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COMMUNICATIONS

Published on Web 01/27/2004

Multiple Hydrogen Bonds Tuning Guest/Host Excited-State Proton Transfer Reaction: Its Application in Molecular Recognition

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Among various types of approaches for biorecognition, the principle of using hydrogen bonds to confer binding strength and selectivity is of particular interest[1a−g] mainly due to their relative flexibility in geometry compared to rigid covalent bonds.[1h,i] Because guest molecules of biological interest may possess various numbers of proton-donating and/or -accepting groups, the design and syntheses of host receptors providing multiple hydrogen-bonding sites are necessary to maximize the recognition capacity. We further proposed that induced by the multiple hydrogen bonds, the redistribution of π electrons might result in unusual photophysical properties such as the host/guest type of excited-state proton-transfer (ESPT) reaction,[2] providing a superb opportunity for enhancing signal transduction.

In an effort to apply this concept to molecular recognition, we have examined numerous multiple-hydrogen-bonding (HB) systems, among which 3,4,5,6-tetrahydrobis(pyrido[3,2-g]indolo)[2,3-a:3′, 2′-j]acridine (**1a**, Scheme 1), designed and synthesized by Thummel and co-workers,[3] is an exquisite case in point. **1a** was designed so that pyrrole and pyridine moieties function as the proton donor and acceptor, respectively. Two symmetric push−pull conjugated units form a V-shaped framework with a cleft of appropriate size to provide as many as five HB sites. This, in combination with a flexible dimethylene skeleton, renders a preorganized motif particularly suitable for the multiple-HB recognition. The HB association between **1a** and urea derivatives has been investigated via monitoring of the ^{1}H NMR chemical shifts.[3]. We report here certain previously unrecognized, remarkable photophysical properties in that the catalytic versus noncatalytic **1a** HB systems (vide infra) play a key role in tuning ESPT, which leads to a feasible design for sensing multiple-HB-site analytes of biological interest.

Upon titration of **1a** with acetic acid, the 405 nm vibronic band ascribed to the S_0-S_1 ($\pi\pi^*$) transition of free **1a** in benzene revealed bathochromic shifts with the appearance of an isosbestic point at 410 nm (Figure 1). The measured absorbance $[A_0/(A - A_0)]$ as a function of [acetic acid]$^{-1}$ fit a linear relationship,[4] supporting the 1:1 HB complex formation. The ratio for the intercept versus slope deduced a K_a value of $(8.0 \pm 0.5) \times 10^3$ M^{-1} (see Supporting Information). During the titration, drastic quenching of the 420 nm fluorescence intensity was observed, accompanied by the appearance of a weak, large Stokes shifted emission maximized at ~600 nm and an isoemissive point at 580 nm (see insert of Figure 1). A linear plot of $F_0/(F - F_0)$ versus [acetic acid]$^{-1}$ for both bands reconfirmed the 1:1 complex formation, and K_a was deduced to be $(8.3 \pm 0.3) \times 10^3$ M^{-1} (see Supporting Information).[4] The excitation spectrum monitored at the 420 nm band is identical to the absorption profile of free **1a**, while it is red shifted with respect to that of the 420 nm band upon being monitored at the 600 nm band (see Supporting Information). These results, in combination with significantly different lifetimes between 420 nm (1.60 ns) and 600 nm (0.24 ns) bands, led us to conclude that the dual fluorescence originates from different ground-state precursors, namely, the uncomplexed **1a** and 1:1 **1a**/acetic acid HB complex. ESPT takes place in the 1:1 **1a**/acetic acid HB complex (Scheme 2), resulting in an ~7200 cm^{-1} Stokes shifted imino-like tautomer emission. A further approach using the femtosecond fluorescence upconversion technique (see Supporting Information) revealed a system-response limited (<150 fs) rise component at the 600 nm band, indicating the occurrence of an ultrafast, possibly barrierless ESPT reaction in the **1a**/acetic acid HB complex.

