Organic & Supramolecular Chemistry

Polarization-Enhanced Hydrogen Bonding in 1,8-Dihydroxynaphthalene: Conformational Analysis, Binding Studies and Hydrogen Bonding Catalysis

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In this article, the presence and effects of polarization-enhanced hydrogen bonding in 1,8-dihydroxynaphthalene (1,8-DHN) were investigated in detail through a series of experimental and computational studies. First, the conformation of 1,8-DHN, and its ability to make intra- and intermolecular hydrogen bonds were investigated in solid state by X-ray crystallography, in solution by NMR spectroscopy, and computationally by density functional theory. Second, equilibrium binding constants, which were determined by ^{31}P-NMR titration studies, demonstrated stronger complexation of Ph_3PO with 1,8-DHN compared to mono-naphthol derivatives 8-methoxy-1-naphthol and 1-naphthol. In the final section, 1,8-DHN was observed to be an effective catalyst for the Friedel-Crafts-type addition reaction of indoles to β-nitrostyrenes, and a rationale for this catalytic activity was provided via computational studies. All the findings described in this work support the enhanced hydrogen bond donating ability of 1,8-DHN due to polarization caused by the six-membered intramolecular hydrogen bond present in its structure.

1. Introduction

Hydrogen bonding is a ubiquitous non-covalent interaction with widespread applications ranging from biochemistry and supramolecular chemistry to catalysis, crystal engineering and materials science.[1] Understanding the key features of this interaction is crucial for the design of structural motifs with novel or improved functions. An important phenomenon in the area of hydrogen bonding is cooperativity of a hydrogen-bonded network in which the total hydrogen bond (HB) energy of the network is larger than the sum of the energies of individual HBs.[1a,b,2] One type of such cooperative effects arises from the enhancement of the HB donating ability of Y–H due to the polarization caused by the X–H···Y hydrogen bonding interaction (Figure 1a). This effect has been termed as polarization-enhanced hydrogen bonding,[1b] polarization-assisted hydrogen bonding,[1f] and σ-bond cooperativity.[1a,b,d] In an elegant work reported by Hunter and co-workers in 2018, effect of polarization on the solvation properties of various alcohol-based solvents was investigated in detail.[3] An example of infinite 1D chains formed by intermolecular polarization-assisted HBs is the crystal structure of phenol (Figure 1b).[4,1f] On the other hand, enhancement of HB donating ability due to the presence of an intramolecular HB is also frequently encoun-

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.202002960

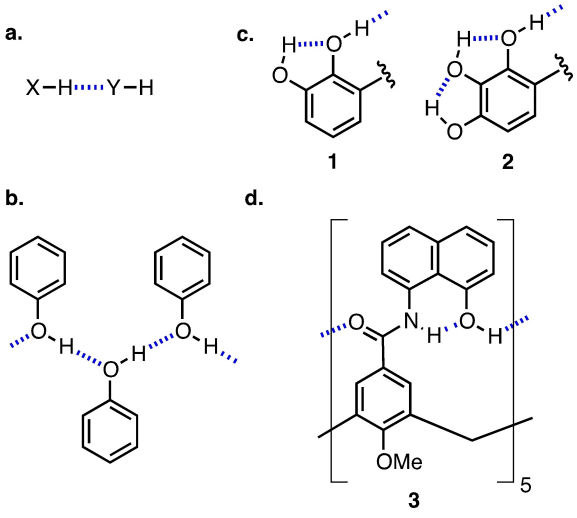


Figure 1. Examples of polarization-assisted hydrogen bonds.

tered. In 2017, Cockroft and co-workers investigated cooperativity effects in hydrogen-bonded chains formed by catechol (**1**) and pyrogallol (**2**) derivatives via the use of well-designed molecular balances (Figure 1c).[5] Recently, Lledó and co-workers reported a calix[5]arene-based receptor (**3**) for coronene that is stabilized by a cooperative network of HBs governed by the 8-amido-1-naphthol moieties present in the receptor (Figure 1d).[6]

Another research area in which polarization-enhanced HBs have been utilized effectively is organocatalysis, and in particular, hydrogen bonding catalysis.[7] In this respect, alcohols and phenols represent an important subclass of HB donor catalysts where such cooperative effects have been showcased.[8] For instance, the intramolecular HB between the two –OH groups in TADDOLs (**4**) was proposed to lead to an increase in the HB donating strength of the second –OH group making them effective HB donor catalysts (Figure 2).[9,10] The structures and dynamics of HBs in TADDOL derivatives have recently been investigated in solution by NMR and IR spectroscopy.[11] Within the same context, enhancement of HB donating ability due to the intramolecular HB interaction may play an important role in the success of BAMOLs (**5**) as highly active chiral hydrogen bonding catalysts.[12] In 2008, Schreiner and co-workers reported an efficient catalytic alcoholysis reaction of styrene oxides, which was proposed to operate by a cooperative network of HBs with the use of mandelic acid and a thiourea as HB donors.[13] Pyrogallol and catechol derivatives were shown by Maseras, Kleij and co-workers to be effective HB donor catalysts in the cycloaddition reaction between CO_2 and epoxides to form carbonates.[14] The high catalytic activities observed in this study were attributed to the cooperativity effect of the adjacent phenolic groups in these diol and triol systems. In 2007, the Maruoka group developed a new class of axially chiral dicarboxylic acids with binaphthalene backbone as effective HB donor catalysts (Figure 2).[15a] The presence of an intramolecular HB between the two carboxylic acid moieties of **6** was demonstrated by XRD analysis.[15b] In an intriguing work reported by Berryman and co-workers in 2018, polarization-enhanced halogen bonding and preorganization imparted by the intramolecular HBs were demonstrated to be the key factors leading to the success of compound **7** as a strong halogen bond donor (Figure 2).[16] Recently, Franz and co-workers reported a detailed study on the catalytic activity and HB donating strength of polyhedral oligomeric silsesquioxane silanols, and demonstrated the cooperativity effects caused by the intramolecular HBs between the silanol groups.[17]

