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A Colorimetric Proton Sponge

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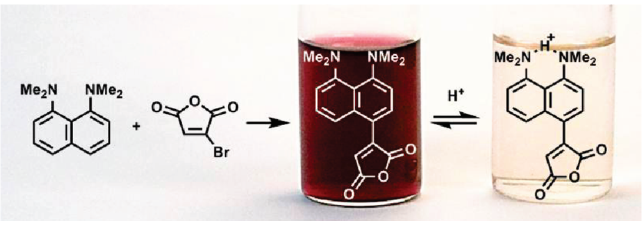

1,8-Bis(dimethylamino)naphthalene ("Proton Sponge") and bromomaleic anhydride react quickly at room temperature, generating 3-(4,5-bis(dimethylamino)napthalen-1-yl)furan-2,5-dione (4-maleicanhydridoproton sponge or "MAPS"). MAPS is a deep purple solid that exhibits positive solvatochromism in solution. It is a weaker base than Proton Sponge. When protonated in solution, MAPS loses its color, but the color change can be reversed by deprotonation with a stronger base. MAPS thus acts as a colorimetric version of a proton sponge.

1,8-Dimethylaminonaphthalene, trademarked by Aldrich as Proton Sponge, is a widely used base in organic and inorganic chemistry. It is often chosen due to its high basicity (BH$^+$ pK_a = 12.34 in H_2O[1] and 18.62 in MeCN[2]) and slow uptake of protons. It is also generally regarded as an innocent, non-nucleophilic, and noncoordinating base relative to other amines. However, it has been shown that Proton Sponge (PS) can act as a *carbon* nucleophile in electrophilic aromatic substitution reactions.[3] Due to the electron-donating nature of the amino groups, Proton Sponge (like other anilines) is more reactive than unsubstituted aromatics to typical electrophilic aromatic substitution reactions (nitration,[4,5] Friedel–Crafts acylation,[6] Vilsmeier–Haack reaction,[7] etc.). Reactions with carbon electrophiles are typically slow, except with very exotic and strong electrophiles.[3,8–12]

Maleic anhydrides readily undergo hydrophosphination with secondary phosphines.[13,14] More specifically, bromomaleic anhydride (BMA) reacts with 2 equiv of secondary phosphine, forming unique bisphosphines that can be used as bidentate ligands.[15] After addition of 1 equiv of phosphine, HBr is eliminated, re-forming the double bond and allowing the second equivalent of phosphine to react. While investigating the utility of this reaction with *coordinated* secondary phosphines, we combined coordinated phosphine, bromomaleic anhydride, and Proton Sponge to neutralize the HBr byproduct. Upon addition of Proton Sponge to the reaction mixture, a deep purple product formed within seconds. Control reactions showed that Proton Sponge and bromomaleic anhydride reacted in the *absence* of the metal complex or the phosphine to generate this new product. Slow evaporation of the reaction solution resulted in deep purple crystals suitable for X-ray diffraction, which were found to be 4-maleicanhydridoproton sponge (MAPS).

Proton Sponge and bromomaleic anhydride react within seconds at room temperature in a variety solvents (chloroform, dichloromethane, acetonitrile, THF). This reaction can be viewed as *both* an electrophilic aromatic substitution, with bromomaleic anhydride acting as the electrophile, and as a Michael reaction, with Proton Sponge acting as the nucleophile. Because HBr is a byproduct of this coupling, 2 equiv of Proton Sponge are needed for the reaction to reach completion. One equivalent couples with BMA, while the other neutralizes HBr (Scheme 1). Attempts at using a different base (such as sodium methoxide) to avoid using 2 equiv of Proton Sponge in the reaction resulted in decomposition of the product.

SCHEME 1. Coupling of Proton Sponge and Bromomaleic Anhydride

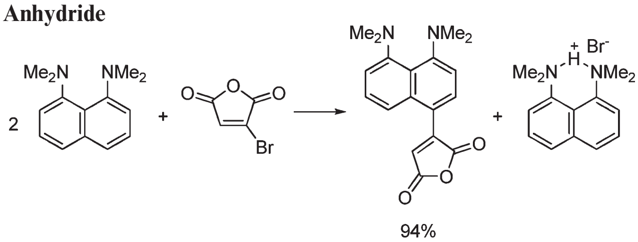

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TABLE 1. Selected Structural Parameters of MAPS and PS

molecule	N−N distance (Å)	C1−C9−C10−C4 torsion angle (deg)	sum of C−N−C angles (deg)	N1−C1−C9 (α) (deg)	N2−C8−C9 (β) (deg)	C1−C9−C8 (γ) (deg)	naphthalene−maleic anhydride torsion angle (deg)
Λ-MAPS	2.825	16.7 17.7	353.5 348.6	121.1	119.9	123.1	26.8
Δ-MAPS	2.832	15.9 16.8	350.8 347.2	121.1	120.2	124.1	25.0
PS	2.79	8.9 10.5	347.1	120.1	120.8	125.8	n/a

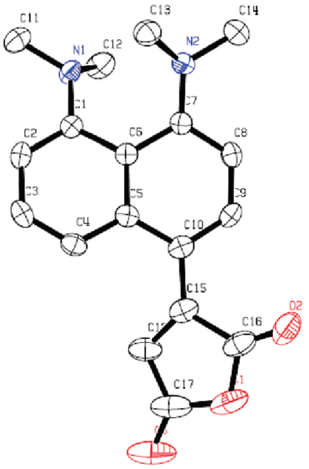

FIGURE 1. ORTEP plot of MAPS. The ellipsoids are drawn at 50% probability, and the hydrogen atoms have been omitted for clarity.