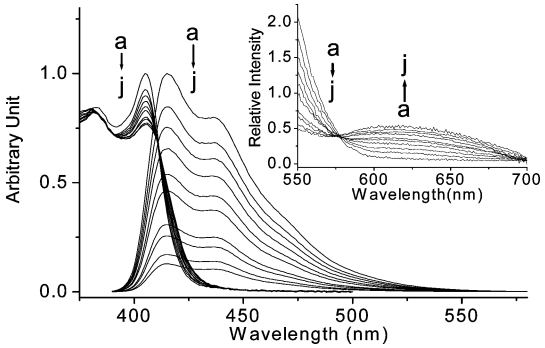
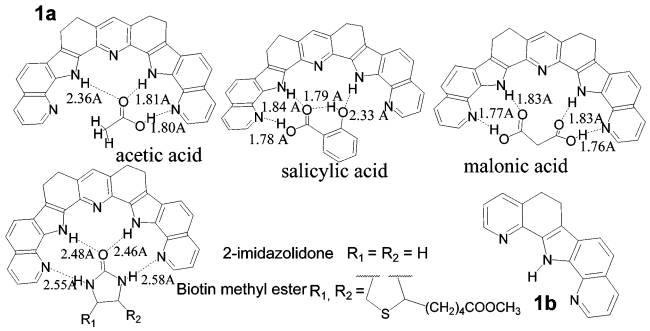


Figure 1. Absorption and emission of **1a** (1.2×10^{-5} M) in benzene by adding [acetic acid] of (a) 0, (b) 1, (c) 2, (d) 4, (e) 6, (f) 10, (g) 20, (h) 40, (i) 50, (j) 80 equiv (1 equiv = 1.5×10^{-5}M). Insert: Enlargement of fluorescence titration at >550 nm.

Scheme 1. Optimized Structures of Various **1a**/Guest Complexes Calculated by PM3 Method



Other biosignificant carboxylic acids possessing multiple HB sites such as malonic acid and salicylic acid (see Scheme 1) were also investigated. From the absorption titration, K_a values were deduced to be $(1.1 \pm 0.1) \times 10^5$ and $(5.4 \pm 0.2) \times 10^3$ M^{-1} for **1a**/malonic acid and **1a**/salicylic acid HB complexes, respectively. For both systems, similar to the case of **1a**/acetic acid, the decrease of 420 nm fluorescence accompanied by the appearance of a weak, ~600 nm emission was observed during the titration,[5] supporting the

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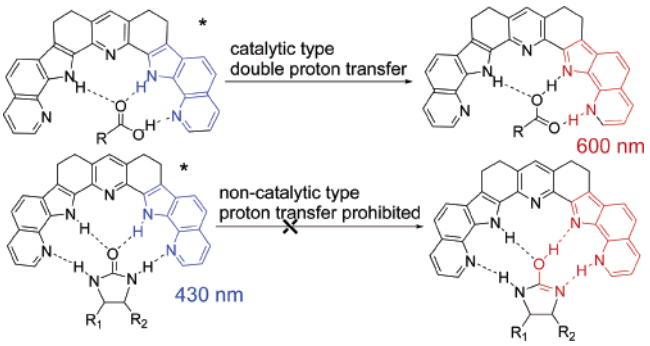
10.1021/ja039240f CCC: $27.50

Scheme 2



occurrence of an ESPT reaction through the HB complex formation. Although attempts to grow single crystals of corresponding **1a**/carboxylic acids HB complexes were not successful, their structure might qualitatively be rationalized by the molecular modeling,[6] in which the **1a**/acetic acid complex revealed a stable complexation incorporating triple hydrogen bonds, while a well-fitted quadruple HB **1a**/malonic acid complex was resolved (see Scheme 1). For the case of the **1a**/salicylic acid triple-HB complex, the K_a value smaller than that of **1a**/acetic acid is possibly due to the preorganization of the phenyl moiety in fitting the cleft of **1a** (see Scheme 1). Support for the multiple HB formation is also given by the synthesis of 6,13-dihydro-5*H*-1,12,13-triaza-dibenzo[a,i]fluorene (**1b**, Scheme 1; Supporting Information), which is considered as a half unit of **1a**, so that an upper limit of dual hydrogen bonds can be formed with acetic acid. Although the formation of **1b**/acetic acid hydrogen-bonded complex was observed as well, a much smaller association constant of $(5.8 \pm 0.2) \times 10^2$ M^{-1} was deduced in benzene.

Upon addition of urea derivatives such as 2-imidazolidone and biotin methyl ester (BME see Scheme 1), the absorption titration revealed spectral red shifts similar to those of **1a**/carboxylic acids. However, during the fluorescence titration, instead of the quenching of 420 nm emission, as in the case of carboxylic acids due to ESPT, the 420 nm fluorescence exhibits a bathochromic shift throughout the titration (Figure 2). The appearance of an isoemissive point at ~425 nm with a dual lifetime ($\tau_f \sim 1.60$ and 3.61 ns), in combination with a straight line for the plot of $[F_0/(F - F_0)]$ versus $[\text{imidazolidone}]^{-1}$ (see insert of Figure 2), is consistent with the 1:1 **1a**/imidazolidone (or **1a**/BME) HB complexation. Accordingly, K_a values of $(2.0 \pm 0.2) \times 10^4$ and $(1.0 \pm 0.5) \times 10^4$ M^{-1} were deduced for **1a**/imidazolidone and **1a**/BME, respectively. The large association constants can be qualitatively rationalized by the quadruple HB **1a**/imidazolidone complex resolved from X-ray structure[3] as well as modeling (Scheme 1).