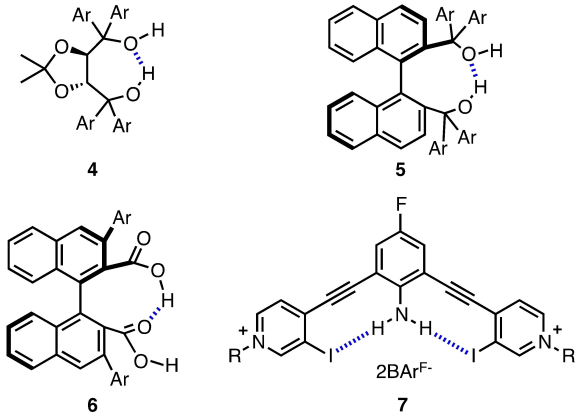


Figure 2. Intramolecular HBs leading to enhancement in hydrogen and halogen bond donating strengths.

During the course of our studies on total synthesis of natural products derived from 1,8-dihydroxynaphthalene (1,8-DHN, **8**), we became interested in the nature and potential applications of polarization-assisted hydrogen bonding in 1,8-DHN (**8**) due to the six-membered intramolecular HB between the two –OH groups (Figure 3a). In 2002, Foti et al. showed that 1,8-DHN (**8**) has a strong hydrogen atom donating ability in radical reactions with promising antioxidant activity.[18] In addition, the intra- and intermolecular hydrogen bonding properties of **8** were investigated by IR spectroscopy.[18a] Diol **8** was determined to be more acidic than 1-naphthol (**10**) in water ($pKa_{1(8)} = 6.71$, $pKa_{(10)} = 9.22$), whereas its $pKa_{2(8)}$ for the second acid dissociation is > 13.0.[19] These results can be attributed to the high stability of the mono-anionic species formed after the first deprotonation of **8** due to the presence of a strong intramolecular HB. Our preliminary results on the

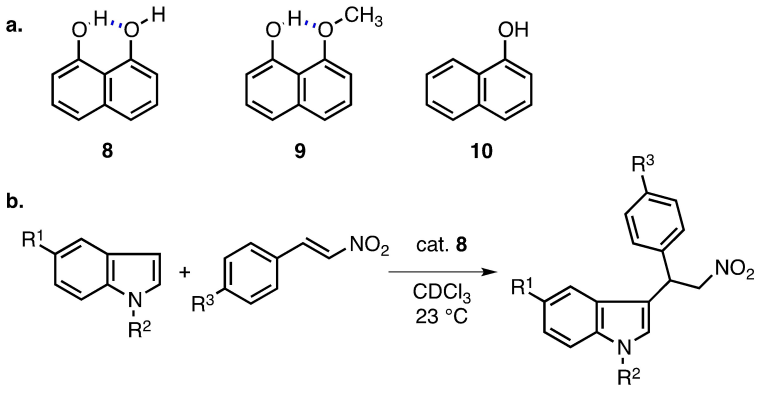


Figure 3. (a) Structures of 1,8-DHN (**8**), 8-methoxy-1-naphthol (**9**) and 1-naphthol (**10**); (b) The Friedel-Crafts-type addition of indoles to β-nitrostyrenes catalyzed by diol **8**.

use of NMR spectroscopy for the evaluation of the HB donating ability of diol **8** were recently reported.[20] Herein, we are reporting a full account of our studies on the polarization-enhanced hydrogen bonding in 1,8-DHN (**8**). In the first section, we investigated the conformation of **8**, and the nature of its intra- and intermolecular HBs by X-ray crystallography, NMR spectroscopy, and by computational methods. In the second part, the complexation of triphenylphosphine oxide (Ph_3PO) with 1,8-DHN (**8**), 8-methoxy-1-naphthol (**9**) and 1-naphthol (**10**) was examined through the measurement of equilibrium binding constants using ^{31}P-NMR titration (Figure 3a). In the final part, the utilization of diol **8** as an effective hydrogen bonding catalyst in the addition reactions of indoles to β-nitrostyrenes is described (Figure 3b). The results obtained in this section have been supported by computational studies.

2. Results and Discussion

2.1. Conformational Analysis

X-Ray Analysis. In a study reported in 2017, the crystal structure of the 1,8-DHN derivative **11** was shown to have two intramolecular HBs (Figure 4).[21] However, since the two aldehyde groups might have an effect on the conformation of this molecule, we sought to determine the crystal structure of unsubstituted 1,8-DHN (**8**). The single-crystal XRD analysis of **8** revealed a hydrogen-bonded chain structure held together by intra- and intermolecular hydrogen bonds (CCDC 1948677).[22] The crystal structure confirmed the presence of intramolecular HBs between the –OH groups of diol **8**, and the corresponding H···O distances have been determined to be 1.80 and 1.82 Å (Figure 4). On the other hand, intermolecular hydrogen bonds with H···O distances of 1.82 and 1.89 Å lead to the formation of an infinite chain structure.[22]

