquired in the phase-sensitive mode. Data were collected in a 1024x256 matrix with a spectral width of 910 Hz and 1 s of relaxation delay and then processed in a 1024x1024 matrix. 2D inverse proton detected heteronuclear shift correlation spectra were obtained using the hmqc pulse sequence. Data were collected in a 2048x512 matrix with a spectral width of 5490 Hz in the proton domain and 20000 Hz in the carbon domain, and processed in a 2048x1024 matrix. The experiment was optimized for one bond heteronuclear coupling constant of 180 Hz. The null time was empirically optimized at 300 ms.

The ^{13}C solid-state spectra of pure compounds have been registered on a Bruker AC 200 spectrometer working at 50.32 MHz under conditions of CP (cross polarization) and MAS (magic angle spinning), using a 7 mm Bruker DAB 7 probehead which achieves rotation frequencies about 3.5-4.5 kHz. The standard CP/MAS pulse sequence was applied with 7 ms ^1H-90° pulse width, 3-5 ms contact pulses and 5 s repetition time, the spectral width being 20,000 Hz. All chemical shifts are given with respect to the spectrometer reference frequency which was calibrated by the glycine signal at 176.1 ppm.

AM1 semiempirical calculations were carried out using the standard program implemented in the MOPAC 6.0 package.[11] The reported energies correspond to fully optimized geometries. Force constants matrices have been calculated in all cases to determine if the ΔH_f values corresponds to minima or to transition states according to the number of imaginary frequencies.

Synthetic procedures.

Addition of imidazole to 1,4-benzoquinone. To a solution of 1,4-benzoquinone (0.79 g, 7.31 mmol) in dioxane (5 mL) was added imidazole (0.497 g, 7.31 mmol). The reaction was stirred for 1 h at rt, and the solvent was evaporated in vacuo. The ^1H NMR spectrum of the reaction crude revealed the presence of 2-(imidazol-1´-yl)-1,4-dihydroxybenzene (31%), 2,3-bis(imidazol-1´-yl)-1,4-dihydroxybenzene (28%) and 2,5-bis(imidazol-1´-yl)-1,4-dihydroxybenzene (41%). Pure compounds were isolated by chromatography using as eluent 8:2 dichloromethane/ethanol: *2-(imidazol-1´-yl)-1,4-dihydroxybenzene* (**1a**): (R_f 0.32) mp. 198-200°C (ethanol); IR (KBr) 3490-2900 cm^{-1} (OH), 2770-2080 cm^{-1} (OH); MS, m/z 176 (100, M^+); Anal. $C_9H_8N_2O_2$; Calc. (%): C, 61.36; H, 4.58; N, 15.90. Found (%): C, 61.00; H, 4.54; N, 14.99.; *2,3-bis(imidazol-1´-yl)-1,4-dihydroxybenzene* (**2a**): (R_f 0.08) mp. 303-305°C (dimethylformamide) Lit. 302-305°C;[13] IR (KBr) 3296-2030 cm^{-1} (OH); MS, m/z 241 (100, M^+-1).; *2,5-bis(imidazol-1´-yl)-1,4-dihydroxybenzene* (**3a**): (R_f 0.03) mp. >350°C (dimethylformamide) Lit. 352-355°C;[12] IR (KBr) 3296-2080 cm^{-1} (OH); MS, m/z 242 (100, M^+).

Table 11. ^1H NMR (200.14 MHz) data in [$^2H_6$]DMSO solution of imidazole derivatives .

