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Hydroxy- and Methoxy-Benzene Derivatives with Benzenediazonium Salts: Chemical Behavior and Tautomeric Problems

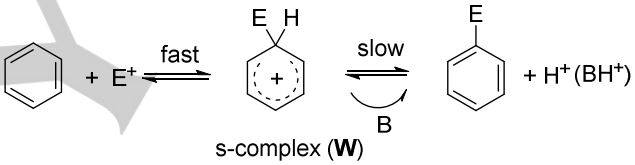
Gabriele Micheletti,*[a] Carla Boga,[a] Luciano Forlani,[a] Erminia Del Vecchio,[a] Nicola Zanna,[a] Andrea Mazzanti,[a] Magda Monari[b]

Abstract:. The azo coupling reaction between 4-nitrobenzenediazonium tetrafluoroborate and a series of benzene derivatives bearing as electron donating substituents at least one hydroxy or methoxy group has been carried out. Depending on the nucleophile and its relative ratio with the diazonium salt it was possible to obtain mono-, di-, and, only in the case of phloroglucinol, evidence of trisubstitution products. The reaction between 3,5-diaminoanisole- or 3,5-diaminophenol- derivatives and two equivalents of diazonium salt gave, in the first case, the product derived from a mono attack, and a diadduct in the second case; their X-ray diffraction analysis showed an highly symmetric structure for the latter. The different behavior of hydroxy- with respect to the methoxy-substituted compounds was particularly evident for phloroglucinol and 1,3,5-trimethoxybenzene and it may be rationalized on the basis of the different electronic effect of the substituents. The propensity to undergo H/D exchange reaction on the aromatic ring was investigated on a series of substrates and the comparison of the results obtained provided new insights on this kind of phenomenon and permitted a better explanation of the findings reported here, by introducing a new particular interaction which competes with the σ-complex formation between proton and phloroglucinol.

Introduction

Aromatic rings strongly activated by powerful electron donating groups are substrates particularly suitable for mechanistic investigations on the electrophilic aromatic substitution. The carbon-carbon bond forming reactions between neutral or charged electrophilic reagents and naphthols,[1] 2-amino-1,3-thiazole derivatives,[2] and 1,3,5-triaminobenzenes[3] allowed us to isolate and investigate σ complexes, including those that are simultaneously Wheland (**W**) and Meisenheimer (**M**) complexes.[2a,4,5] In particular, the reaction between triaminobenzenes and diazonium salts permitted to elucidate the reaction mechanism of the azo coupling reaction by studying it in separate steps, owing the stability of the **W** complexes.[3a] The obtained results clearly indicated, contrarily to that usually claimed on the rate limiting step of S_EAr reactions, that the proton elimination and the re-aromatization process from the **W** intermediate is not the driving force of the reaction but it is the rate-limiting process.[6] Furthermore, we obtained a clear evidence of the reversibility of the whole azo coupling reaction.[7] As a consequence, the usually reported pathway of this electrophilic reaction result is modified as reported in Scheme 1, in which the possible π complexes[8] have been omitted.

These findings our us to focus attention towards the reactions of benzene rings activated by electron donating substituents bearing the oxygen atom, such as 1,3,5-trihydroxybenzene (**1**, also called phloroglucinol) and 1,3,5-trimethoxybenzene (**2**) that, in principle, may be expected to behave as nucleophilic reagents with a power similar to that of the triaminobenzenes previously studied.



Scheme 1. Reaction pathway for the azo coupling reaction; the step indicated by B means a proton abstraction by base catalysis.

Moreover, phloroglucinol and its derivatives are interesting molecules from synthetic,[9] biological[10-12] and pharmaceutical[13-20] point of view.

Based on the above considerations, we planned to start a study on phloroglucinol (**1**), 1,3,5-trimethoxybenzene (**2**) and some of their derivatives using benzenediazonium salts as electrophiles with the aim to obtain new compounds of interest in applicative field and to deepen their chemical behavior and their tautomeric properties.

Results and Discussion

Scheme 2 shows the possibility to obtain mono-, di-, and tri-substituted products by reaction of the substrates **1** and **2** with the 4-nitrobenzenediazonium tetrafluoroborate (**3)**, which is one of the most powerful electrophilic aryldiazonium salts.[21] The mono substitution on **1** and **2** (in CH_3CN, reaction A in Scheme 2) in an equimolar amount with **3** is a simple and fast reaction affording the salts of the azo compounds **4H** and **5H** (R = H, CH_3, respectively). The free bases **4** and **5** may be obtained after flash chromatography or by simple filtration (or percolation) of the tetrafluoroborate salt **4H** (or **5H**) on silica gel or basic alumina. The reaction between **2** and an excess (more than three times) of *p*-nitro benzenediazonium tetrafluoborate (**3**)

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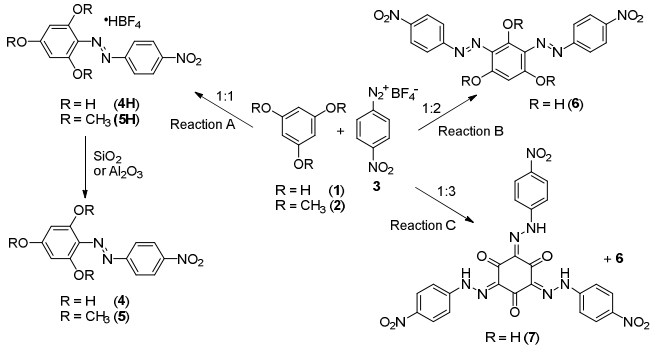
gave almost quantitatively **5H**, which is poorly soluble in the reaction medium (and in other usual solvents), and spontaneously precipitates. It has to be noted that, to the best of our knowledge, no diadducts from **2** and diazonium salts have been reported so far.

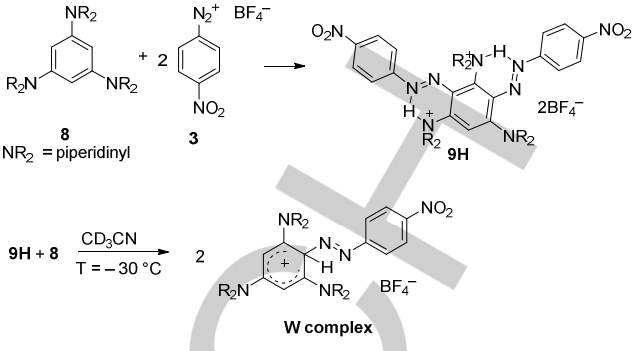


Scheme 2. Reactions of 1 or 2 with 3.

From the reaction between phloroglucinol (**1**) and **3**, in the relative ratio 1:2, a very complicated reaction mixture was obtained, in which compound **4H** was present, together with some other unidentified compounds (the presence of compound **6H**, in this reaction mixture, cannot be excluded). When phloroglucinol was reacted with three equivalents of **3** in acetonitrile, a mixture of insoluble compounds was formed from which compound **6** was separated (less than 5%) by chromatography on alumina, whereas the presence of **7** was revealed by mass spectrometry.

It has to be noted that the obtaininig of the tris(phenylazo)phloroglucinol was described by Perkin as early as in 1897,[22] and later other reports on the synthesis of similar compounds have appeared[23] whereas only fewer example of diadducts with **6**-like structure, mostly derived from alkylphloroglucinols, have been described.[24]

Previously,[7,25] we reported that the reaction, in CD_3CN, of some 1,3,5-triaminobenzenes with two equivalents of **3** affords the product of the double attack. This latter was also observed when the reaction was carried out directly in the NMR spectroscopy tube, in CD_3CN at -30 °C with the reagents in an equimolar amount, without waiting for the complete dissolution of the triaminobenzene derivative, as shown in Scheme 3 for the reaction between tris(*N*-piperidinyl)benzene (**8**) and **3**. As **8** slowly dissolved, compound **9H** released a diazonium moiety to yield the mono substituted derivative, *via* the Wheland intermediate (**W** complex, see Scheme 3).[7]



Scheme 3. Reaction between **3** and the triaminobenzene derivative **8**.