NMR Studies. The conformational analysis of 1,8-DHN (**8**) in solution phase was studied by ^{1}H-NMR spectroscopy in $CDCl_3$ and d^6-DMSO solvents (Figure 5).[20] A thorough analysis was reported by M. H. Abraham, R. J. Abraham and co-workers on the ^{1}H-NMR spectra of various HB donors in $CDCl_3$ and d^6-DMSO, and it was pointed out that the HB donating ability correlates well with the difference in chemical shifts in these two solvents.[23] When the ^{1}H-NMR spectra of 1-naphthol (**10**) were recorded in $CDCl_3$ and d^6-DMSO (0.05 M), the chemical shift of the –OH hydrogen was observed to be 5.28 and 10.08 ppm, respectively (Figures 5a and 5b). The $\Delta\delta$ value of 4.80 ppm indicates the availability of the –OH group of **10** for an intermolecular HB interaction. The situation appeared to be very different in the case of 8-methoxy-1-naphthol (**9**) despite being another mono-phenol derivative. Indeed, the ^{1}H-NMR spectra of **9** in $CDCl_3$ and d^6-DMSO exhibited almost identical δ(OH) values (9.32 and 9.37 ppm, respectively; Figures 5c and 5d). Whereas the high chemical shift of 9.32 ppm in $CDCl_3$ demonstrates that the –OH group of **9** is internally hydrogen bonded to the –OMe group, the extremely small $\Delta\delta$ value of 0.05 ppm shows that the same –OH group is not a strong HB donor for additional intermolecular HB interaction. This result is in accordance with the conclusion of Abraham and co-workers for intramolecular HBs.[23a] Finally, only one signal at 7.83 ppm was observed for the two –OH hydrogens of 1,8-DHN (**8**) in its ^{1}H-NMR spectrum in $CDCl_3$. This signal can be viewed as a time-average signal due to the rapid equilibrium between the two H-bonded conformers of **8** (Figure 5e). When the ^{1}H-NMR spectrum of **8** was recorded in d^6-DMSO, the –OH hydrogens were found to resonate at 10.83 ppm, corresponding to a $\Delta\delta$ value of 3.00 ppm (Figure 5f).

Computational Studies. After the completion of the conformational analysis of 1,8-DHN (**8**) in solid state and

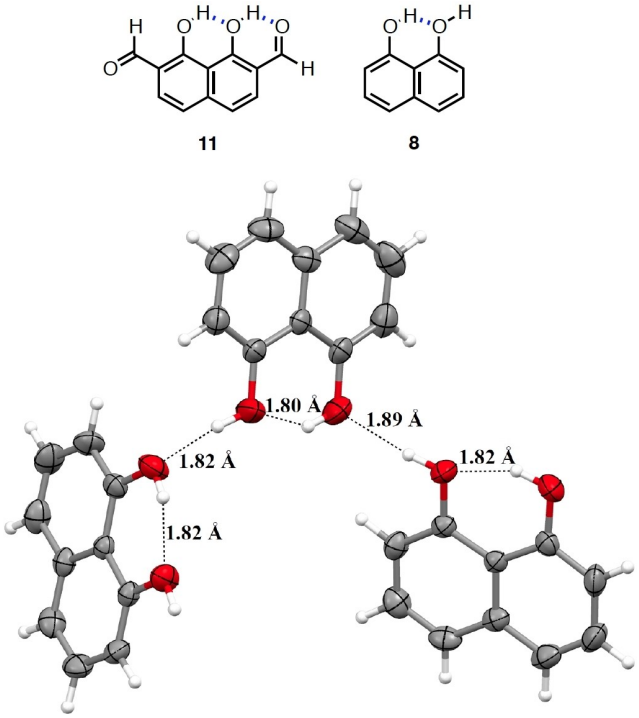


Figure 4. X-ray crystal structure of 1,8-DHN (**8**) with thermal ellipsoids at 30% probability level.

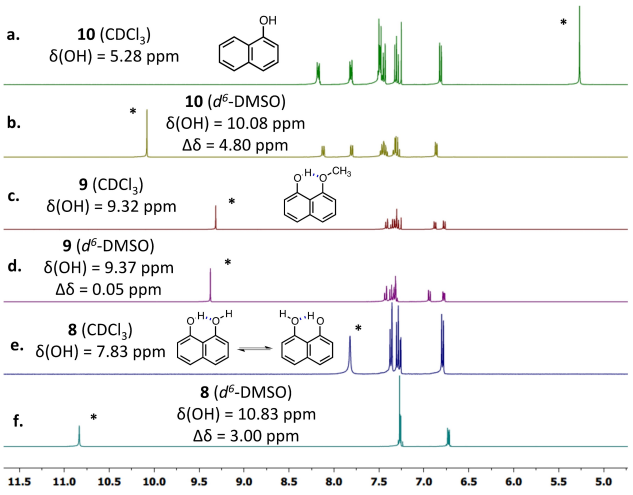


Figure 5. Stacked ^{1}H-NMR specta of (a) **10** in $CDCl_3$; (b) **10** in d^6-DMSO; (c) **9** in $CDCl_3$; (d) **9** in d^6-DMSO; (e) **8** in $CDCl_3$; (f) **8** in d^6-DMSO.

solution phase, we performed theoretical computations on the structures of 1,8-DHN (**8**) and 8-methoxy-1-naphthol (**9**) in the gas phase using the density functional theory (DFT). For the accurate description of the long-range interactions, the ωB97XD functional[24] was employed along with the 6–311++G(d,p) basis set.[25] The zero-point vibrational energy (ZPVE) corrections were added to the electronic energies to obtain relative energies. All computations were performed with the Gaussian software.[26] In accordance with the results obtained from solid state and solution studies, the energy-minimized structure of 1,8-DHN exhibits an intramolecular hydrogen bond (conformation **8**, Figure 6). This conformer was computed to be 6.9 kcal/mol more stable than conformer **8′**, in which the two –OH groups face opposite directions. When a similar analysis was performed for 8-methoxy-1-naphthol, internally hydrogen-bonded conformer **9** was found to be 7.2 kcal/mol lower in energy than conformer **9′** which lacks such a HB (Figure 6). The slightly larger ΔE value for the latter conformer pair may be attributed to the higher HB accepting ability of the $-OCH_3$ group compared to –OH due to electron-donating nature of the methyl group.