Accordingly, depending on the properties of the guest molecules, the photophysics of the **1a**/guest complex vary drastically. On the basis of the chemical aspects of guest-molecule-assisted ESPT, we can classify the **1a**/guest HB complexes into two categories. As depicted in Scheme 2, the carboxylic acid assisted ESPT in **1a** can be specified as a *catalytic* process because following the ESPT reaction the molecular structure of the carboxylic functional group remains unchanged. Conversely, both **1a** and urea derivatives such as 2-imidazolidone and BME would have tautomerized (i.e., lactam → lactim) simultaneously if ESPT in **1a**/ureas HB complexes had taken place. This type of reaction is defined as a *noncatalytic* process, in which ESPT depends not only on the host (i.e., the receptor) but also on the isomerization of the guest molecule (i.e., the analyte) and is thus expected to be energetically less favorable. A qualitative approach from the PM3 method indicates that catalytic ESPT in **1a**/acetic acid is thermodynamically allowed by ~3 kcal/mol. In contrast, it is prohibited in the case of the noncatalytic **1a**/2-imidazolidone HB complex due to the ~4 kcal/mol endergonic energy required for simultaneous tautomerization of **1a** and 2-imidazolidone (see Supporting Information).

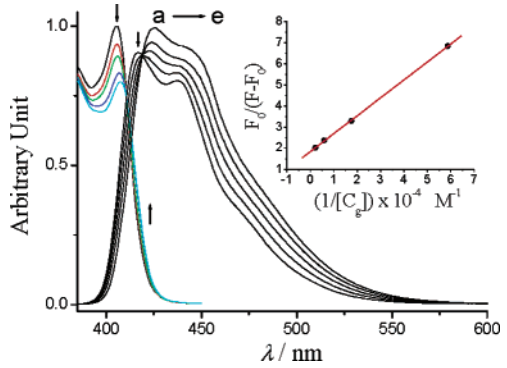


Figure 2. Fluorescence titration spectra of **1a** (1.2×10^{-5} M) in benzene upon adding 2-imidazolidone of (a) 0, (b) 3, (c) 10, (d) 30, (e) 80 equiv (1 equiv = 5.7×10^{-6} M). Insert: Plot of $F_0/(F - F_0)$ at 475 nm versus $[\text{imidazolidone}]^{-1}$ and its best least-squares fitting curve.

In conclusion, we present a recognition concept utilizing multiple-hydrogen-bond fine-tuned excited-state double-proton-transfer reaction. The catalytic versus noncatalytic ESPT demonstrates its suitability in differentiating carboxylic acids and urea derivatives. Although current applications of **1a** are limited in organic solvents, future conceptual design may focus on water-soluble multiple-HB receptors, in which the V-shape cleft allows only a few water molecules to be accommodated so that the multiple-HB strength for substrates of interest is competitively strong. In the case of **1a**, ESPT was observed by addition of H_2O ($>10^{-4}$ M) in CH_3CN. The occurrence of ESPT in protic solvents has the advantage of selectively probing urea derivatives due to the prohibition of ESPT in **1a**/ureas complexes. The enhancement of normal emission may thus be exploited as the signal transduction. Syntheses focusing on the multiple-hydrogen-bond-coupled ESIPT reaction in aqueous solution are currently in progress.

Supporting Information Available: Detailed experimental procedures and absorption, emission, time-resolved and X-ray studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) A_0 and A are the absorbance of free **1a** and the measured absorbance during the titration, respectively. Similarly, F_0 and F denote the fluorescence intensity of free and titrant added **1a**. See Supporting Information for details.

(5) Noted that upon adding higher concentrations ($>10^{-3}$ M) of malonic acid or salicylic acid protonation takes place, possibly due to increases in the local polarity, resulting in **1a** cationic emission maximum at ~530 nm.

(6) Molecular modeling was performed by the semiempirical PM3 method using a Spartan program package (release 3.1.6, Wavefunction, Inc., Irvine, 1994).

JA039240F