We emphasize that the solubility of **8** played an important role in obtaining the di-substituted derivative, instead of the expected mono substituted compound, because the reaction mixture, initially, presents a large excess of **3** with respect to **8**, which is present mostly as solid part. Attempts to obtain the trisubstituted products of **8** failed, probably because other processes take place on the di-substituted derivative.[25] Obviously, in the crude reaction mixture, compound **9H**, bearing two positive charges, is not prone to undergo a further electrophilic attack to form the trisubstituted derivative.

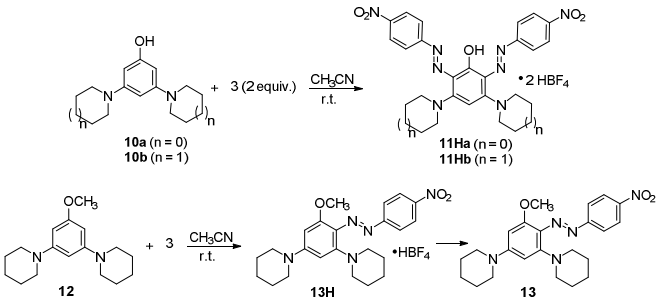
In the case of the 1,3,5-trihydroxybenzene (**1**) and 1,3,5-trimethoxybenzene (**2**) we were not able to obtain evidence (neither at room temperature nor at –35 °C) of the presence of **W** complexes.

Clearly, the obtaining of mono-, di-, or tri-azo compounds by azo copuling reaction depends on three main points: the relative ratio between the reagents, the relative solubility of the reagents and of the reaction products, and the electron releasing power of the substituents (OH, OCH_3 and NR_2) on the starting compound, whose trend is: NR_2 > OH >OCH_3, if the σ_p Hammett parameter is used in evaluating their electron donor ability (σ_p values are – 0.83, – 0.13, – 0.16 for NR_2, OH and OCH_3, respectively).[26] The σ_p values of the OH and OCH_3 groups are very close, as well as other parameters related to their electron donating power by resonance mechanism, such as σ_R, but, as a matter of fact, the OH group easily allows polysubstitution reaction, while OCH_3 does not permit it.

The obtaining of trisubstituted derivatives such as **7** from phloroglucinol partially agrees with the electron donating properties of the OH group in comparison with the OMe group, as tested by the σ values of the Hammett treatment.[26] Even if the electron donating properties of the OH and OCH_3 groups are compared by using σ^+ parameters ($\sigma+_{OH}$ = – 0.92, $\sigma+_{OMe}$ = – 0.78) the electron donating power of the OH groups is not so large to afford convincing explanation for the different chemical behavior shown by the derivatives substituted with the two groups. However, in our opinion, the dissociation of the –O-H group affording the strong electron donating group ($–O^-$ group) may produce the polysubstitution reaction observed for **1**.

Based on the above findings, we considered that azo-coupling reactions with other benzene derivatives bearing strong electron-donating groups might be useful to investigate the

different behavior of methoxy derivatives in comparison with hydroxy derivatives. For this purpose, we prepared the substrates **10a**, **10b**, and **12** of Scheme 4, which, presumably, have similar activation activity toward electrophilic reagents, and we checked their reaction toward **3**.



Scheme 4. Azo coupling reaction of 1,3-diaminobenzene derivatives 10a, 10b, and 12 with 3.

Compounds **10a** and **10b** are hydroxy-derivatives while compound **12** is a methoxy-derivative, a fixed parent of **10b** in its aromatic tautomeric form. When reacted with two equivalents of **3**, the compound **12** afforded as main product the mono derivative **13H** (which gave **13** after column chromatography), while from **10a** and **10b** the products of di-substitution **11Ha** and **11Hb** (this latter is formed also in the absence of **3**) were recovered.

Compounds **11Ha**, **11Hb** and **13** were characterized by usual spectroscopic methods and **11Hb** and **13** also by X-ray diffraction analysis. Different possible structures for **11Hb** and **13** are represented in Figure 1, and their X-ray structures are shown in Figures 2 and 3.

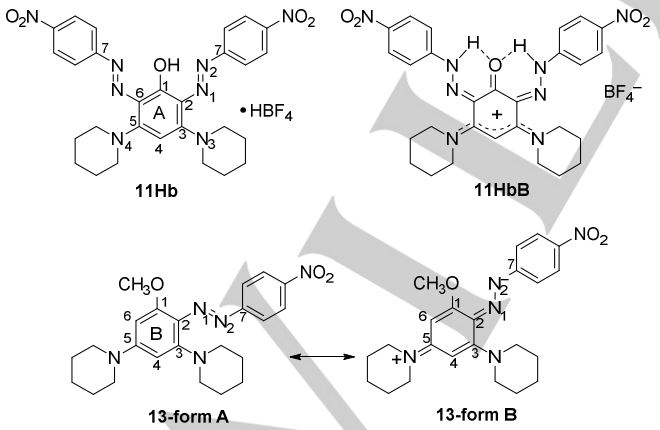


Figure 1. Possible structures for **11Hb** and **13**.

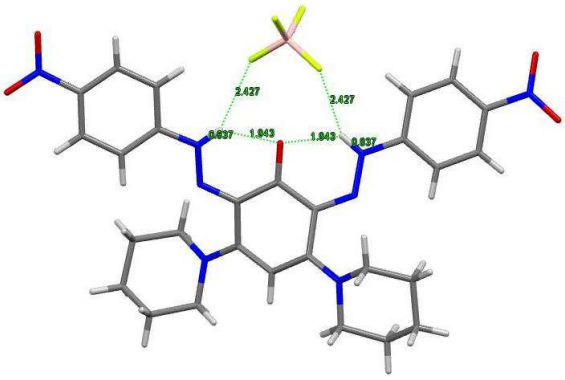


Figure 2. X-Ray structure of **11Hb**.

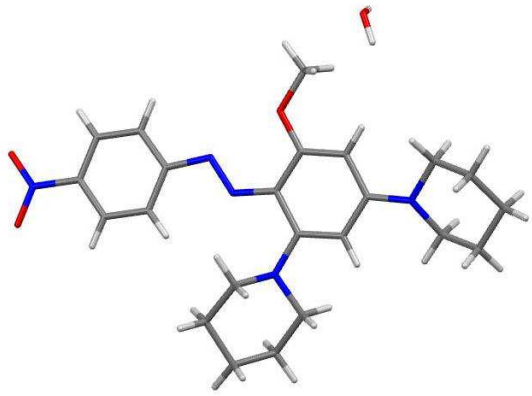


Figure 3. X-Ray structure of 13.

The X-ray crystal structure of compound **11Hb** (Figure 2) (as tetrafluoroborate salt), shows that the molecule has a crystallographically imposed C_2 symmetry with the twofold axis passing through C4, H4, C1, O1 and the boron atom of the anion. Obviously, this symmetry is absent in the neutral compound **13** (Figure 3) where all the atoms are in general positions and water molecule is present in the asymmetric unit. For comparison purposes of the two crystal structures the labelling of the atoms in **11Hb** and **13** has been unified following the one in Figure 1. Table 1 collects the most relevant bond distances (in Å). In compound **13** the C1-C6 and C3-C4 bond lengths [1.378(2) Å in both cases] of the ring **B** are shorter than the others thus indicating the presence of a quinoid structure caused by the presence of the azo group in position 2 and of the piperidinyl group in position 5 and explained by assuming an internal electron charge transfer from the nitrogen atom of the piperidinyl group to the nitrogen of the azo group, as depicted in **13-form B** (Fig. 1).

Table 1. Selected distances of both **11Hb** and **13**.