2.2. Binding Studies

In the second phase of our study, we attempted to assess the HB donating ability of 1,8-DHN (**8**) through a series of complexation experiments using NMR spectroscopy. As described in our initial report, the chemical shift changes (Δδ) in the ^{31}P-NMR spectra of Ph_3PO in $CDCl_3$ upon complexation to naphthol derivatives **8**, **9** and **10** were determined first.[20] While a Δδ value of 3.24 ppm was observed for a 1:1 mixture of diol **8** and Ph_3PO in $CDCl_3$, using 2 equivalents of 1-naphthol (**10**) induced a lower chemical shift change (2.33 ppm) indicating higher HB donating ability of diol **8** compared to **10** (Table 1).[27] As expected from the conformational analysis studies described above, 8-methoxy-1-naphthol (**9**) does not act as a strong HB donor, and led to almost no change in the ^{31}P-NMR spectrum when mixed with Ph_3PO in a 1:2 ratio (Δδ = −0.02 ppm). It should be noted that UV-Vis and ^{31}P-NMR spectroscopies have previously been applied successfully to the quantification of HB donating strengths of various HB donors.[28,29,30]

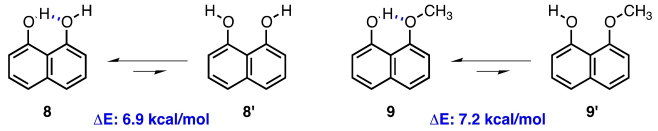


Figure 6. Computational conformational analysis of 1,8-DHN (8) and 8-methoxy-1-naphthol (**9**).

Table 1. ^{31}P- and ^{13}C-NMR studies for the complexation of **8**, **9** and **10** with Ph_3PO and cyclohexanone in $CDCl_3$.[a]

HB Donor	Ph_3PO:HB Donor	Ph_3PO δ (ppm)	Δδ (ppm)	Cy:HB Donor	Cyclohexanone δ (ppm)	Δδ (ppm)
–	–	29.71	–	–	212.20	–
1,8-DHN (**8**)	1:1	32.95	3.24	1:1	214.46	2.26
8-methoxy-1-naphthol (**9**)	1:2	29.69	−0.02	1:2	212.17	−0.03
1-naphthol (**10**)	1:2	32.04	2.33	1:2	213.80	1.60

[a] The concentrations of Ph_3PO and cyclohexanone (Cy) in these NMR experiments were 0.10 M.

A similar set of experiments was designed to investigate the binding of naphthol derivatives **8**, **9** and **10** to cyclohexanone by ^{13}C-NMR spectroscopy (Table 1).[20] In agreement with the results described above, a 1:1 mixture of diol **8** and cyclohexanone induced a larger chemical shift difference (Δδ = 2.26 ppm) in the C=O carbon signal of cyclohexanone compared to **9** and **10** (Δδ = −0.03 and 1.60 ppm, respectively). These results underscore once again that diol **8** is a stronger HB donor than naphthol derivatives **9** and **10** due to the polarization induced by the intramolecular hydrogen bond.

In the current work, we set out to determine the binding constants for the complexation of 1,8-DHN (**8**), 8-methoxy-1-naphthol (**9**) and 1-naphthol (**10**) with Ph_3PO by NMR titration experiments in order to make a better comparison. The binding constants for hydrogen-bonded complexes are known to be significantly higher in solvents that do not behave as HB donors or acceptors.[31,32] However, due to the low solubility of 1,8-DHN (**8**) in moderately polar solvents such as $CHCl_3$ and CH_2Cl_2, all the titration experiments described herein were carried out in CH_3CN to ensure homogeneity of the solutions. Initially, a Job plot analysis using ^{31}P-NMR spectroscopy supported a 1:1 ratio for the hydrogen bonding interaction between **8** and Ph_3PO (Figure 7).[33] However, recent studies demonstrated that Job plot method sometimes provide erroneous results in supramolecular chemistry, and should be utilized with caution.[34] We next performed ^{31}P-NMR titration studies in order to determine the binding constant for the complexation of **8** (guest) to Ph_3PO (host) (Figure 7). The data of the titration experiments were analyzed by the freely available Bindfit software.[35,36] Whereas the data can be fitted well to both 1:1 and 1:2 (host:guest) binding models, multiple experiments at the same and different concentrations provided more consistent results with the 1:1 binding model. The titration experiments, repeated three times at the same host concentration, gave $K = 18.8 \pm 2.1\ M^{-1}$.[22] Finally, it should be noted that the ^{1}H-NMR spectra of 1,8-DHN (**8**) alone, which were recorded at different concentrations in CD_3CN, indicate that the self-association of this compound via intermolecular hydrogen bonding is negligible under these conditions.[22]

Following the successful implementation of ^{31}P-NMR spectroscopy to the investigation of complexation of 1,8-DHN (**8**) to Ph_3PO, we turned our attention to a possible HB interaction between 8-methoxy-1-naphthol (**9**) and Ph_3PO. For this purpose, an NMR titration experiment was carried out using Ph_3PO as host and compound **9** as guest in CH_3CN (Figure 8). No change was observed in the chemical shift of the Ph_3PO phosphorus atom in ^{31}P-NMR spectra up to 8 equivalents of guest molecule added. This result clearly confirmed that 8-methoxy-1-naphthol (**9**) is not capable of acting as a strong HB donor, and does not make a HB interaction with Ph_3PO in CH_3CN.

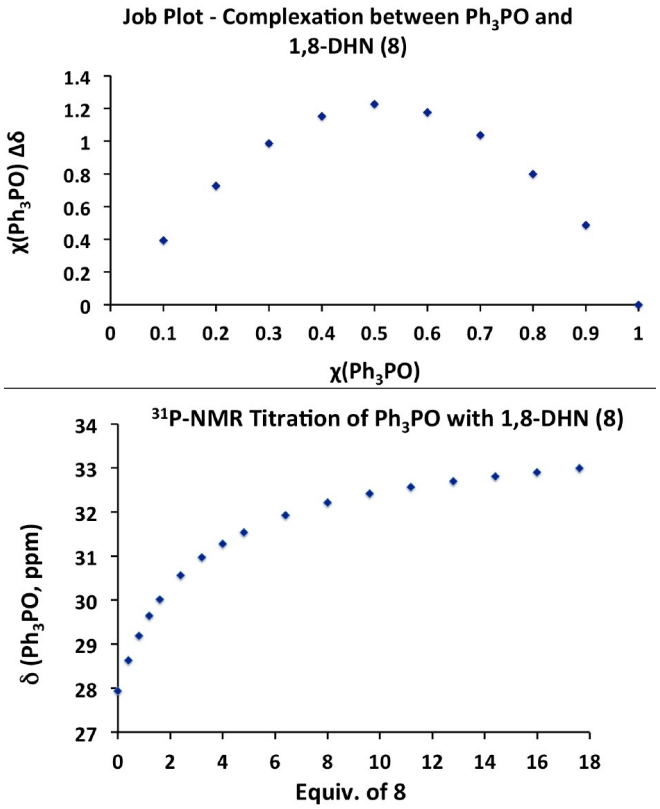


Figure 7. ^{31}P-NMR titration studies for the complexation between 1,8-DHN (**8**) and Ph_3PO in CH_3CN.