Compound	H_3	H_5	H_6	$H_{2'}$	$H_{4'}$	$H_{5'}$	OH-1 (4)	Others
1a	6.70(d)	6.63(dd)	6.85(d)	7.90(dd)	7.00(dd)	7.40(dd)	9.46(s)	-------
	^3J= 8.6; ^4J= 2.8			$^4J(H_{2'},H_{4'})$= 1.0			9.16(s)	
				$^4J(H_{2'},H_{5'})$= $^3J(H_{4'},H_{5'})$= 1.2				
2a	----	6.98(s)	6.98(s)	7.40(dd)	6.81(dd)	6.91(dd)	9.65(s)	-------
				$^4J(H_{2'},H_{4'})$= 1.0				
				$^4J(H_{2'},H_{5'})$=$^3J(H_{4'},H_{5'})$= 1.2				
3a	7.01(s)	-----	7.01(s)	7.92(dd)	7.04(dd)	7.41(dd)	10.0(s)	-------
				$^4J(H_{2'},H_{4'})$= 1.1				
				$^4J(H_{2'},H_{5'})$=$^3J(H_{4'},H_{5'})$= 1.3				
1b	6.53(d)	6.69(dd)	6.83(d)	----	6.82(d)	7.03(d)	9.29(s)	CH_3: 2.11(s)
	^3J= 8.7; ^4J= 2.8				$^3J(H_{4'},H_{5'})$= 1.3		9.11(s)	
2b *d,l*	----	7.02(s)	7.02(s)	----	6.52(d)	6.59(d)	9.71(s)	CH_3: 2.13(s)
					$^3J(H_{4'},H_{5'})$= 1.3			
meso	----	7.02(s)	7.02(s)	----	6.66(d)	7.00(d)	9.66(s)	CH_3: 1.95(s)
					$^3J(H_{4'},H_{5'})$= 1.3			
3b	6.82(s)	----	6.82(s)	----	6.86(d)	7.12(d)	9.80(s)	CH_3: 2.16(s)
					$^3J(H_{4'},H_{5'})$= 1.3			
5a	----	8.29(m)	7.65(m)	7.45(dd)	6.85(dd)	6.95(dd)	n.o.	-------
		(with H_8)	(with H_7)	$^4J(H_{2'},H_{4'})$=$^4J(H_{2'},H_{5'})$=$^3J(H_{4'},H_{5'})$= 1.1				

n.o.= not observed

Table 12. ^{13}C NMR (50.32 MHz) data in [$^{2}H_6$]DMSO solution of imidazole derivatives.

Compound	C_1	C_2	C_3	C_4	C_5	C_6	$C_{2'}$	$C_{4'}$	$C_{5'}$	Others
1a	142.8 ^{3}J= 9.2 ^{3}J= 7.0 ^{2}J= 2.3	125.0 ^{3}J= 6.7	112.0 ^{1}J= 158.3 ^{3}J= 5.1	150.5 ^{3}J= 9.8 ^{2}J= 3.2 ^{2}J= 3.2	115.5 ^{1}J= 159.9 ^{3}J= 5.0	118.0 ^{1}J= 159.7	137.8 ^{1}J= 212.0 ^{3}J= 9.4 ^{3}J= 6.9	127.9 ^{1}J= 189.1 ^{3}J= 10.8 ^{2}J= 10.8	120.6 ^{1}J= 192.5 ^{2}J= 16.6 ^{3}J= 3.2	-------
2a	145.5 ^{3}J= 11.0 ^{2}J= 3.7 ^{2}J= 7.3	121.1	121.1	145.5 ^{3}J= 11.0 ^{2}J= 3.7 ^{2}J= 7.3	116.8 ^{1}J= 162.0	116.8 ^{1}J= 162.0	138.2 ^{1}J= 210.9 ^{3}J= 10.6 ^{3}J= 6.4	127.7 ^{1}J= 188.5 ^{3}J= 10.9 ^{2}J= 10.9	122.0 ^{1}J= 192.2 ^{2}J= 16.7 ^{3}J= 3.2	-------
3a	142.9	123.9	113.5 ^{1}J= 160.6	142.9	123.9	113.5 ^{1}J= 160.6	137.4 ^{1}J= 211.8 ^{3}J= 10.1 ^{3}J= 6.1	128.3 ^{1}J= 188.7 ^{3}J= 10.8 ^{2}J= 10.8	120.2 ^{1}J= 192.4 ^{2}J= 16.6 ^{3}J= 3.0	-------
1b	144.6	124.9	114.2 ^{1}J= 159.1 ^{3}J= 5.4	149.9	116.4 ^{1}J= 160.0 ^{3}J= 5.4	117.3 ^{1}J= 160.0	144.6	126.5 ^{1}J= 187.0 ^{2}J= 9.6	121.3 ^{1}J= 190.3	CH_3 13.0 ^{1}J= 128.3
2b *d,l*	145.7	122.3	122.3	145.7	117.1 ^{1}J= 161.1	117.1 ^{1}J= 161.1	144.7	126.7 ^{1}J= 187.2 ^{2}J= 9.4	119.6 ^{1}J= 190.0 ^{2}J= 16.5	CH_3 12.2 ^{1}J= 128.4
meso	145.6	122.2	122.2	145.6	117.0 ^{1}J= 161.2	117.0 ^{1}J= 161.2	144.0	126.0 ^{1}J= 187.3 ^{2}J= 9.7	121.4 ^{1}J= 191.4 ^{2}J= 16.3	CH_3 12.0 ^{1}J= 128.4
5a[a]	143.3	113.8	113.8	143.3	123.8 (with C_8) ^{1}J= 162.6 ^{3}J= 4.0	129.0 (with C_7) ^{1}J= 165.8 ^{3}J= 8.0	139.0 ^{1}J= 224.3 ^{3}J= 5.3 ^{3}J= 5.3	124.9 ^{1}J= 205.1 ^{2}J= 12.7 ^{3}J= 4.2	121.0 ^{1}J= 204.1 ^{2}J= 11.8 ^{3}J= 6.5	C_{4a}= 127.1 C_{8a}= 127.1

