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Structural Substituent Effect in the Excitation Energy of a Chromophore: Quantitative Determination and Application to S-Nitrosothiols

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## Abstract

A methodology for the prediction of excitation energies for substituted chromophores on the basis of ground state structures has been developed. The formalism introduces the concept of “*structural substituent excitation energy effect*” for the rational prediction and quantification of the substituent effect in the excitation energy of a chromophore to an excited electronic state. This effect quantifies exclusively the excitation energy variation due to the structural changes of the chromophore induced by the substituent. Therefore, excitation bathochromic and hypsochromic shifts of substituted chromophores can be predicted on the basis of known ground and excited potential energy surfaces of a reference unsubstituted chromophore, together with the ground state minimum energy structure of the substituted chromophore. This formalism can be applied if the chemical substitution does not affect the nature of the electronic excitation, where the substituent effect can be understood as a force acting on the chromophore and provoking a structural change on it. The developed formalism provides a useful tool for quantitative and qualitative determination of the excitation energy of substituted chromophores and also for the analysis and determination of the structural changes affecting this energy. The proposed methodology has been applied to the prediction of the excitation energy to the first bright state of several S-nitrosothiols using the potential energy surfaces of methyl-S-nitrosothiol as a reference unsubstituted chromophore.

## I Introduction

The substituent effect has become one of the major research topics in physical organic chemistry during the past decades. This fact is due to the need of setting a systematic description of the influence of chemical substitution on physical and chemical molecular properties. In this sense, great strides have been made to explain the effect of different substituents in the description of synthetic, mechanistic, and catalytic properties; in the prediction of chemical reactions and equilibria; and even in the control of agonist/antagonist properties in hormone receptor modulators. (1, 2)

In order to make this possible, different relationships between substituent groups and chemical properties have been developed to date. Among them, those providing a quantitative description of these relations are useful tools for predicting and interpreting chemical properties. As a consequence, much emphasis was given to quantitative structure–activity relationships (QSAR) and linear free energy relationships (LFER).

The first empirical quantitative relationship was observed by Hammett (eq 1) in 1937, (3) where a relation between substituted ( $k$ ) and unsubstituted ( $k_0$ ) aryl reaction rate constants is proposed to be proportional to the product of a term ( $\rho$ ) depending on the specific reaction and a term ( $\sigma$ ) depending on the specific substituent.

$$\log \frac{k}{k_0} = \rho\sigma \quad (1)$$

He introduced the idea that for any two reactions with two aromatic reactants only differing in the type of substituent (*meta* or *para* positions), the change in Gibbs activation energy is proportional to the change in Gibbs energy. This LFER allowed elucidation of the reaction mechanism concerning the ionization of substituted benzoic acids. Subsequent modifications of the Hammett equation were proposed. The Swain–Lupton equation (4) emerged from the idea of Swain and Lupton that two variables are enough (taking into account resonance effects and field effects) to describe the effects of any substituent, therefore redefining the Hammett's substituent parameter,  $\sigma$ . Other modifications to the Hammett equation are the Taft equation, (5-7) which describes the steric effects of a substituent apart from field, inductive, and resonance effects, and the Yukawa–Tsuno equation, (8) which introduces a new term to the original Hammett relationship that reflects the extent of resonance stabilization for a reactive structure that enhances the transition state's charge. These LFERs were found to be useful tools in interpreting and predicting organic reactions and their mechanisms in the ground state.

Moreover, the substituent effect has important consequences in processes involving excited states, such as the variation of the maximum absorption wavelength of a given chromophore. The prediction of this spectroscopical property, and its eventual modulation, is of special interest in the development of photochromic compounds used as photoresponsive materials, (9) materials with nonlinear optical properties, (10) organic light-emitting diodes, (11, 12) etc. In some cases, the Hammett equation has successfully correlated the rates of some reactions in the excited state for a series of molecules differently substituted with the Hammett constants of the same substituents derived for reactions proceeding in the ground state. Instead, in other cases, it has been observed that the influence of the substituent on the

photochemical reaction is different from that found in the ground state, (13) and subsequently  $\sigma^{\text{hv}}$ , (14)  $\sigma_{\text{ex}}$ , (15, 16)  $\sigma^*$ , (17, 18)  $\sigma^{\text{hv}}$ , (19) and  $\sigma_{\text{cc}^{\text{ex}}}$  (20) parameters were introduced as an attempt to describe photochemical substituent effects. As an additional attempt, the Hammett equation has been reformulated in order to correlate the substituent effect with the absorption frequency, (21) in any case leaving the application of the Hammett equation to the description of excited state properties as a non-prominent *trial and error* methodology.