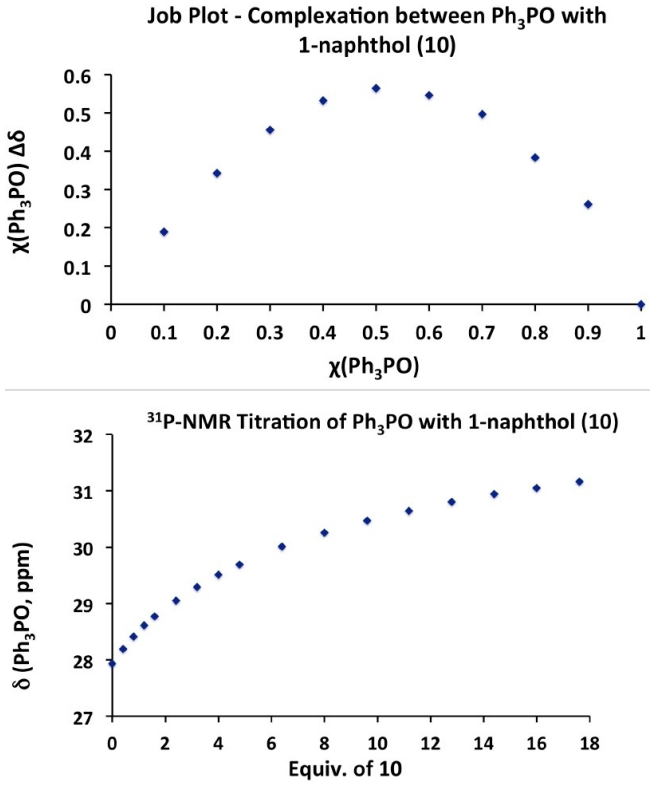


Figure 9. ^{31}P-NMR titration studies for the complexation between 1-naphthol (**10**) and Ph_3PO in CH_3CN.

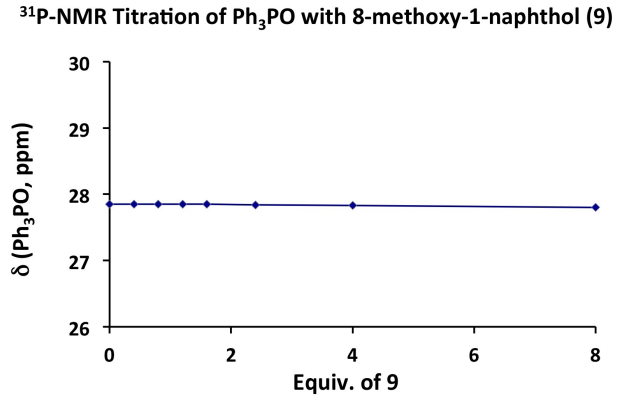
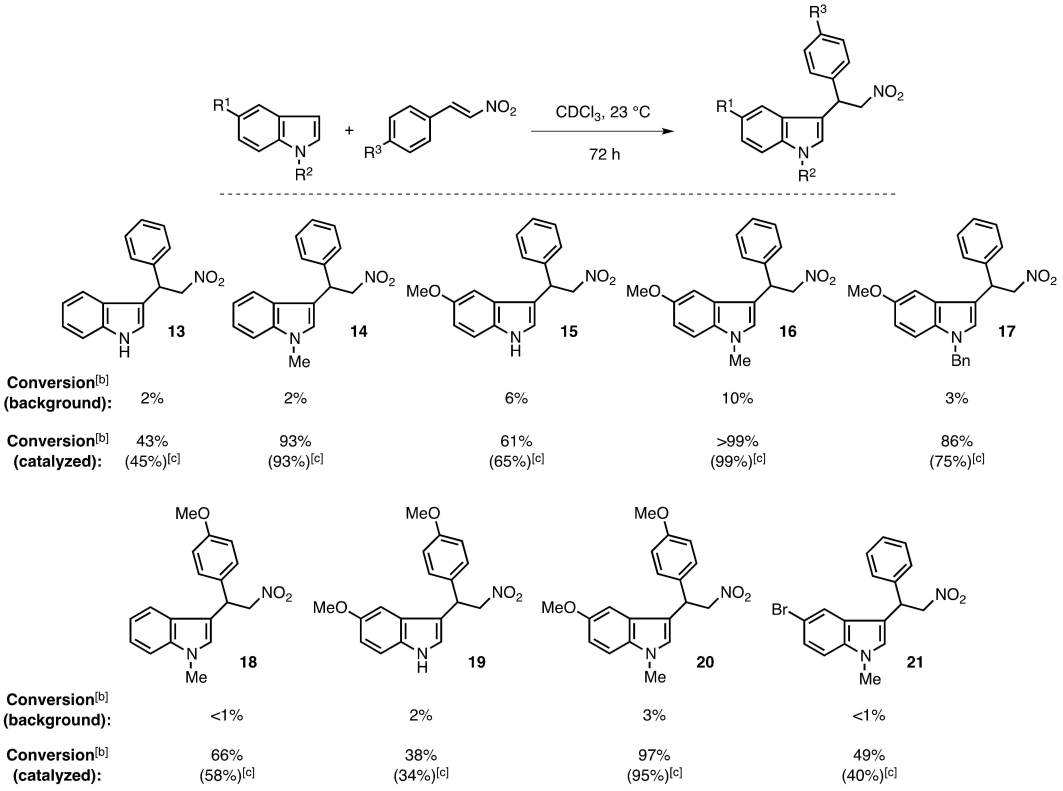


Figure 8. ^{31}P-NMR titration studies using 8-methoxy-1-naphthol (**9**) and Ph_3PO in CH_3CN.