Bond	11Hb	13	Bond	11Hb
C1-C2[a]	1.453(2)	1.422(2)	C1-C2[a]	1.453(2)
C1-C6	1.453(2)	1.378(2)	C1-C6	1.453(2)
C2-C3[a]	1.470(2)	1.427(2)	C2-C3[a]	1.470(2)
C5-C6	1.470(2)	1.397(2)	C5-C6	1.470(2)
C3-C4[a]	1.394(2)	1.378(2)	C3-C4[a]	1.394(2)
C4-C5	1.394(2)	1.406(2)	C4-C5	1.394(2)
N1-N2[a]	1.322(2)	1.263(2)	N1-N2[a]	1.322(2)
N3-N4	1.322(2)	–	N3-N4	1.322(2)
N1-C2[a]	1.308((2)	1.385(2)	N1-C2[a]	1.308((2)
N3-C6	1.308(2)	-	N3-C6	1.308(2)
N2-C7[a]	1.395(2)	1.434(2)	N2-C7[a]	1.395(2)
N4-C6	1.395(2)	–	N4-C6	1.395(2)
O-C1	1.231(3)	1.346(2)	O-C1	1.231(3)
C3-N3[a]	1.328(2)	1.420(2)	C3-N3[a]	1.328(2)
C5-N4	1.328(2)	1.380(2)	C5-N4	1.328(2)

[a] The two consecutive bonds are identical due to the presence of the symmetry operation -x, y, 0.5-z.

In compound **11Hb**, the same electron-withdrawing effect of both azo groups toward the piperidinyl groups produces the shortness of C3-C4 and C4-C5 bonds [1.394(2) Å], that are identical due to the presence of the symmetry operation -x, y, 0.5-z (see Fig. SI-1).

This internal charge transfer acts also on the N1-N2 bond distance [1.263(2) Å for **13** and 1.322(2) Å for **11Hb**]; N1-N2 reveals a slightly higher π character in **13** than in N1-N2 bonds of **11Hb**. The *para*-nitrophenyl moieties partecipate to the resonance effect with the results to have quite complete co-planarity between aromatic rings in both compounds, **11Hb** and **13**. Consequently, the N1-C2 bond is shorter in **11Hb** [1.308(2) Å] than in **13** [1.385(2) Å], due to the electronic effect.

In **11Hb** the C3-N3 and C5-N4 bond distances [1.328(2) Å] are shorter than the corresponding distances in **13**, which are 1.420(2) Å and 1.380(2) Å, respectively. These bond distances are an interesting indication that in **13**, a part of the π electronic cloud of aromatic ring is localized on bonds external to the so-called aromatic ring. In other words, both piperidinyl groups in **13** are involved in a direct electron transfer towards the azo groups.

The O-C1 bond in **11Hb** [1.231(2) Å] is shorter than the analogous bond in the methoxy derivative **13** (1.346(2) Å) indicating the high electron donating power of the negatively charged oxygen which reaches a sp^2 configuration similar to that of keto group, while the O-C1 bond distance of **13** is that expected for a methoxy group bound to an aromatic ring.

All these data indicate that **11Hb** in the solid state presents a character near to a bis-hydrazone derivative as reported in **11HbB** of Fig. 2, with a six-membered 'chelate' structure, in agreement with a recent paper[23e] reporting a phloroglucinol derivative bearing three arylazo groups, similar to compound **7** of Scheme 2.

Moreover, in **11HbB** there are two strong intramolecular hydrogen bonding interactions between the N and O atoms, [N…O 2.577(2) Å] with the hydrogen bound to the nitrogen bearing the nitrophenolate group as can be inferred by the short value of the C-O1 bond which falls into the typical range for ketones and the lengthening of the N1-N2 bond with respect to the same bond in **13**. Therefore, in the solid state, of the two possible tautomeric forms **11Hb** and **11HbB**, the latter is the most stable being favored also by the C_2 symmetry of this molecule that might be useful in delocalizing the electronic cloud Also the symmetry, probably, participates in lowering the energy of the transition state of the reaction here reported, by electronic delocalization in conjugated bonds, involving heteroatoms too. An X-ray diffraction study and DFT calculations carried out on 2-tert-butyl-4-methoxy-6-(quinoline-8-ylazo)-phenol (Figure 4)

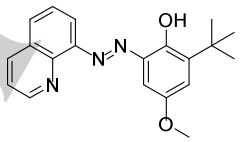
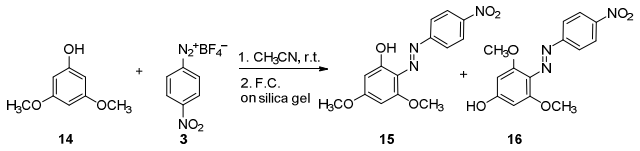


Figure 4. Structureof 2-tert-butyl-4-methoxy-6-(quinoline-8-ylazo)-phenol.

also indicate that the tautomeric equilibrium in the solid state is displaced towards the hydrazone/quinone ('NH') form rather than an 'OH' form.[27] The reported results suggest that the tris(hydrazone) tautomer might be preferred to the tris(azo)tautomer, because the former is stabilized by hydrogen bonding assisting the resonance.

The different behavior of the hydroxy-substituted compounds **10a,b**, that gave the di-substitution reaction, with respect to **12**, where the hydroxy group is substituted with the methoxy group, for which a mono-substitution occurs, may be tentatively explained by the different activation ability of the two - hydroxy and methoxy - groups, as discussed above.

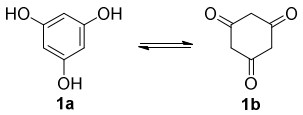
After that, we tried the reaction between **3** and 3,5-dimethoxyphenol (**14**). As shown in Scheme 5, the only recovered products, both with 1:1 and 2:1 molar ratio between **14** and **3**, were the mono azo derivatives **15** and **16**, isolated in 46:54 relative molar ratio. This behavior, different from that observed in the case of the reaction between **10a** and **10b** and **3** (Scheme 4), can be explained by the different electron-donor ability of the piperidinyl group with respect to the methoxy one.



Scheme 5. Reaction between 3,5-dimethoxyphenol and **3**.

Another possible explanation for the difference in reactivity of hydroxy and methoxy derivatives may be ascribed to the tautomerism of hydroxy derivatives such as phloroglucinol that, obviously, is absent in trimethoxybenzene. Below we try to gain some information on this prototropic problem.

A particular problem about the chemical properties of phloroglucinol **1** regards the structure, since it may exist in (at least) two tautomeric forms[28] (**1a** and **1b**) as depicted, in a simplified form, by the equilibrium shown in Scheme 6.



Scheme 6. Tautomeric forms of phloroglucinol.

Phloroglucinol is usually considered to be in aromatic form.[28b] However, the obtaining of some derivatives typical of ketones, such as the formation of a trioxime in the reaction between **1** and hydroxylamine,[29] or the formation of a tri-bisulfite adduct of **1b** by the reaction with sodium bisulfite[30] have been reported as indicating the presence of the triketo form **1b**. The two tautomeric forms of phloroglucinol derivatives were investigated by NMR spectroscopy[31] and spectral evidences on the dependence of the prototropic equilibrium of phloroglucinol on pH value have been reported.[32] We tried to obtain some information about the equilibrium in Scheme 6 by using the hydrogen/deuterium exchange reaction on several substrates including **1**, **2**, and some other derivatives suitable to elucidate the tautomerism of aromatic rings bearing hydroxy groups.

Figure 5 shows the structures of the considered substrates.