[a] Due to the insolubility of this compound, the ^{13}C NMR spectrum was registered in a mixture of [$^{2}H_6$]DMSO/CF_3CO_2H. See ref. 12 for assignments.

Table 13. ^{1}H NMR (200.14 MHz) data in [$^{2}H_6$]DMSO solution of benzimidazole derivatives .

Compound	H_3	H_5	H_6	$H_{2'}$	$H_{4'}$	$H_{5'}$	$H_{6'}$	$H_{7'}$	OH-1 (4)
1c	6.79(d) ^{3}J= 9.5; ^{2}J= 3.1	6.76(d)	6.94(d)	8.29(s)	7.69(m)	7.23(m)	7.25(m)	7.29(m)	9.38(s) 9.19(s)
2c *d,l*	----	7.17(s)	7.17(s)	8.01(s)	7.46(d)	7.10(t)	7.13(t)	7.27(d)	9.81(s)
meso	----	7.18(s)	7.18(s)	8.17(s)	7.45(d)	7.02(m)	6.97(t)	7.00(m)	9.78(s)
3c	7.17(s)	----	7.17(s)	8.42(s)	7.77(m)	7.29(m)	7.31(m)	7.44(m)	9.98(s)
5c *d,l*	----	8.36(m) (with H_8)	7.73(m) (with H_7)	7.82(s)	7.46(m)	7.15(m)	7.15(m)	7.29(m)	9.64(s)
meso	----	8.36(m) (with H_8)	7.73(m) (with H_7)	8.19(s)	7.46(m)	6.96(m)	6.96(m)	6.96(m)	9.68(s)

Table 14. ^{13}C NMR (50.32 MHz) data in [$^{2}H_6$]DMSO solution of benzimidazole derivatives .