Finally, the complexation of 1-naphthol (**10**) to Ph_3PO was examined by ^{31}P-NMR spectroscopy in order to make a quantitative comparison with the results obtained using 1,8-DHN (**8**). A 1:1 binding was revealed by the Job plot analysis, which was further supported by the fitting of the NMR titration data to a 1:1 model (Figure 9). The titration experiments using Ph_3PO as host and 1-naphthol (**10**) as guest in CH_3CN were performed twice, and provided $K = 6.5 \pm 0.4\ M^{-1}$.[22] These results showed that compound **10** is a weaker HB donor than 1,8-DHN (**8**), and supported the beneficial role of the polarization-assisted HB present in diol **8**.

2.3. Catalytic Studies

The ability of 1,8-DHN (**8**) to act as a HB catalyst was examined in the Friedel-Crafts-type conjugate addition reaction of indoles to β-nitrostyrene derivatives (Scheme 1).[37] For each substrate pair, the catalytic reactions with 10 mol% catalyst loading were run at 23 °C in $CDCl_3$ as duplicates, and the average conversion values, which were determined by ^{1}H-NMR spectroscopy, were compared with those obtained for the background reactions under the same reaction conditions. In addition, yields of each product after purification by column chromatography have been determined for the catalyzed reactions. In all cases, significant rate enhancements were observed with the use of **8** as a HB catalyst. The background reactions of indole and *N*-methylindole with β-nitrostyrene (**12**) in the absence of a catalyst are extremely slow giving the conjugate addition products with only 2% conversion after 72 h. On the other hand, with 10 mol% of 1,8-DHN (**8**) as catalyst, unsubstituted indole afforded adduct **13** with 43% conversion, whereas the use of *N*-methylindole gave rise to a significant increase in rate of the catalytic conjugate addition reaction to give product **14** with both conversion and isolated yield values of 93%. The rate enhancement differences of indole and *N*-methylindole may be attributed to the presence of the N–H moiety in unsubstituted



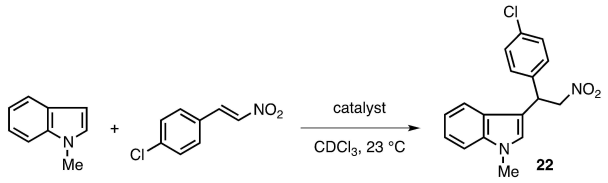
Scheme 1. Friedel-Crafts-type conjugate addition reactions of indoles to β-nitrostyrene derivatives.[a] The catalytic reactions were carried out using 0.50 mmol of indole, 0.75 mmol of β-nitrostyrene and 0.05 mmol of 1,8-DHN (**8**) in $CDCl_3$ (0.50 mL) at 23 °C for 72 h. [b] All background and catalyzed reactions were run as duplicates, and average conversion values, determined by ^{1}H-NMR spectroscopy, are reported. [c] Isolated product yields after purification by column chromatography are given in parentheses.

indole, which can also act as a HB donor.[38] Indeed, when indole was used as a substrate in the catalytic reaction, a competition between the two HB donors, indole and 1,8-DHN (**8**), is expected for complexation to the HB acceptor β-nitrostyrene (**12**). Even though **8** is a stronger HB donor than indole, its concentration is much lower throughout most of the reaction as it is used with 10 mol% loading. Therefore, it is reasonable to expect that a significant portion of β-nitrostyrene molecules is hydrogen-bonded to indole molecules while this complexation will not lead to a considerable increase in the reactivity of β-nitrostyrene (**12**) due to the low HB donating ability of the indole N–H group. On the other hand, *N*-methylindole is devoid of a relatively strong HB donor group and therefore, does not compete with 1,8-DHN (**8**) for complexation to β-nitrostyrene. A similar rate enhancement with *N*-substitution was observed in the conjugate addition reactions of 5-methoxyindole derivatives. Whereas the conjugate addition product **15** was observed to form with 61% conversion, *N*-Me- and *N*-Bn-substituted 5-methoxyindoles gave adducts **16** and **17** with $>$99% and 86% conversion values. It should be noted that purification by chromatography afforded adducts **15**, **16** and **17** in 65, 99 and 75% isolated product yields, respectively.

We next investigated the conjugate addition of indoles to the more electron-rich 4-methoxy-β-nitrostyrene (Scheme 1). Due to the lower electrophilicity of this Michael acceptor, the catalytic reactions of *N*-methylindole and 5-methoxyindole gave adducts **18** and **19** with lower conversion values, 66% and 38%, respectively. However, adduct **20** was observed to form faster with a conversion of 97% when 5-methoxy-*N*-methylindole was used as substrate. This product (**20**) was isolated in 95% yield after purification by column chromatography. Finally, when 5-bromo-*N*-methylindole was tested as a slightly electron-deficient indole derivative in the conjugate addition reaction to β-nitrostyrene, adduct **21** was found to form with 49% conversion, and was isolated with 40% yield.