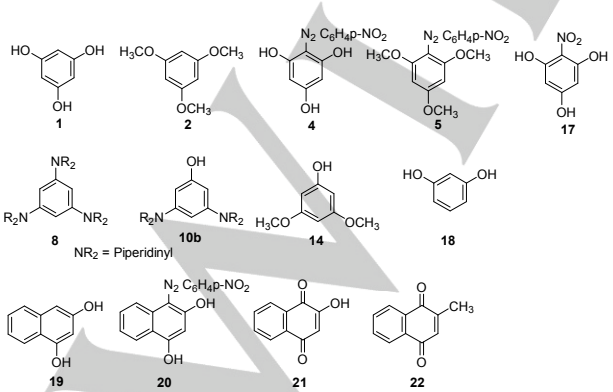
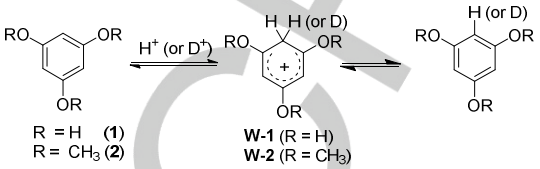


Figure 5. Compounds tested in the hydrogen/deuterium exchange reaction.

Usually, the keto/enol tautomeric process is catalysed by both, acids and bases. As reported in the literature,[28b,33,34] in the presence of acid (63-70% $HClO_4$), the equilibrium in Scheme 6, probably, occurs via a σ complex with the proton as electrophilic reagent, as depicted in Scheme 7.



Scheme 7. H/D exchange reaction of **1** and **2** *via* Wheland intermediate.

Table 2 collects the obtained results.

Table 2. Results of H/D exchange[a] for aromatic derivatives shown in Chart 1, at 25°C, in the mixture DMSO-d_6/CD_3OD (96/4 v/v, unless otherwise indicated).

Entry	Compound	Added reagent	% of H/D	Time[b]
1	1[c]	–	n.e. [d]	3 days
2	1[e]	DCl	n.e.[d]	3 days
3	1	Et_3N	65	3 days
4	1	DBU	90	3 days
5	4[f]	–	98	30 min
6	2	–	n.e.[d]	3 days
7	2[e]	DCl	95	5 h
8	2	Et_3N	n.e.[d]	3 days
9	5	–	n.e.[d]	3 days
10	5[e]	DCl	<10[g]	3 days
11	8[h]	Et_3N	n.e.[d]	3 days
12	8	D_2SO_4	>97	1 min
13	17	Et_3N	20	3 days
14	14	Et_3N	n.e.[d]	3 days
15	14	Et_3N	n.e.[d]	3 days
16	10b	Et_3N	n.e.[d]	3 days
17	18	Et_3N	n.e.[d]	3 days
18	19	–	n.e.[d]	3 days

19	**19**[i]	Et_3N	80	3 days
20	**20**	–	98	20 min
21	**21**	–	65	20 min
22	**22**[i]	–	n.e.[d]	3 days

[a] Exchange, observed in the ^{1}H NMR spectrum, related to hydrogen atoms bound to aromatic carbon atoms; when CD_3OD was used OH/OD exchange was also observed. [b] Time after which is reached the percent of exchange indicated. [c] Reaction of **1** with O-deuterated picric acid showed about 35% of H/D exchange both after 5 min and after 5 days. [d] No exchange observed. [e] When DCl 35% in D_2O was used, the reaction was carried out in DMSO-d_6. [f] The product between phloroglucinol and *p*-methoxybenzenediazonium tetrafluoroborate showed 95% of H/D exchange after 30 min. [g] This compound shows a de-methylation reaction, and very poor H/D exchange. [h] Compound **8** in neutral or basic medium did not showed H/D exchange also after week; in the presence of 35% DCl in D_2O did not exchange probably because of formation of a σ complex;[35] with excess of D_2SO_4 the exchange occurred (see SI-27-28). [i] Exchange of both protons of the substituted cycle. [l] in the presence of Et_3N quickly **22** reacts giving a complex mixture of unidentified compounds.

From results summarized in Table 2, some data are worthy of consideration:

i. In ”neutral” medium both compounds, **1** and **2**, did not exchange in DMSO-d_6/CD_3OD (Table 2, entries 1 and 6). Consequently, H/D exchange cannot be considered a “spontaneous” reaction of the reported substrates: probably, in the absence of catalyst, this is a very slow process.

ii. Phloroglucinol (**1**) did not show appreciable H/D exchange in the presence of DCl, (Table 2, entry 2) but the exchange occurs in the presence of a base (Table 2, entries 3 and 4). An opposite behavior has been shown by **2**, which quickly undergoes H/D exchange in acidic medium (Table 2, entry 7), confirming previous data of Schubert and Quacchia regarding the acid catalyzed reaction,[33b] but it does not exchange in the presence of Et_3N (Table 2, entry 8).

iii. Compound **5** shows a slow H/D exchange (less than 10% in 3 days, see Table 2, entry 10), but in this case, de-methylation reaction takes place to complicate the NMR spectral data. Surely, **5** is less prone to undergo H/D exchange in the presence of DCl, than **2,** likely due to the electronic withdrawing effect of the azo group (the σ value of the azo group is 0.64).[26] This can be explained by the main protonation equilibrium on the nitrogen atoms of the azo group, enforcing the electron withdrawing effect of this substituent.

iv. The presence of three hydroxy groups seems to be essential to have exchange in the presence of base: 1,3-dihydroxybenzene **18** is not reactive (Table 2, entry 17).

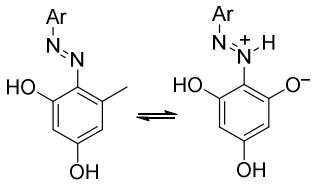
v. If the aromatic resonance energy is lowered as in 1,3-dihydroxynaphthalene **19**, the H/D exchange, in the presence of Et_3N, occurs almost in the same time of **1** (Table 2, entry 19).

vi. The introduction of a nitro group on phloroglucinol (compound **17**) depresses the H/D exchange in the presence of Et_3N (entry 13 of Table 2) This can be explained by considering that the nitro group enhances the acidity of the hydroxy group favoring the formation of an anionic species, but the localization of the negative charge out of the ring (on the oxygen of the nitro group) reduces the proton affinity of carbon atoms thus decreasing the amount of H/D exchange.

vii. Base catalysed H/D exchange cannot be explained by the mechanism of Scheme 7, even if the formation of anionic species of the hydroxy-containing aromatic substrate strongly enhances the nucleophilicity of the ring carbon atom.

viii. The introduction of an azo group on **1**, (compound **4**, Table 2, entry 5), favors the H/D exchange without addition of DCl.

ix. Azo compounds **4** and **20** show H/D exchange in “neutral” medium (Table 2, entries 5, 20, 21) because of internal base catalysis, like that reported in Scheme 8, which may be the first step for a catalysed tautomeric process in the presence of base. Obviously, the internal catalysis of Scheme 8 cannot occur for the trimethoxy derivative **5** (Table 2, entries 9, 10), which did not give H/D exchange.



Scheme 8. Internal base catalysis acting in compound **4**.

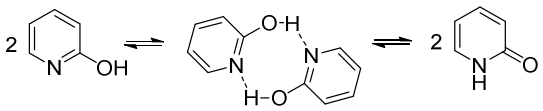
x. Compounds **19**, **20**, and **21** are naphthol derivatives, and they exchange the hydrogen atoms on the substituted cycle in neutral (**20** and **21** in entries 20 and 21, respectively) or basic medium (**19**, entry 19), owing to the occurrence of equilibrium.

xi. In agreement with the above, lawsone (**21**) quickly exchanges the proton in position 3 in a spontaneous process (entry 21 of Table 2), *i.e*. without the presence of a base, while **22** does not exchange. This can be considered an indication of the involvement, also in this case, of the quinone form.

We reported a similar situation in amino azo containing heterocycles showing a *N*/*N* tautomerism[36] or in the case of hydroxy-pyridines and related compounds (in this case N/O tautomerism).[37] In these examples the presence of association to form dimers such as that reported in Scheme 9, produces the protons close to both interested centres.

