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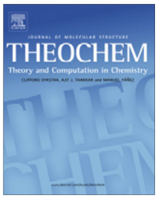

Electrostatic effects on the energetics and geometry of a cyanine dye

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ABSTRACT

Computations using B3LYP density functional method with 6-31G (d,p) and 6-311 + G (d,p) basis sets were carried out on a cationic cyanine dye at various locations of the Br^- counter ion. It was found that the Br^- position and its accompanying electric field have a significant affect on the charge distribution within the cationic dye. Furthermore, the enthalpy of anion/cation interaction was highly sensitive to the Br^- location. Bringing the Br^- either closer or further than the optimum is substantially destabilizing. The flexible cyanine dye molecule tends to fold to accommodate electrostatic interactions. On the other hand, less activation energy was required for the approach of F^- towards the cyanine dye (6 kcal/mol vs. 15 kcal/mol for the Br^- approach).

1. Introduction

Electrostatic effects are widely recognized as having important consequences for the structure, energy and reactivity of organic systems. [1] For example, electrostatics governs, in part, rotational barriers in amides; [2] the stereochemistry of addition to unsaturation; [3] the acidity of carbon acids; [4] and micellar reactivity. [5] It has been written that “much of chemistry is at least partially controlled by electrostatic interactions”. [1]

Electrostatic interactions also play a role in the antibiotic binding to DNA [6] and the properties of polypeptides. [7] In the field of enzyme catalysis, it has been argued that there exists “compelling evidence for the overwhelming importance of electrostatic contributions”. [8] According to this viewpoint, a pre-organized electrostatic stabilization of transition states by enzymes supersedes all other possible sources of catalysis (ground-state destabilization, dynamical and spatiotemporal effects, entropic considerations, desolvation, etc.). Whether a purely electrostatic enzyme model is valid or not, it is clear both chemistry and biochemistry alike would profit from a deeper understanding of electrostatics. [9]

An electrostatic effect is defined as a change in charge distribution arising from interactions among ionic or polar molecules. Metals, hydrogen-bonded systems, and induced dipoles are included in the definition. Four specific examples will further illustrate the prevalence and importance of electrostatics: (a) The pK_a values of *racemic*-2,3-di-t-butylsuccinic acid are 2.2 and 10.3 (an 8.1 unit decrease in acidity between the first and second ionization of the two carboxyl groups). [10] This huge effect is attributable to a strong intramolecular hydrogen-bond in the mono-anion and to an unfavorable electrostatic repulsion within the di-anion. (b) The enzyme acetoacetate decarboxylase is 50% inhibited by 0.10 M F^- but only by 0.0007 M ClO_4^-, thereby demonstrating that electrostatics can be associated with high selectivity. [11] (c) Taft σ^* polar substituent constants (which are relatively free from steric effects) for the CH_3-group (0.00) and for the Cl_2CH-group (+1.94) show that two α-chlorines electrostatically accelerate the basic hydrolysis of aliphatic esters by two orders of magnitude. [12] (d) Free energies of activation have been subdivided into electrostatic and covalent interactions. [13] If there is a large energy difference between the HOMO of a donor base and the LUMO of an acceptor acid, the reaction is dominated by electrostatic forces and is said to be charge-controlled. Such is the case in the nitration of pyridine-N-oxide at the 4-position as opposed to the covalently favored 2-position. Electrostatics can clearly determine regioselectivity.

2. Calculation methods

Computations utilized DFT at B3LYP/6-31G (d,p) and B3LYP/6-311 + G (d,p) methods that were carried out using the quantum chemical package Gaussian-98. [14] Starting geometries of the molecules were initially optimized at the AM1 [15] and HF/6-31G levels of theory. The calculations were carried out with full optimization of all geometrical variables. Global minimum structures of the cyanine dyes were found by conducting a 360° rotation

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of the dimethylamino group about the C/C bond to which it is connected (i.e. by altering the N/C/C/C dihedral angle in increments of 36°). The "reaction coordinate method" [16] was used to calculate the energy for each conformation along the reaction pathway. Thus, one bond-length was constrained at the appropriate degree of freedom while all other variables were freely optimized. The calculations with the incorporation of water were performed using the integral equation formalism model of the Polarizable Continuum Model (PCM). [17]

3. Results and discussion

This brief survey of electrostatics serves as a prelude to our own computational approach to the subject. We have focused on cyanine dye systems of the type shown below:

$$(CH_3)_2N^+{=}CH{-}CH{=}CH{-}CH{=}CH{-}N(CH_3)_2 \cdot Br^-$$

According to classical resonance theory, the cationic charge is shared equally between the two nitrogens:

$$(CH_3)_2N^+{=}CH{-}CH{=}CH{-}CH{=}CH{-}N(CH_3)_2$$
$$\leftrightarrow (CH_3)_2N{-}CH{=}CH{-}CH{=}CHCH{=}N^+(CH_3)_2$$

In a quantum mechanical description, the nitrogens are negatively charged with the positive charge being distributed among the nitrogen's substituents. (Even the nitrogens of guanidinium ion are highly negative). [18] The question arose as to how the positioning of the Br^- counter ion influences the charge distribution and conformation of the cyanine dye. Our search for information on this question was computational; to our knowledge an equivalent examination of electrostatic effects has not yet been carried out.