After the demonstration of 1,8-DHN (**8**) as an active HB catalyst for the conjugate addition reactions of indoles, we sought to confirm the beneficial effect of the intramolecular HB present in **8** via a series of control experiments. To this end, we investigated the Friedel-Crafts-type reaction between *N*-methylindole and 4-chloro-β-nitrostyrene to form adduct **22** in the presence of a variety of HB donors (Table 2). Firstly, adduct **22** formed with only 2% conversion after 72 h in the absence of a HB donor (entry 1). When 1,8-DHN (**8**) was used as a catalyst with 10 mol% loading, conversion to **22** was observed to be quantitative ($>$99%) after 72 h, whereas 8-methoxy-1-naphthol (**9**) gave **22** with only 5% conversion even with 20 mol% loading (entries 2 and 3). The latter result is in accordance with the NMR titration studies discussed in the previous section

Table 2. Comparison of the catalytic activities of naphthols **8**, **9** and **10**.[a]



entry	catalyst	catalyst mol %	conversion (%)[b] 72 h	24 h
1	–	–	2	N.D.
2	**8**	10	>99 (99)[c]	87
3	**9**	20	5	N.D.
4	**10**	20	77	25

[a] The catalytic reactions were carried out using 0.50 mmol of *N*-methylindole and 0.75 mmol of 4-chloro-β-nitrostyrene in $CDCl_3$ (0.50 mL) at 23 °C for 72 h. As catalysts, 0.05 mmol (10 mol%) of **8**, or 0.10 mmol (20 mol%) of **9** and **10** were tested. [b] All reactions were run as duplicates, and average conversion values, determined by ^{1}H-NMR spectroscopy, are reported. [c] Isolated product yield after purification by chromatography is given in parentheses.

indicating that 8-methoxy-1-naphthol (**9**) does not act as a HB donor and thus, is not capable of activating 4-chloro-β-nitrostyrene towards the conjugate addition reaction. When the HB donor 1-naphthol (**10**) was tested as a catalyst with 20 mol% loading, the conversion to adduct **22** was observed to be 77% after 72 h (entry 4). For a better comparison, the conversion values for the reactions with 1,8-DHN (**8**) and 1-naphthol catalysts were determined after 24 h. Whereas diol **8** afforded adduct **22** with 87% conversion, the reaction with 1-naphthol HB catalyst was observed to be lower yielding with a conversion value of 25% (entries 2 and 4). These results strongly support the beneficial effect of the intramolecular HB of 1,8-DHN (**8**) on its catalytic activity.

Computational studies. In the final section, we opted to provide a rationale for the high activity of 1,8-DHN (**8**) as a HB catalyst in the addition reactions of indoles to β-nitrostyrenes. To this end, the binding of 1,8-DHN (**8**) and 1-naphthol (**10**) to β-nitrostyrene (**12**) was investigated computationally. These computations were performed at the ωB97XD/6-311++G(d,p) level. To investigate the intermolecular interactions, the non-covalent interaction (NCI) energies and binding free energies were evaluated at 23 °C and 1 bar.[39] All NCI energies, hence, binding energies were counterpoise corrected.[40] Binding free energies were obtained by adding thermal Gibbs corrections to the corresponding NCI energies, which correspond to the binding energies at zero Kelvin. Both HB donors were found to interact with one of the oxygens of the nitro group of β-nitrostyrene (**12**) via a single-point HB interaction (Figure 10). We should add that, despite all our attempts, we could not locate a minimum energy structure for a **8**·**12** complex with two HB interactions between the two –OHs of **8** and the two oxygens of **12**, and which lacks an intramolecular HB in the 1,8-DHN core. The ΔG value for the formation of **8**·**12** complex was calculated to be −6.3 kcal/mol, whose magnitude is 1.9 kcal/mol higher than the ΔG value for the formation of **10**·**12**

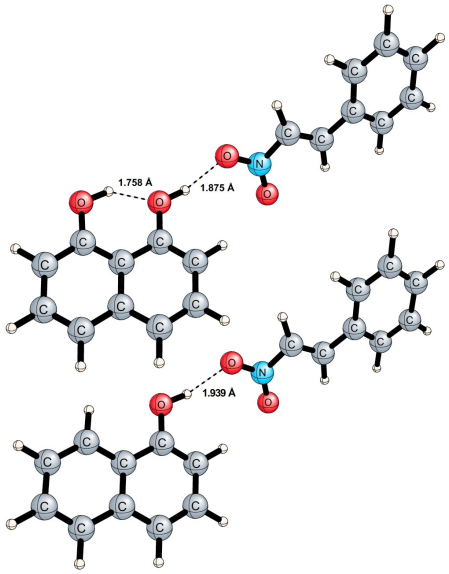


Figure 10. Computational studies on the binding of 1,8-DHN (**8**) and 1-naphthol (**10**) to β-nitrostyrene (**12**).

complex (−4.4 kcal/mol). The stronger binding of **8** is also reflected in the hydrogen bond distances in these two complexes. The HB distance in the **10**·**12** complex was observed to be 1.939 Å, whereas **8**·**12** complex exhibits an intermolecular HB distance of 1.875 Å, indicative of a stronger non-covalent interaction. Finally, the LUMO energy of β-nitrostyrene (**12**) was compared with those of complexes **8**·**12** and **10**·**12**. The LUMO of the **8**·**12** complex was computed to be 0.71 eV lower in energy compared to the LUMO of β-nitrostyrene (**12**) alone. On the other hand, the **10**·**12** complex was calculated to have a LUMO, whose energy is 0.54 eV lower than that of β-nitrostyrene (**12**). Since a decrease in the LUMO energy results in an increase in the electrophilicity of a compound, these results explain well why both HB donors **8** and **10** are capable to enhancing the reaction rate of the addition of indoles to β-nitrostyrenes. More importantly, a lower LUMO energy of the **8**·**12** complex provides a rationale for the high catalytic activity of 1,8-DHN (**8**) as a HB donor.