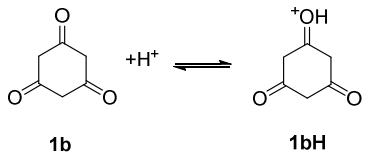
Moreover, some theoretical calculations on the pathway of

tautomerism in heterocyclic series agree with prototropic equilibrium via the dimmer formation.[38]
Also in the case of phloroglucinol some self-assembling may be operative in the tautomeric process.



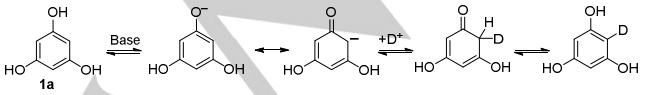
Scheme 9. Dimer formed by self-association of 2-hydroxypyridine.

In conclusion, the keto-enol tautomerism is operating in producing H/D exchange reaction on phloroglucinol and on related compounds.
The H/D exchange on **1** is favoured by bases and not by acids, which are surely able to protonate the carbonyl groups of **1b**, without affording H/D exchange. Protonated **1b** (**1bH**, see Scheme 10), have the only possibility to return back to the **1b** specie.



Scheme 10. Formation of protonated form of **1b** in acidic medium.

Apparently, the lack of H/D exchange in the presence of acid may be conceived as indicating the absence of the aromatic form **1a**. In other words, phloroglucinol seems to be active in base-catalyzed H/D exchange in the non-aromatic form **1b** only. This conclusion does not agree with the NMR data in DMSO-d_6, CD_3CN and in CD_3OD; in these solvents (see Experimental) there is one ^{13}C NMR signal in the range δ = 94–96 ppm, related to a sp^2 hybridized carbon atom and proton-coupled mode experiments indicate that this signal is responsible for the resonance of a carbon atom bound to an hydrogen atom (C-H).
Furthermore, the reactions here reported between **1** and diazonium salts are usually labelled in the field of aromatic electrophilic substitution reaction which, surely, starts from the presence of the aromatic form **1a**.
The base catalysed H/D exchange as indicated by data as indicated in Table 2, is drawn in Scheme 11 which shows the usual base catalysed enol/keto tautomerism with proton exchange.



Scheme 11. Base-catalyzed enol/keto tautomerism with H/D exchange in phloroglucinol

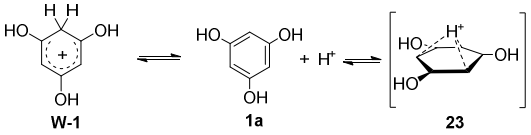
Scheme 11 is a reasonable pathway to explain also other results reported in Table 2, regarding other hydroxy-bearing substrates.

Finally, it is of interest to provide explanation on why, under present experimental conditions, the proton is not able to afford a σ-complex as indicated for phloroglucinol (even if in more drastic experimental conditions),[33a] trimethoxybenzene,[33b] and triaminobenzenes.[35] As discussed above, the electronic effect of the OH group (as indicated by σ_p values of the Hammett treatment) indicates that the phloroglucinol is slightly more prone than 1,3,5-trimethoxybenzene in similarly accepting a positive charge of electrophilic reagents. In other words, the lack of H/D exchange of phloroglucinol, under our experimental conditions, needs a different explanation than the difference in the electronic effect of –OH and OCH_3 groups. A further complication may be a possible intervention of the solvent[28a] (D_2O, for herein used DCl solutions) that might play an important role in depressing the attack of the proton on the carbon atom of phloroglucinol and 1,3,5-trimethoxybenzene to give the Wheland intermediate. Actually, this latter has been found under strong conditions, such as 65-70% $HClO_4$ solutions.[33] Recently, a study about the complexity of hydration of phloroglucinol[40] has been reported, where hydrate phloroglucinol molecules are linked by O−H···O hydrogen bonds through water molecules, but also intermolecular hydrogen bonds occur in its anhydrate status.

By summarizing, some main points worthy of consideration about the interaction of the proton with **1** are:

- The trihydroxybenzene **1** is an electron donor, due to the ring π electrons and the electronic pairs of the oxygen atoms, strong enough to yield the donicity of the whole molecule able to stabilizing the π complex in comparison with the σ complex.
- The hydroxy group is able to give intermolecular hydrogen bonding interaction (surely not relevant in the case of trimethoxybenzene) in assembling two or more molecules of **1** including the proton, and in self-assembling too.[39]
- The above point emphasizes that there is high probability to have strongly symmetric structures which are destroyed by the formation of a σ bond to the Wheland complex (**W-1** in Scheme 7).
- The absence of sigma complex in mixtures of **1** and DCl, (as indicated by NMR spectral data) may be explained by considering that the proton appears to be not able to discriminate the carbon atom to form a new σ bond as in the Wheland complex **W-1**. This resembles what has already been reported by us in explaining the “proton dance” regarding the proton interaction with tris(amino)benzene derivatives.[35] The interaction between proton and phloroglucinol might involve the π-ring electrons and in minor extent the oxygen atoms of the OH groups. The first interaction is indicated as structure **23** in scheme 12. Probably,is favored by the high symmetry of **23** which depresses its energy level with respect to the less symmetric situation of **W-1**, and also by formation of a sandwich

involving two (or more) molecules of phloroglucinol and a proton can not be excluded



Scheme 12. Schematic representation of the interaction between proton and phloroglucinol.

Reasonably, both complex **W-1** and interactions **23**, involve phloroglucinol in the aromatic form **1a**.

In the case of the interaction between tris(amino)benzenes and 4,6-dinitrobenzofuroxan the energy difference between the π complex and the σ complex (the **WM** complex) is very low, about 15 kcal/mol.[40] In that case, the electrophile/nucleophile interaction afforded **WM** complexes which were analysed and characterized by NMR spectroscopy at low temperature[4a] and showed the electrophilic moiety (4,6-dinitrobenzofuroxan) to be enable to choose the carbon atom in fixing the σ-bond[4a] in a situation similar to that depicted by **23**.

Conclusions

In conclusion, the following points can summarize the main findings of this study:

1. The azo-coupling reaction between equimolar amounts of 4-nitrobenzenediazonium tetrafluoroborate (**3**) and phloroglucinol (**1**) or 1,3,5-trimethoxybenzene (**2**), in acetonitrile, afford in almost quantitative yields the expected products of monosubstitution as salts of the tetrafluoroboric acid, as already found in the case of 1,3,5-tris(*N*-piperidinyl)benzene (**8**).[3]
2. The H/D exchange reactions provide an indirect indication to confirm the phloroglucinol (**1**) undergoes prototropic equilibria, even if the reaction between **1** and the 4-nitrobenzenediazonium tetrafluoroborate (**3**) does not appear to be affected by the presence of tautomeric forms other than the usual aromatic form, as shown by reaction A of Scheme 2.
3. Attempts to obtain a second and a third attack of the diazonium salt, producing di- and tri-substituted azo derivatives of **2** failed: also in the presence of excess of **3** the only product obtained is that derived from a mono attack. The introduction of the first azo group reduces the nucleophilic power of trimethoxybenzene (σ_p of -N=NPh group is evaluated to be 0.64, σ_m is 0.29),[26] thus other attacks on **2** of the diazonium salt are not favored, *a fortiori,* when the azo group is bearing a positive charge in the salt form.
4. On the contrary, the introduction of the first azo group on phloroglucinol does not prevent it from further attacks of the electrophilic reagent because it poorly reduces the high electron donating effects of the hydroxyl groups, until to have tri-substitution reaction. The electronic effect of the involved groups, as measured by σ_p value of the Hammett treatment, as well as σ_p^+, showing a moderately more efficient ability in delocalizing a positive charge of the OH group with respect to that of OCH_3 group, might explain this conclusion.
5. Also in the case of reactions of the triaminobenzene derivative **8**, the electron-withdrawing power of the azo group poorly contrast the strong electron-releasing effect of the three amino groups (σ_p^+ of dimethylamino group is reported to be – 1.7).[26] In this case, some solubility characters of reagents/products are important parameters in complicating the first reaction affording the disubstituted derivative, while the third attack cannot occur.
6. The rationalization of the steps of the substitution reactions on **1**, **2**, and **8** may be explained by a simple balance between the relative electron-donating electronic effect of hydroxy, methoxy and amino groups and the electron-withdrawing effect of the entering moiety, the azo group, in particular, in its protonated form.
7. The attacks to form **7** are in three subsequent steps passing through the mono- and di-substituted compound. Probably, the first attack is in the field of the aromatic electrophilic substitution, while the second and the third attacks are in the field of the addition/elimination reaction on alkenes (on substrates like as **4B** and **6B** of Fig. 6).