Nevertheless, different empirical rules were developed in order to rationalize substituent effects in chromophores: the Woodward rules are among the most outstanding empirical rules in the study of chemical reactivity in organic chemistry. Woodward demonstrated that the wavelength of the absorption maximum in the UV spectra is strictly correlated with the extent of the carbon–carbon double bond substitution in conjugated systems, including carbonyl compounds, mono/disubstituted benzene derivatives, and benzoyl derivatives. (22) These rules have been extensively applied, broadly studied, and expanded by Fieser et al. (23) and Scott (24) by adding a considerable amount of experimental data. Another empirical rule to calculate the absorption band maxima and extinction coefficients of conjugated molecules, especially polyenes, is the Fieser–Kuhn rule, (25) which complements Woodward–Fieser rules that are applicable only to molecules with one to four conjugated double bonds.

Here, we present a general methodology for the prediction of absorption energies in substituted chromophores, focusing on the structural modifications that the substituent causes, with respect to the unsubstituted chromophore. After defining the substituent structural effect with respect to the vertical excitation energy, the methodology is formally developed, realizing how the substituent effect can be used to properly tune the absorption spectra of a molecule and determining which internal coordinates control the excitation energy modulation.

The developed methodology is applied to S-nitrosothiols (RSNOs), a family of compounds of biological and medical relevance for their capability to release nitric oxide (NO) when irradiated in the visible and UV regions, (26-29) therefore making the study of the S–N photocleavage attractive for possible use in phototherapy. (30, 31) We recently studied the absorption energy required to initiate photocleavage in a wide variety of RSNOs, showing the possibility of NO release modulation as a function of the substituent. (32)

## II Developed Methodology

### Substituent Structural Effect and Excitation Energy

Chemical substitution of a given chromophore can alter different physical and chemical properties of the chromophore. Among these properties, the molecular structure is usually affected by substituent groups. These structural changes can affect, in general, all the internal coordinates of the chromophore and can induce modifications on the relative stability of some electronic excited states regarding the ground state. Moreover, if the substituent does not participate in the excitation (i.e., the promoted electrons do not involve orbitals with significant contribution of the substituent), it is expected that the nature of the considered excited electronic state will not change. This situation is quite common, for example when the excited state of a chromophore has a given nature (e.g.,  $\pi,\pi^*$ ), and the substituent does not present electrons participating in the excitation, (e.g., no conjugated  $\pi$  electrons). This concept is also present in the widely used multiconfigurational method CASSCF (Complete-Active-Space Self-Consistent-Field), (33) where the selected active space must include those occupied molecular orbitals participating in the electronic excitations, and therefore defining the nature of the excited state to be studied.

In this work, we focus on this situation, where the substituent has no significant effect on the nature of the studied excited state and also does not participate in the excitation itself. Within this premise, which defines the applicability limits of the developed methodology, it is possible to analyze the effect of the structural changes due to chemical substitution, and their effect on the excitation energy.

It is possible to formally divide the molecular entity (chromophore-substituent) into two fragments, being the electronic energy of the system in the ground state ( $E_{GS}$ ) equal to

$$E_{GS} = E_{GS}^{\text{chrom}} + E_{GS}^{\text{subs}} + E_{GS}^{\text{chrom/subs}} \quad (2)$$

where  $E_{GS}^{\text{chrom}}$  is the electronic energy of the chromophore,  $E_{GS}^{\text{subs}}$  is the corresponding energy of the substituent, and  $E_{GS}^{\text{chrom/subs}}$  is the energy of interaction between both parts of the molecule with all terms referred to the ground state.