In order to further support our hypothesis that 1,8-DHN (**8**) activates β-nitrostyrene (**12**) via hydrogen bonding, we investigated their complexation in $CDCl_3$ by ^{1}H-NMR titration studies.[22] The –OH signal of 1,8-DHN was found to be affected significantly as a result of such a HB interaction. Indeed, this hydrogen experienced a downfield shift of 0.59 ppm upon addition of 18 equivalents of β-nitrostyrene (**12**). The titration data were found to fit best to a 1:1 binding model providing a binding constant (K) value of 3.7 M^{-1}.[36] The lower magnitude of this binding compared to that between 1,8-DHN and Ph_3PO

can be attributed to the weaker HB accepting ability of the $-NO_2$ group compared to a phosphine oxide.[41]

Next, we sought to examine computationally the binding of diol **8** to a different HB acceptor functionality, and selected formaldehyde (**23**) for this purpose. The carbonyl group of formaldehyde has only one oxygen that can act as a HB acceptor, as opposed to the two oxygens of the nitro group of β-nitrostyrene (**12**) as potential HB acceptors. Despite these structural differences, the binding modes of 1,8-DHN (**8**) to these two HB acceptors were calculated to be very similar. Indeed, our efforts to locate a minimum energy structure for a complex between **8** and formaldehyde (**23**) in which **8** acts as a dual HB donor (two-point HB interaction) failed, and both 1,8-DHN (**8**) and 1-naphthol (**10**) were computed to make complexes with formaldehyde (**23**) via a single-point HB interaction (Figure 11). The ΔG values for the complexation of 1,8-DHN (**8**) and 1-naphthol (**10**) to formaldehyde (**23**) were computed to be -2.7 and -1.2 kcal/mol, respectively. The shorter intermolecular HB distance of 1.872 Å in the **8·23** complex compared to 1.943 Å in the **10·23** complex is in agreement with the computed ΔG values. Finally, the LUMO energy of formaldehyde (**23**) was calculated to decrease by 0.82 eV upon binding to diol **8**, whereas hydrogen bonding with 1-naphthol (**10**) led to a decrease in the LUMO energy of **23** by only 0.57 eV. These computational results are in accordance with the results of the ^{13}C-NMR experiments using cyclohexanone as the HB acceptor, and indicate that 1,8-DHN (**8**) might be an effective catalyst for the activation of carbonyl groups as well in addition to β-nitrostyrenes.

3. Conclusion

In conclusion, 1,8-dihydroxynaphthalene (**8**) has been shown to be a powerful HB donor due to polarization effect caused by the intramolecular hydrogen bond between the two –OH groups. First, single-crystal X-ray diffraction analysis of 1,8-DHN (**8**) exhibited an infinite chain structure constructed by intra- and intermolecular HBs. Afterwards, the hydrogen bonding behavior of diol **8**, 8-methoxy-1-naphthol (**9**) and 1-naphthol (**10**) in solution phase was investigated via a series of ^{1}H-NMR experiments. Finally, computational studies in the gas phase revealed the favorable nature of the intramolecular HBs in compounds **8** and **9**.

In the second part, binding studies were carried out for the complexation of HB donors **8**, **9** and **10** to Ph_3PO using ^{31}P-NMR spectroscopy. Determination of binding constants by NMR titration experiments confirmed the higher HB donating ability of diol **8** compared to 1-naphthol (**10**), whereas 8-methoxy-1-naphthol (**9**) was found to be an extremely ineffective HB donor because of the intramolecular hydrogen bond present in its structure.

In the last part of this work, the catalytic activity of 1,8-DHN (**8**) as a HB donor catalyst was examined in the Friedel-Crafts-type addition reaction of indoles to β-nitrostyrenes. In all cases, high rate enhancements were observed with the use of diol **8** with 10 mol% catalyst loading compared to background reactions. In addition, the higher catalytic activity of **8** compared to mono-naphthol derivatives **9** and **10** was demonstrated through careful control experiments. The energetically more favored binding of diol **8** to both β-nitrostyrene (**12**) and formaldehyde (**23**) than that of 1-naphthol (**10**) was shown by computational investigation of the ΔG values of these complexation processes. Finally, the complexation of diol **8** was calculated to decrease the LUMO energies of both HB acceptors, β-nitrostyrene (**12**) and formaldehyde (**23**), significantly more compared to the complexation of 1-naphthol (**10**).

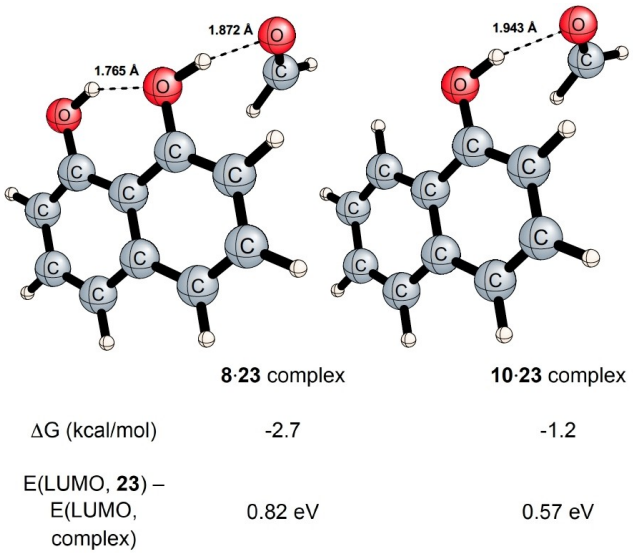


Figure 11. Computational studies on the binding of 1,8-DHN (8) and 1-naphthol (10) to formaldehyde (**23**).

Supporting Information Summary

Experimental procedures, X-ray crystallographic data, details of NMR titration experiments, characterization data, coordinates of computed structures and computational details, ^{1}H and ^{13}C {^{1}H}-NMR spectra are provided in the Supporting Information. Deposition Number CCDC 1948677 (for **8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/ .

Acknowledgements

Y.E.T. acknowledges the BAGEP Award of the Science Academy, Turkey. Financial support from the Scientific and Technological Research Council of Turkey (TÜBİTAK; Grant No: 116Z506) is gratefully acknowledged. We also acknowledge Scientific and Technological Research Application and Research Center, Sinop University, Turkey, for the use of the Bruker D8 QUEST diffractometer.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: cooperative effects · 1,8-dihydroxynaphthalene · hydrogen bonds · NMR titration · organocatalysis

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Submitted: July 27, 2020
Accepted: October 30, 2020