Compound	C_1	C_2	C_3	C_4	C_5	C_6	$C_{2'}$	$C_{3'a}$	$C_{4'}$	$C_{5'}$	$C_{6'}$	$C_{7'}$	$C_{7'a}$
1c	144.3	123.0	113.5 ^{1}J= 157.2	150.2	116.3 ^{1}J= 170.3	117.8 ^{1}J= 160.3	144.3 ^{1}J= 209.6	143.0	119.5 ^{1}J= 159.6	121.9 ^{1}J=159.3	122.9 ^{1}J= 160.8 ^{3}J= 8.4	111.2 ^{1}J= 163.4	134.1
2c	147.1	121.0	121.0	147.1	118.4 ^{1}J= 162.5	118.4 ^{1}J= 162.5	145.0 ^{1}J= 210.6	142.4	119.5 ^{1}J= 163.0 ^{3}J= 6.0	122.6 ^{1}J=166.9	123.8 ^{1}J= 161.4 ^{3}J= 6.8	111.1 ^{1}J= 164.4	134.3
	147.1	120.9	120.9	147.1	118.4	118.4	144.9 ^{1}J= 211.8	142.3	119.5	122.5 ^{1}J=159.9	123.4 ^{1}J=161.5 ^{3}J= 7.7	110.9 ^{1}J= 164.4	134.3
3c	144.7	126.9	115.3 ^{1}J= 161.1	144.7	126.9	115.3 ^{1}J= 161.1	144.2 ^{1}J= 211.2	143.0	119.7 ^{1}J= 157.4	122.2 ^{1}J=159.4 ^{3}J= 7.7	123.2 ^{1}J= 160.9 ^{3}J= 8.0	111.1 ^{1}J= 161.1	134.0
5c[a]	143.2	115.4	115.4	143.2	122.8 (with C_8) ^{1}J= 163.8	126.9 (with C_7) ^{1}J= 161.9	144.5 ^{1}J= 210.8	142.3	119.0	121.4	122.6	110.3 ^{1}J= 163.2 ^{3}J= 7.3	134.7
	142.9	115.4	115.4	142.9	122.8	126.9	144.2 ^{1}J= 210.3	142.2	118.8	121.2	122.1	110.3	134.3

[a] $\delta C_{4a} = \delta C_{8a}$ are 126.2 and 126.1.

Addition of 2-methylimidazole to 1,4-benzoquinone. To a solution of 1,4-benzoquinone (2.63 g, 24.39 mmol) in dioxane (40 mL) was added 2-methylimidazole (2 g, 24.39 mmol). The reaction was stirred for 4 h at rt. An aliquot portion of the reaction mixture was evaporated to dryness and the analysis of the reaction crude by ^{1}H NMR revealed the presence of 2-(2´-methylimidazol-1´-yl)-1,4-dihydroxybenzene (10%), 2,3-bis(2´-methyl imidazol-1´-yl)-1,4-dihydroxybenzene (85%) and 2,5-bis(2´-methylimidazol-1´-yl)-1,4-dihydroxybenzene (5%).The 2,3-bis-adduct (**2b**) precipitated from the reaction mixture and was collected by filtration. The solvent of the filtrate was removed under reduced presure and the residue purified by column chromatography using as eluent 76:24 dichloromethane/ethanol: *2-(2´-methylimidazol-1´-yl)-1,4-dihydroxybenzene* (**1b**): (R_f 0.55) mp. 247-250°C (methanol) (dec.) ; MS, m/z 190 (100, M^+); Anal. $C_{10}H_{10}N_2O_2$; Calc. (%): C, 63.17; H, 5.26; N 14.73. Found (%): C, 63.42; H, 5.46; N, 14.21.; *2,3-bis(2´-methylimidazol-1´-yl)-1,4-dihydroxybenzene* (**2b**): (R_f 0.10) mp. >350°C (dec.); MS, m/z 270 (100, M^+); Anal. $C_{14}H_{14}N_4O_2$; Calc. (%): C, 62.21; H, 5.22; N, 20.73. Found (%): C, 62.07; H, 4.95; N, 20.30.