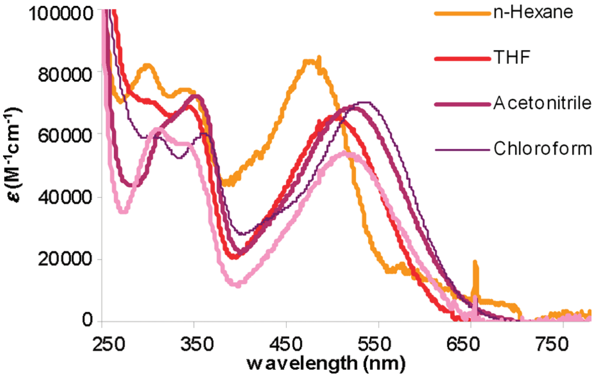

FIGURE 2. UV−vis spectra of MAPS in various solvents.

Researchers following the procedure in the Experimental Section for the synthesis of MAPS may wonder why the THF solvent needs to be removed and then reintroduced following the reaction. The PSH^+Br^- byproduct of the reaction is insoluble in THF, which may lead some to conclude that it can be removed by filtration at this point. However, PSH^+Br^- does not quickly precipitate from the THF reaction solution. When the solvent is evaporated under reduced pressure, both products precipitate from solution, but only MAPS redissolves in THF. Thus, from a practical standpoint, it is easier to conduct the reaction in THF, evaporate off the solvent, redissolve the products in THF, and filter than to wait for the PSH^+Br^- byproduct to precipitate from solution.

The HBr byproduct of the reaction is almost entirely neutralized by PS, suggesting that MAPS is a weaker base than PS. To quantify this, the pK_a of MAPS was determined by titration with PSH^+Cl^- in acetonitrile. The pK_a was found to be 18.00, slightly less basic than the parent proton sponge.

X-ray crystallography confirms the structure of MAPS (Figure 1). The unit cell is monoclinic, with two inequivalent molecules per unit cell. The naphthalene rings, and therefore the dimethylamino groups, are twisted, with the first molecule having a Λ (left-handed) twist and the second having a Δ (right-handed) twist. Table 1 lists important structural parameters. The maleic anhydride ring is twisted 25° out of plane from the naphthalene ring in one of the independent molecules and 27° in the other.

The most important structural parameters of derivatized proton sponges are the orientation of the dialkylamino groups and the planarity of the aromatic system.[16] The naphthalene ring of MAPS is more distorted than PS, with internal (C1−C9−C10−C4) torsion angles of 15.9−17.7° vs 8.9−10.5° for PS. Thus, the N−N interatomic distances of MAPS are slightly longer than PS at 2.825 and 2.832 Å (vs 2.79 Å for PS).[17] On the basis of the torsion angle θ between the nitrogen lone pairs and the naphthalene ring plane, the four nitrogen lone pairs (in the two independent molecules) are between 68% and 77% conjugated to the aromatic ring. (These percentages were calculated using the equation $M = M_0 \cos^2 \theta$, where M is the percent conjugation.[16]) This is more conjugated than PS (59%) and is consistent with the decreased basicity of MAPS compared to PS.[18] (The decreased basicity is due to the electron-withdrawing maleic anhydride group, which removes electron density from the amine moieties, causing MAPS to be less basic than Proton Sponge.) Finally, note that the geometry of each nitrogen is slightly more planar than PS, with C−N−C angles totaling 347.2° to 353.5° (vs 347.1 for PS).

In solution, MAPS exhibits solvatochromism, ranging from orange in hexanes to purple in chloroform (Figure 2). Table 2 lists λ_{max} values and the extinction coefficients in various solvents. MAPS exhibits positive solvatochromism in halogen-free solvents, with λ_{max} correlating with Reichardt's E_T^{30} polarity parameter.[19] Positive solvatochromism has been observed for other substituted proton sponges in their free base and/or protonated forms.[20−23] However, MAPS remains purple in

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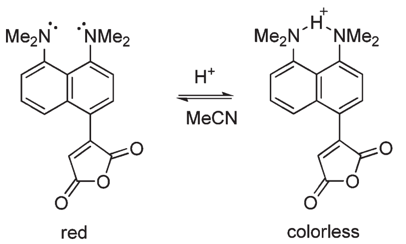
TABLE 2. UV−vis Spectral Data in Various Solvents

solvent	$E_T(30)$	color	λ_{max} (nm)	ε (M^{-1} cm^{-1})
n-hexane	31	orange	480	83200
THF	37	red	504	65200
t-butyl alcohol	43	red	516	53700
acetonitrile	46	red	521	68500
chloroform	35	purple	536	70300