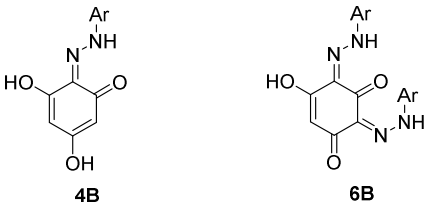
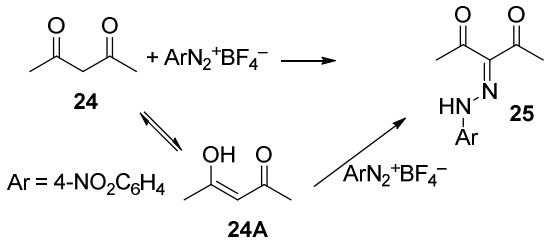


Figure 6. Tautomeric forms of **4** and **6** that undergo further attack of diazonium salt **3**.

Diazonium salts were indicated to react with methyl ketones or with other methylene and methine groups activated by electron-withdrawing groups, yielding hydrazone derivatives.[41] Actually, we checked the reaction between the diketone **24** and the diazonium salt **3**, as reported in Scheme 13.



Scheme 13. Reaction between acetylacetone (**24**) and diazonium salts.

The formation of the hydrazone **25** probably occurs via the enol **24A**, by an addition /elimination reaction and it may be achieved by a final tautomeric equilibria. We emphasize that **24** is a part of the ring of **4B** and of **6B** of Figure 5.

In this way, the different behavior of **1** and **2** is explained by simple tautomeric equilibria. On the other hand, there are evidences[23,30] that the tris(hydrazone) of phloroglucinol is in the triketo form as depicted for **7** in Scheme 2.

Finally, a series of experiments on the H/D exchange, in acidic, basic, or neutral medium, on different substrates, permitted to deepen the role of the tautomeric equilibria involving the hydroxy groups in the exchange reaction.

Experimental Section

General

The ^{1}H and ^{13}C NMR spectra were recorded at 300, 400, or 600 MHz (^{1}H NMR) and 75.46, 100.56, or 150.80 MHz (^{13}C NMR), respectively. *J* values are given in Hz. Signal multiplicities were established by DEPT-135 experiments. Chemical shifts were referenced to the solvent [δ =7.27 and 77.0 ppm for $CDCl_3$), (δ=2.0 and 0.3 ppm for CD_3CN), (δ = 2.5 and 39.5 ppm for DMSO-d_6) for ^{1}H and ^{13}C NMR, respectively]. GC-MS analyses were carried out with a gas chromatograph directly interfaced with a mass selective detector (injection temperature: 250°C; oven temperature was programmed as follows: 60°C for 2 min, increased up to 260°C at the rate of 20°/min, followed by 260°C for 20 min; the carrier gas was helium, used at a flow rate of 1 mL; the transfer line temperature was 280°C; the ionization was obtained by electron impact (EI); acquisition range was 50-500 m/z). EI mass spectra were recorded using a VG-7070E spectrometer at an ionization voltage of 70 eV. ESI-MS and HR-ESI-MS spectra were recorded using Waters 2Q 4000 and Xevo instrument, respectively. Elemental analyses were performed on a Carlo Erba Model EA-1108 elemental analyser. Chromatographic purifications were carried out on silica gel or aluminum oxide (activated, basic, Brockmann I, standard grade ca. 150 mesh) columns at medium pressure. In the Supporting Information, copies of the ^{1}H and ^{13}C NMR spectra of all new compounds are provided. In general, NMR spectra of tetrafluoroborate salts have been carried out in DMSO-d_6, due to their very low solubility in other solvents Their ^{19}F NMR signal (376 MHz, DMSO-d_6) was at δ = –143.5 ppm, referred to hexafluorobenzene (δ = –163.0 ppm) as external standard. In that cases, the spectra showed the same NMR signals of the neutral compound obtained after flash chromatography likely due to the dissociation of the salt in the used solvent

1,3,5-Tris(*N*-piperidinyl)benzene **8** was prepared as described previously.[3] Phloroglucinol (**1**), 1,3,5,-trimethoxybenzene (**2**), 3,5-dimethoxyphenol (**12**), *p*-nitrobenzenediazonium tetrafluoroborate (**3**) and *p*-methoxybenzenediazonium tetrafluoroborate are commercially available, as well as compounds **17**, **18**, **19**, **21**, **22**, and **24**. The NMR signals of phlorolucinol in different solvents are reported below: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.93 (s, 3 H, OH), 5.65 ppm (s, 3 H, CH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.9, 94.1 ppm (CH); ^{1}H NMR (300 MHz, CD_3CN): δ = 6.78 (s, 3 H, OH), 5.82 ppm (s, 3 H, CH); ^{13}C NMR (75 MHz, , CD_3CN): δ = 159.6, 95.3 ppm (CH); ^{1}H NMR (300 MHz, CD_3OD): δ = 5.79 ppm(s, 3 H, CH); ^{13}C NMR (75 MHz, , CD_3OD): δ = 160.1, 95.5 ppm (CH).

Compounds **4**,[42] **5**,[21] **5H**,[43] **10a**,[44,45] **10b**,[46] and **25**,[47] are known and their chemico-physical data agree with those reported; additional data are reported in SI.

General procedure for the synthesis of compounds 4 and 5.

4-Nitrobenzenediazonium tetrafluoroborate (**3**) (0.05 g, 0.2 mmol) was added to an equimolar amount of **1** (or **2**) dissolved in 2 mL of acetonitrile Immediately, the color of the solution became red and after a few min a coral-red solid precipitated. The reaction course was monitored by TLC (eluent: diethyl ether/petroleum light 1/1) until complete disappearance of reagents. Compound **4** and **5H** were recovered as solids after filtration then washed with little amount of acetonitrile and their data agree with those reported.[42,43] Compound **4** was obtained also by FC of the crude reaction mixture, compound **5**[21] was obtained by FC of **5H** (eluent: dichloromethane) and their data agree with those already reported.[21]

Synthesis of 2,4-bis-(4-nitrophenyl)diazenylbenzene-1,3,5-triol (6) and 2,4,6-tris(2-(4-nitrophenyl)hydrazono)cyclohexane-1,3,5-trione (7).

4-Nitrobenzenediazonium tetrafluoroborate (**3**) (0.075 g, 0.6 mmol) was added to **1** (0.2 mmol) dissolved in 5 mL of acetonitrile. Immediately, the colour of the solution became red and after a few min a dark red solid precipitated. After 30 min. the solid was collected by filtration, washed with CH_3CN and dried; its mass data agreed with those of compound **6**. The mother liquor was concentrated under reduced pressure and the residue (red solid, almost insoluble in usual organic solvents) was washed with $CHCl_3$ and dried and its analytical data agreed with those of a complex mixture of compounds, among them the presence of compound **7** was deduced by its HR-ESI-MS spectrum. Compound **6** (less than 5%) was obtained also after chromatography on alumina of the crude reaction mixture.

2,4-Bis-(4-nitrophenyl)diazenylbenzene-1,3,5-triol (**6**). ^{1}H NMR (400 MHz, DMSO-d6, 25 °C): δ = 8.24 (d, 2 H, *J* = 7.7 Hz), 7.50 (d, 2 H, *J* = 7.7 Hz), 5.10 ppm (s, 1 H). ESI-MS (m/z): ES^- = 423 $(M - H)^-$; HRMS (ES^-) m/z: $(M - H)^-$calcd for $C_{18}H_{11}N_6O_7^-$ 423.0695 found 423.0689.