Addition of benzimidazole to 1,4-benzoquinone. To a solution of 1,4-benzoquinone (0.79 g, 7.31 mmol) in dioxane (5 mL) was added benzimidazole (0.86 g, 7.31 mmol). The reaction was stirred under reflux for 5.5h. The reaction was cooled and the solvent was evaporated. The relative proportions of the formed derivatives were determined by ^{1}H NMR of the reaction crude: 2-(benzimidazol-1´-yl)-1,4-dihydroxybenzene (48%), 2,3-bis(benzimidazol-1´-yl)-1,4-dihydroxybenzene (32%) and 2,5-bis(benzimidazol-1´-yl)-1,4-dihydroxybenzene (20%). The crude product was purified by column chromatography using as eluent 84:16 dichloromethane/ethanol: *2-(benzimidazol-1´-yl)-1,4-dihydroxybenzene* (**1c**): (R_f 0.51) mp. 246-248 °C: IR (KBr) 3500-3100 cm^{-1} (OH), 2650-2120 cm^{-1} (OH); MS, m/z 226 (100, M^+); Anal. $C_{13}H_{10}N_2O_2$; Calc. (%): C, 69.02; H, 4.46; N 12.38. Found (%): C, 68.34; H, 4.45; N, 12.15.; *2,3-bis(benzimidazol-1´-yl)-1,4-dihydroxybenzene* (**2c**): (R_f 0.12) mp 312-3 °C: IR (KBr) 3340-2200 cm^{-1} (OH); MS, m/z 342 (100, M^+); Anal. $C_{20}H_{14}N_4O_2.H_2O$; Calc. (%): C, 66.66; H, 4.48; N 15.55. Found (%): C, 66.76; H, 4.32; N, 15.51; *2,5-bis(benzimidazol-1´-yl)-1,4-dihydroxy benzene* (**3c**): (R_f 0.21) mp > 350°C: IR (KBr) 3600-2200 cm^{-1} (OH); MS, m/z 342 (100, M^+); Anal. $C_{20}H_{14}N_4O_2$; Calc. (%): C, 70.17; H, 4.12; N 16.36. Found (%): C, 69.98; H, 4.05; N, 16.01.

Addition of imidazole to 1,4-naphthoquinone. To a solution of 1,4-naphthoquinone (3 g, 18.98 mmol) in dioxane (25 mL) was added imidazole (1.29 g, 18.98 mmol). The reaction was stirred under reflux for 5 h and the resulting precipitate was collected by filtration. (Yield 70%): *2,3-bis(imidazol-1´-yl)-1,4-dihydroxy naphthalene* (**5a**): mp. 231-235°C; Lit. >200 (dec.);[4] MS, m/z 292 (37, M^+), 224 (100, M-$C_3H_4N_2^+$).

Addition of benzimidazole to 1,4-naphthoquinone. To a solution of 1,4-naphthoquinone (3 g, 18.98 mmol) in dioxane (20 mL), benzimidazole (2.24 g, 18.98 mmol) was added . The reaction was stirred under reflux for 10 h and the resulting precipitate was collected by filtration (Yield 65%). The filtrate was evaporated to dryness and the residue showed the presence of 2-(benzimidazol-1´-yl)-1,4-dihydroxynaphthalene (**4c**) [less than 5%, ^{1}H NMR, δ([$^2H_6$]DMSO): OH-1, 10.0; OH-4, 9.16; H_3, 6.77, $H_{2'}$, 8.40], besides the unreacted 1,4-naphthoquinone and benzimidazole. The precipitate was crystallized in ethanol which affords pure *2,3-bis(benzimidazol-1´-yl)-1,4-dihydroxynaphthalene* (**5c**) in the form of a ethanol solvate: mp. 243-247°C (dec.); MS, m/z 392 (67, M^+), 274 (100, M-$C_7H_6N_2^+$); Anal. $C_{24}H_{16}N_4O_2.C_2H_5OH$; Calc. (%): C, 71.22; H, 5.06; N, 12.78. Found (%): C, 71.01; H, 4.96; N, 12.99.

Table 15. Crystal analysis parameters at room temperature.