To become calibrated with regard to expected charge distributions in the cyanine, we first examined a simple nonionic enamine, $(CH_3)_2N{-}CH{=}CH_2$. Optimized geometries and atomic charges, in the absence and presence of water, are shown in Scheme 1. It is seen that the enamine nitrogen bears a large negative charge with positive charge being localized on the ethylene carbon bonded directly to the nitrogen. Hydrogen-bonding of the nitrogen to the $H^{+\delta}$ of a water dipole clearly has little effect on the overall charge distribution in the enamine.

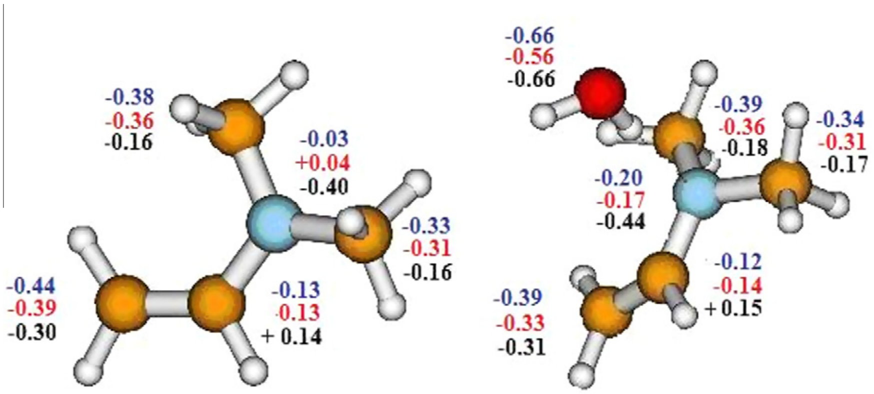
Next we examined simple immonium ions, $(CH_3)_2N^+{=}CHCH_3{\cdot}Br^-$ and $(CH_3)_2N^+{=}CH{-}CH{=}CHCH_3{\cdot}Br^-$ (Scheme 2). Unexpectedly, spontaneous covalent bond formation occurred in $(CH_3)_2N^+{=}CHCH_3$ between Br^- and the =CH- carbon. Addition of a water molecule to the system resulted in a Br^-/H_2O hydrogen-bond that precluded Br/C bond formation (not shown). Bromide/carbon bond formation was not observed in $(CH_3)_2N^+{=}CH{-}CH{=}CHCH_3{\cdot}Br^-$, with or without the presence of water (Scheme 2), possibly due to steric effects and to the destruction of conjugation it would cause.

Despite its formal positive charge, the charge on the nitrogen is (+0.08 to −0.35 depending on the method used). An all- anti conformation is visible in the compound. Hydrogen-bonding of Br^- to one or two water molecules hardly affects the charge distribution and, in fact, only reduces the charge on Br^- from −0.72 to −0.67. In order to explore in depth the relationship between the counter ion and the conjugated system reactivity, DFT calculations have been repeated with F^-, Cl^- and I^- as counter ions. The calculation results reveal that Cl^- and I^- show similar behavior to that of Br^- while in the case of F^-, F/C bond formation was observed (activation energy = 6 kcal/mol). The latter supports the notion that steric effects might be the dominant factor for precluding Br/C bond formation.

With these background data in hand, we then computed the global minimum (GM) structure of the cyanine dye, $(CH_3)_2N^+{=}CH{-}CH{=}CH{-}CH{=}CH{-}N(CH_3)_2{\cdot}Br^-$. The GM structure was found by conducting 360° rotation of the dimethylamino group about the C/C bond to which it is connected. The geometry of the GM structure shown in Scheme 3 exhibits a syn-anti orientation in regard to the dimethylamino groups.

The following comparisons are evident from Scheme 3 and Tables 1a, 1b, 2a and 2b, where Tables 1a and 2a list the calculated properties by B3LYP/6-31G (d,p) and Tables 1b and 2b depict those calculated by B3LYP/6-311 + G (d,p):

(a) The charges on the "cationic" nitrogens of the cyanine dye (+0.022 and + 0.015 as calculated by B3LYP/6-311 + G (d,p)) are about equivalent to each other and to the charge on the nitrogen in the free-amine of Scheme 1 (+0.080, as calculated by B3LYP/6-311 + G(d,p)). Thus, formal nitrogen charge has little bearing on computed nitrogen charges. (b) The nitrogen-attached alkyl group in the cyanine dye show enhanced positive charge relative to the free-amine in Scheme 1 (e.g.+0.154 and +0.186 vs. −0.130). (c) In contrast to the resonance portrayal of the cyanine dye, the nitrogens in the computer-GM structure are not conformationally identical. N-2 assumes an eclipsed geometry relative to C-5 about the C_3C_4-bond, whereas N-8 assumes a trans (anti) relationship with C-5 about the C_6C_7-bond (Tables 1b and 2b). DFT calculations of the structure by which the two nitrogens reside in the anti-anti conformation shown in Scheme 4 reveal that this conformation is about 1 kcal/mol less stable than that with the syn–anti geometry (d) The distances between the Br^- and the two dye nitrogens in the optimized structure are similar but not identical (4.37 and 4.80 Å as calculated by B3LYP/6-311 + G (d,p)). As will be shown,



Scheme 1. DFT-optimized geometries and atomic charges for $(CH_3)_2N{-}CH{=}CH_2$. Numbers in black, red and blue were calculated by B3LYP/6-31G (d,p) in the gas phase, B3LYP/6-311 + G (d,p) in the gas phase and B3LYP/6-311 + G (d,p) in water, respectively.