2,4,6-Tris(2-(4-nitrophenyl)hydrazono)cyclohexane-1,3,5-trione (**7**). MS (m/z): ES^- = 572 $(M - H)^-$. HRMS (ES^-) m/z: $(M - H)^-$calcd for $C_{24}H_{14}N_9O_9^-$ 572,0920 found 572.0914.

General solvent-free procedure for the synthesis of compounds 10a and 10b.

1,3,5-Trihydroxybenzene (0.25 g, 2 mmol) was dissolved in 1 mL of pyrrolidine (12 mmol) or piperidine (10 mmol) and the reaction progress was monitored by GC-MS analysis. The formation of compound **10a** resulted completed after 5 h at room temperature and **10b** was obtained

after 40 h at reflux. Flash chromatography of the crude reaction mixture (eluent: diethyl ether) gave the product. It has to be noted that reactions and product purification were carried out in the dark, in order to minimize the decomposition of the reaction product, that appears to be light and moisture sensitive, giving a green oxidation by-product.[44] Chemico-physical data of **10a**[45] and **10b**[46] agree with those reported in the literature (see SI).

General procedure for the synthesis of compounds 11Ha and 11Hb.

A solution of compound **10** (0.2 mmol) in acetonitrile (6.0 mL) was added to a solution of **3** (0.095 g, 0.4 mmol) in acetonitrile (2.0 mL). Immediately, the color of the mixture became red, and a solid precipitated. After 5 min the TLC analysis (eluent: diethyl ether) revealed absence of **10**. After about 20 min the solid was recovered by filtration and characterized.

2,6-Bis((*E*)-1-(4-nitrophenyl)diazen-1-ium-2-yl)-3,5-di(pyrrolidin-1-yl)phenolate tetrafluoroborate (11Ha). 0.044 g (35%), m.p.>260 °C (dec). ^{1}H NMR (400 MHz, CD_3CN, 25 °C): δ = 8.36 (d, H, *J* = 9.2 Hz, CH), 7.68 (d, 4 H, *J* = 9.2 Hz, CH), 5.66 (s, 1 H, CH), 4.22-4.16 (m, 4 H, CH_2N), 3.80-3.70 (m, 4 H, CH_2N), 2.13-2.07 ppm (m, 8 H, $C\underline{H}_2CH_2N$). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ = 176.6, 152.8, 146.6, 144.2, 127.6, 125.8 (CH), 117.1 (CH), 93.4 (CH), 55.0 (CH_2), 52.4 (CH_2), 26.4 (CH_2), 23.4 ppm (CH_2). HRMS (ES^+) m/z: (M^+ +1) calcd for $C_{26}H_{27}N_8O_5$ 531.2099 found 531.2097; ESI MS (ES^+) m/z: 531 (M^+ +1); ESI MS (ES^-) m/z: 87 $(M-H)^-$.

2,6-bis((*E*)-1-(4-nitrophenyl)diazen-1-ium-2-yl)-3,5-di(piperidin-1-yl)phenolate tetrafluoroborate (11Hb). 0.057 g (28%), m.p.>237 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 14.1 (s, OH), 8.36 (d, H, *J* = 9.5 Hz, CH), 7.77 (d, 4 H, *J* = 9.5 Hz, CH), 6.21 (s, 1 H, CH), 4.00-3.86 (m, 8 H, CH_2N), 3.60-3.33 (br.s., 1 H), 1.91-1.70 ppm (m, 12 H, $C\underline{H}_2CH_2N$ and $C\underline{H}_2CH_2CH_2N$). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ = 176.3, 158.1, 146.6, 144.1, 127.4, 125.8 (CH), 117.0 (CH), 97.0 (CH), 52.7 (CH_2), 26.3 (CH_2), 23.6 ppm (CH_2). HRMS (ES^+) m/z: (M^+ +1) calcd for $C_{28}H_{31}N_8O_5$ 559.2412 found 559.2410; ESI MS (ES^+) m/z: 559 (M^+ +1); ESI MS (ES^-) m/z: 87 $(M-H)^-$. Crystal Data and Structure refinement for **11b** are shown in Table 3. CCDC 1482444 contains the supplementary crystallographic data for compound **11Hb**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of 1,1'-(5-methoxy-1,3-phenylene)dipiperidine (12).

1,3-Dichloro-5-methoxybenzene (0.45 g, 2.54 mmol), piperidine (1.5 mL, 15 mmol), potassium *t*-butylate (1.2g, 10mmol) and toluene (2.5 mL) were introduced in an autoclave that was sealed and the system was introduced in an oil bath and warmed at ~155 °C. After 24 h the system was allowed to stand then toluene (10 mL) and water (30 mL) was added. After extraction with dichloromethane (3 x 30 mL) the combined organic layers were dried over anhydrous $MgSO_4$, and the filtrate was concentrated. Compound **12** (0.44 g, 63%) was recovered as pale red liquid after purification by FC (eluent: *n*-hexane/diethyl ether 7/3) of the residue. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.16 (t, *J* = 2.1 Hz, 1 H), 6.04 (d, *J* = 2.1 Hz, 2 H), 3.77 (s, 3 H, OCH_3), 3.13 (t, *J* = 5.6 Hz, 8 H, NCH_2), 1.74-1.66 (m, 8 H, $NCH_2C\underline{H}_2$), 1.61-1.53 ppm (m, 4 H, $NCH_2CH_2C\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ = 161.0, 154.1, 98.8 (CH), 94.7 (CH), 55.0 (OCH_3), 51.0 (CH_2), 25.9 (CH_2), 24.4 ppm (CH_2). MS (EI) m/z: 274 (M^+, 100), 259 (30), 245 (27), 231 (10), 217 (14), 203 (6), 190 (17), 176 (9). Elemental analysis calcd (%) for $C_{17}H_{26}N_2O$: C 74.41, H 9.55, N 10.21; found: C 74.53, H 9.58, N 10.24.

Synthesis of compounds 13, 15, 16, and 20.

4-Nitrobenzenediazonium tetrafluoroborate (**3**) (0.05 g, 0.2 mmol) was added to an equimolar amount of **12** (or **14**, or **19**) dissolved in 5 mL of acetonitrile. Immediately, the color of the solution became red and after a few min a solid precipitated. The reaction course was monitored by TLC until complete disappearance of reagents. Chromatographic purification on silica gel of the crude reaction mixture gave compounds **13**, **15**, **16**, and **20**.

(*E*)-1,1'-(5-Methoxy-4-((4-nitrophenyl)diazenyl)-1,3-phenylene)dipiperidine (13). Red solid 0.077 g (91%), m.p.: >125 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.28 (d, *J* = 9.1 Hz, 2 H), 7.85 (d, *J* = 9.1 Hz, 2 H), 6.10 (d, *J* = 2.0 Hz, 1 H), 6.06 (d, *J* = 2.0 Hz, 1 H), 3.94 (s, 3 H, OCH_3), 3.50-3.41 (m, 4 H, NCH_2), 3.19-3.10 (m, 4 H, NCH_2), 1.85-1.44 ppm (m, 12 H, $NCH_2C\underline{H}_2$ and $NCH_2CH_2C\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ = 157.6, 155.4, 153.4, 146.0, 127.0, 124.7, 121.3, 113.2, 96.1, 91.6, 56.4, 54.2, 48.9, 26.2, 25.6, 24.3, 24.2 ppm. ESI-MS (m/z): ES^+ = 424 (M^++1), 446 (M^++Na). Elemental analysis calcd (%) for $C_{23}H_{29}N_5O_3$: C 65.23, H 6.90, N 16.54; found: C 65.34, H 6.92, N 16.51. Crystal Data and Structure Refinement for **13** are shown in Table 3. CCDC 1482311 contains the supplementary crystallographic data for compound **13**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3,5-Dimethoxy-2-((4-nitrophenyl)diazenyl)phenol (15). orange solid 0.022 g (36%) m.p.: 223-240 °C (dec.). ^{1}H NMR: (300 MHz, DMSO-d_6, 25°C) δ = 8.36 (d, *J* = 9.1 Hz, 2 H), 7.90 (d, *J* = 9.1 Hz, 2 H), 6.12 (d, *J* = 2.3, 1 H), 6.03 (d, *J* = 2.3, 1 H), 3.91 (s, 3 H, OCH_3), 3.87 ppm (s, 3H, OCH_3). ^{13}C NMR: (100 MHz, DMSO-d_6) δ = 169.1, 165.8, 159.9, 151.5, 145.9, 126.2, 125.5, 120.2, 94.6, 93.2, 56.44 (OCH_3), 56.40 ppm (OCH_3). ESI MS (ES^-) m/z: 302 (M – H)$^-$. Elemental analysis calcd (%) for $C_{14}H_{13}N_3O_5$: C 55.45, H 4.32, N 13.86; found: C 55.53, H 4.33, N 13.82.