SCHEME 2. Acid−Base Switchable Colorimetric Behavior in Acetonitrile



chloroform ($\lambda_{max} = 536$ nm) and dichloromethane, even though these solvents are *less* polar than acetonitrile ($\lambda_{max} = 521$ nm). The apparently anomalous λ_{max} values in these two solvents may be due to their hydrogen-bonding ability, as indicated by their large α values.[24]

The deep color of the neutral compound is presumably due to the presence of conjugated electron-donor (amine) and electron-acceptor (anhydride) groups on the molecule. The standard interpretation[25,26] is that excitation by visible light causes the nitrogen lone pair to donate via conjugation to the maleic anhydride moiety. Protonation of the nitrogen atoms should prevent this mode of excitation. In fact, MAPS can be protonated in wet acetonitrile by glacial acetic acid, resulting in a loss of color. When PS is added to the acetonitrile solution of protonated MAPS, MAPS is deprotonated and color is restored (Scheme 2).

Although the reaction of PS and bromomaleic anhydride was unanticipated, similar reactivity has previously been seen with other tertiary anilines and activated alkenes. For example, tertiary anilines are known to act as carbon nucleophiles toward tetracyanoethylene[27] as well as halogenated maleic anhydrides and maleimides.[28,29] Note, however, that this type of reactivity has not previously been observed for Proton Sponge, even though it has been reacted before in the presence of tetracyanoethylene.[30]

The coupling of PS with BMA is not only a synthetic curiosity but may allow for efficient functionalization of proton sponges. Dimethylaniline has been functionalized with various maleic anhydrides to form dyes.[29] In addition, maleic anhydrides can undergo condensation reactions with primary amines to form maleimides. Work is ongoing in our laboratory to synthesize solid-supported proton sponges,[31,32] which could be used for easy column-purification of products or as heterogeneous catalysts.

Experimental Section

X-ray Crystallography. X-ray diffraction intensities for MAPS were collected at 173(2) K on a Bruker Apex CCD diffractometer using Mo Kα radiation λ = 0.71073 Å.[33] The space group was determined on the basis of systematic absences. The absorption correction was applied by SADABS.[34] The structure was solved by direct methods and Fourier techniques and refined on F^2 using full-matrix least-squares procedures. All non-H atoms were refined with anisotropic thermal parameters. H atoms were found from the residual map and refined with isotropic thermal parameters. An absolute configuration could not be determined because the compound is a weak anomalous scatterer. All calculations were performed by the Bruker SHELXTL (v. 6.10) package.[35]

Synthesis of 4-Maleicanhydridoproton Sponge (MAPS). 1,8-Bis(dimethylamino)naphthalene (954 mg, 0.45 mmol) in 10 mL of THF was added to bromomaleic anhydride (393 mg, 0.22 mmol) in 5 mL of THF with stirring. Upon mixing, the reaction mixture immediately turned deep red. After the mixture was stirred for 15 min, the solvent was removed under reduced pressure, and the residue was redissolved in 50 mL of THF and filtered to remove PSHBr. The solvent was removed under reduced pressure, yielding a purple hygroscopic solid (645 mg, 94%): mp 116−127 °C; ^{1}H NMR (500 MHz, $CDCl_3$, COSY, NOESY) δ 2.81 (s, 2CH_3), 2.95 (s, 2CH_3), 6.87 (d, J = 8.65 Hz, H2), 6.88 (s, H14), 6.96 (d, J = 7.56 Hz, H7), 7.41 (t, J = 8.01 Hz, H6), 7.58 (d, J = 8.52 Hz, H5), 7.91 (d, J = 8.51 Hz, H3); ^{13}C δ 43.2 (CH_3), 43.3 (CH_3), 109.4 (CH), 112.4 (CH), 115.3, 116.1 (CH), 121.6 (CH), 128.0 (CH), 131.8 (CH), 135.0, 136.2, 146.2, 151.7, 154.8, 165.3, 166.6; IR 2962.5 (m), 1824.4 (m), 1754.9 (s), 1660.0 (s), 801.8 (m). Anal. Calcd for $C_{18}H_{18}N_2O_3 \cdot {}^1/_3H_2O$: C, 68.34; H, 5.95; N, 8.86. Found: C, 68.42; H, 6.07; N, 8.95.

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Supporting Information Available: NMR spectra of MAPS (^{1}H, ^{13}C, ^{1}H−^{1}H COSY, and ^{1}H−^{1}H NOESY), pK_a titration data, and crystallographic data tables. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. The correct chemical name, 1,8-bis(dimethylamino)naphthalene, was added to the beginning of the last paragraph in the Experimental Section in the version reposted ASAP September 24, 2010.

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