Crystal data

Chemical formula	$C_{20}H_{14}N_4O_2 \cdot 2CH_4O$	Crystal system	Orhorombic
Mr	200.26	Space group	*Pccn*
a (Å)	9.0432(3)	α (°)	90
b (Å)	12.7974(7)	β (°)	90
c (Å)	17.1898(10)	γ (°)	90
Z	4	*Dx* (gr/cm³)	1.36
V (Å³)	1989.4(2)	Radiation	CuKα
Wavelength (Å)	1.5418	No. of reflections for	
θ range for lattice parameters (°)	2-45	lattice parameters:	75
Absorption coefficient (cm^{-1})	7.44	Temperature (K)	295
Crystal colour	Colorless	Crystal description	Prism
Crystal size (mm)	0.10 x 0.33 x 0.83		

Data collection

Diffractometer type	Philips PW1100, four circle. Graphite oriented monocromator.		
Measurement time	1 min./reflection	Detector apertures (°)	1 x 1
Collection method	ω/2θ scans	θ_{max} (°)	65
No. of standard reflections (interval)	2 (90 min.). No variation	Scan width (°)	1.5
No. of independent reflections	1692	No. of observed reflections, I>3σ(I)	1402

Refinement

Treatment of hydrogen atoms	See experimental part	Refinement: Least-Squares on *Fo*. Full matrix	
R	0.065	No. of parameters refined	180
wR	0.074	Degrees of freedom	1222
$(\Delta\rho)_{max}$ (e/Å³)	0.29	Ratio of freedom	7.8
<Shift/error>	0.03	Max. thermal value (Å²)	U11[C(13)]=0.096(3)

Weighting scheme: Empirical as to give no trends in $<\omega\Delta^2F>$ vs. <|Fobs|> and $<\sin\theta/\lambda>$.

Table 16. Final atomic coordinates and $Ueq=(1/3)\Sigma[Uij \cdot a_i^* \cdot a_j^* \cdot a_i \cdot a_j \cdot \cos(a_i,a_j)]x10^4$

Atom	x	y	z	Ueq	Atom	x	y	z	Ueq
N(1)	0.3958(2)	0.2875(2)	0.2244(1)	367(6)	C(71)	0.3620(3)	0.3715(2)	0.2724(1)	364(7)
C(2)	0.5132(3)	0.2378(2)	0.2575(2)	455(8)	C(8)	0.3243(3)	0.2641(2)	0.1523(1)	351(7)
N(3)	0.5573(3)	0.2806(2)	0.3230(1)	499(8)	C(9)	0.4019(3)	0.2753(2)	0.0828(1)	379(7)
C(31)	0.4637(3)	0.3657(2)	0.3335(1)	425(8)	C(10)	0.3242(3)	0.2618(2)	0.0134(1)	429(8)
C(4)	0.4612(4)	0.4413(3)	0.3919(2)	553(10)	O(11)	0.5470(2)	0.3000(2)	0.0862(1)	492(6)
C(5)	0.3565(4)	0.5190(2)	0.3873(2)	566(10)	O(12)	0.6589(2)	0.3465(2)	-0.0523(1)	489(6)
C(6)	0.2556(4)	0.5228(2)	0.3261(2)	530(9)	C(13)	0.6242(7)	0.4461(3)	-0.0805(3)	772(16)
C(7)	0.2555(3)	0.4489(2)	0.2676(2)	442(8)					

Crystal Structure Determination of 2,3-bis(benzimidazol-1'-yl)-1,4-dihydroxybenzene (**2c**). Details of the X-ray analysis are given in Table 15. The crystal was sealed into a Lindemann capillary to prevent decomposition. The structure was solved by direct methods (SIR92)[14] and refined by least-squares procedures on Fobs. The two halves of the molecules are related by a crystallographic two-fold axis. All hydrogens were obtained from difference Fourier synthesis and included in the refinement process as isotropic. The scattering factors were taken from the International Tables for X-Ray Crystallography.[15] In Table 16 are listed the final atomic coordinates and equivalent thermal factors for non-hydrogen atoms, according to the numbering scheme of Fig. 1a. The calculations were carried out with the XRAY80,[16] PESOS,[17] and PARST[18] set of programs running on a VAX6410 computer.

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