3,5-Dimethoxy-4-[(4-nitrophenyl)diazenyl]phenol (16). orange solid 0.026 g (43%) m.p.: 220-228 °C (dec.). ^{1}H NMR: (400 MHz, DMSO-d_6, 25°C) δ = 8.27 (d, *J* = 9.2 Hz, 2 H), 7.67 (d, *J* = 9.2 Hz, 2 H), 5.78 (br.s, 2 H), 3.84 ppm (br.s, 6 H, OCH_3). ^{13}C NMR: (100 MHz, DMSO-d_6) δ = 184.9, 158.9, 148.9, 142.8, 125.5, 125.2 115.7, 102.0, 56.4 ppm (OCH_3). ESI MS (ES^-) m/z: 302 (M – H)$^-$. Elemental analysis calcd (%) for $C_{14}H_{13}N_3O_5$: C 55.45, H 4.32, N 13.86; found: C 55.55, H 4.33, N 13.81.

2-((4-Nitrophenyl)diazenyl)naphthalene-1,3-diol (20). Orange solid, 0.044 g (71%) m.p.: >260 °C (dec.). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 12.31 (br.s, OH), 8.31 (dd, J_1 = 7.9 Hz, J_2 = 1,1 Hz, 1 H), 8.23 (d, *J* = 9.3 Hz, 2 H), 7.90 (dd, J_1 = 7.3 Hz, J_2 = 1,3 Hz, 1 H), 7.73 (d, *J* = 9.3 Hz, 2 H), 7.63 (dt, J_1 = 7.3 Hz, J_2 = 1,3 Hz, 1 H), 7.50 (dt, J_1 = 7.3 Hz, J_2 = 1,1 Hz, 1H), 5.98 ppm (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ = 181.0, 167.2, 148.0, 142.6, 133.0, 130.6, 127.7, 125.7, 125.3, 123.8, 122.5, 115.5, 104.5 ppm. ESI MS (ES^-) m/z: 308 (M – H)$^-$. Elemental analysis calcd (%) for $C_{16}H_{11}N_3O_4$: C 62.14, H 3.59, N 13.59; found: C 62.27, H 3.60, N 13.54.

H/D exchange experiments.

A solution of the considered compound (see Chart 1 and Table 2) dissolved in a mixture DMSO-d_6/CD_3OD 96/4 v/v (in cases in which DCl or D_2SO_4 was used, the solvent was CD_3OD) was introduced into a NMR spectroscopy tube and the ^{1}H NMR spectrum was recorded. The spectra were recorded after different times from the addition, or not, of acid (DCl 35% in D_2O or D_2SO_4 98% in D_2O, ≥ 5 eq.), or bases (~ 1 eq.), as reported in Table 2. p-Dioxane added as internal standard or solvent

peak were used as reference signals to determine the amount of the CH/CD exchange. In the case of compound **19** (Table 2, entry 19), both CH signals of the hydroxylated ring exchanged, and in cases of compounds **20** and **21** (Table 2, entries 20 and 21, respectively) the signal of the hydroxylated ring exchanged.

Crystallographic Data Collection and Structure Determination.

The X-ray intensity data of compounds **11Hb** and **13** were measured on a Bruker Apex II CCD diffractometer. Cell dimensions and the orientation matrix were initially determined from a least-squares refinement on reflections measured in three sets of 20 exposures, collected in three different ω regions, and eventually refined against all data. A full sphere of reciprocal space was scanned by 0.3° ω steps. The software SMART[48] was used for collecting frames of data, indexing reflections and determination of lattice parameters. The collected frames were then processed for integration by the SAINT program,[48] and an empirical absorption correction was applied using SADABS.[49] The structure was solved by direct methods (SIR 2004)[50] and subsequent Fourier syntheses and refined by full-matrix least-squares on F^2 (SHELXTL)[51] using anisotropic thermal parameters for all non-hydrogen atoms. All the hydrogen atoms were added in calculated positions, included in the final stage of refinement and refined with $U(H)=1.2U_{eq}(C)$ and allowed to ride on their carrier atoms. In **12Hb** the molecule lies on a crystallographic twofold axis passing H4, C4, C1, O1 and the boron atom of the BF_4^- counterion. Molecular graphics were generated by using Mercury 3.3.[52] Color codes for all molecular graphics: orange (Cu), blue (N), red (O), grey (C), white (H). Crystal data and details of data collections for compounds **11Hb** and **13** are reported in Table 3.

Table 3. Crystal Data and Structure Refinement for **12Hb** and **14**.

Compound	**11Hb**	**13**
Formula	$C_{28}H_{31}BF_4N_8O_5$	$C_{23}H_{31}N_5O_4$
FW	645.41	441.53
Crystal symmetry	Monoclinic	
Space group	*C2/c*	*P-1*
a, Å	19.0729(16)	10.236(4)
b, Å	11.3920(7)	10.372(4)
c, Å	12.9852(8)	12.130(4)
α, °	90	100.260(4)
β, °	98.511(4)	112.741(4)
γ, °	90	99.401(4)
cell volume, Å^3	2790.3(3)	1129.85
Z	4	2
D_c, Mg m^{-3}	1.536	1.298
μ(Mo Kα), mm^{-1}	0.125	0.091
F(000)	1340	472
crystal size, mm	0.30×0.25×0.20	0.50×0.50×0.30
T, K	153	298
ϑ limits, °	2.09 - 30.10	1.89 – 27.50
Refl. Collected	18251	12544
unique refl. (R_{int})	4086 [R(int) = 0.0734]	5098 (0.0460)
GooF on F^2	1.043	1.023
$R_1(F)$[a], $wR_2(F^2)$[b]	0.0597, 0.1528	0.0756, 0.2185
largest diff. peak and hole, e Å^{-3}	0.612 and -0.379	0.450 and -0.391

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR_2 = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$, where $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3$.

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Keywords: Phloroglucinol • tautomerism • trimetoxybenzene • diazonium salts • H/D exchange

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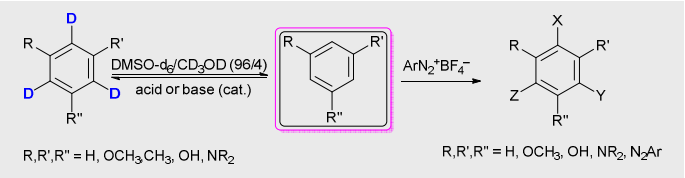

The H/D exchange on phenol derivatives can explain the tautomeric equilibrium of the phloroglucinol and its particular reactivity respect to the electrophilic substitution.

Phloroglucinol tautomerism

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Hydroxy- and Methoxy-Benzene Derivatives with Benzenediazonium Salts: Chemical Behavior and Tautomeric Problems