Likewise, the energy of the excited state is given by

$$E_{ES} = E_{ES}^{\text{chrom}} + E_{GS}^{\text{subs}} + E_{GS}^{\text{chrom/subs}} \quad (3)$$

Note that the excitation is "localized" in the chromophore (as we assume that the substituent is not participating), and therefore the substituent term is the one corresponding to the ground-state since the energy

stabilization/destabilization caused by the substituent is essentially identical for both ground and excited states (i.e., we assume that  $E_{\text{GS}}^{\text{subs}} = E_{\text{ES}}^{\text{subs}}$ ). Furthermore, as discussed above, considering only substituents not affecting the excitation significantly, the chromophore-substituent energy term has to be essentially equal for both states ( $E_{\text{ES}}^{\text{chrom/subs}} = E_{\text{GS}}^{\text{chrom/subs}}$ ). The larger the extent of validity of this equality, the higher the accuracy of the obtained results from the present formalism.

The excitation energy ( $E_{\text{exc}}$ ) can be easily obtained by subtracting eq 2 from eq 3:

$$E_{\text{exc}} = E_{\text{ES}} - E_{\text{GS}} = E_{\text{ES}}^{\text{chrom}} - E_{\text{GS}}^{\text{chrom}} \quad (4)$$

This expression indicates that if the substituent does not contribute differentially to the relative stabilization/destabilization of the ground and excited states, the excitation energy will be governed by the intrinsic properties of the chromophore moiety. Nevertheless, it has to be noted that even if the excitation energy is correctly described by the intrinsic properties of the chromophore, the absolute energy of each state is not. Thus, the ground state of the molecule is affected by the presence of the substituent; specifically it will have an effect on the ground state structure of the molecule. Taking into account the Born–Oppenheimer approximation, every energy term in eq 2 and eq 3 will depend on the molecular coordinates of the chromophore ( $\mathbf{q}_c$ ), substituent ( $\mathbf{q}_s$ ), or both ( $\mathbf{q}_c; \mathbf{q}_s$ ). Therefore, if we take the first derivatives of the energy for the ground electronic state (eq 2), we obtain

$$\nabla E_{\text{GS}}(\mathbf{q}_c; \mathbf{q}_s) = \nabla E_{\text{GS}}^{\text{chrom}}(\mathbf{q}_c) + \nabla E_{\text{GS}}^{\text{subs}}(\mathbf{q}_s) + \nabla E_{\text{GS}}^{\text{chrom/subs}}(\mathbf{q}_c; \mathbf{q}_s) \quad (5)$$

The equilibrium geometry of the ground state must fulfill  $\nabla E_{\text{GS}}(\mathbf{q}_c; \mathbf{q}_s) = 0$ . Since we are only interested in the chromophore structure (as the excitation energy only depends on the chromophore), it is straightforward to obtain eq 6 for the equilibrium structure of the molecule.

$$\nabla E_{\text{GS}}^{\text{chrom}}(\mathbf{q}_c) - \mathbf{F}_{\text{ext}}^{\text{chrom/subs}} = \mathbf{0} \quad (6)$$

where the term  $\mathbf{F}_{\text{ext}}^{\text{chrom/subs}}$  is interpreted as an external force provoked by the effect of the substituent ( $\nabla E_{\text{GS}}^{\text{chrom/subs}}(\mathbf{q}_c; \mathbf{q}_s)$  term). This external force induced by the substituent is characteristic of the specific chromophore/substituent couple and provokes the displacement of the equilibrium structure of the substituted chromophore regarding the unsubstituted chromophore. The new ground state equilibrium structure of the chromophore is determined by the  $\mathbf{F}_{\text{ext}}^{\text{chrom/subs}}$  force, which exerts a displacement of the energy minimum to a new configuration where  $\nabla E_{\text{GS}}^{\text{chrom}}(\mathbf{q}_c)$  equals  $\mathbf{F}_{\text{ext}}^{\text{chrom/subs}}$  (Figure 1), consequently altering the potential energy surface shape by displacing the minimum. The solution to eq 6 provides the chromophore structure with the attached substituent



(R). Finally, by knowing the structure of the substituted chromophore, it is straightforward to predict the excitation shift by using eq 4, which will depend only on the new coordinates of the chromophore under the substituent effect. This procedure is explained in Figure 1.

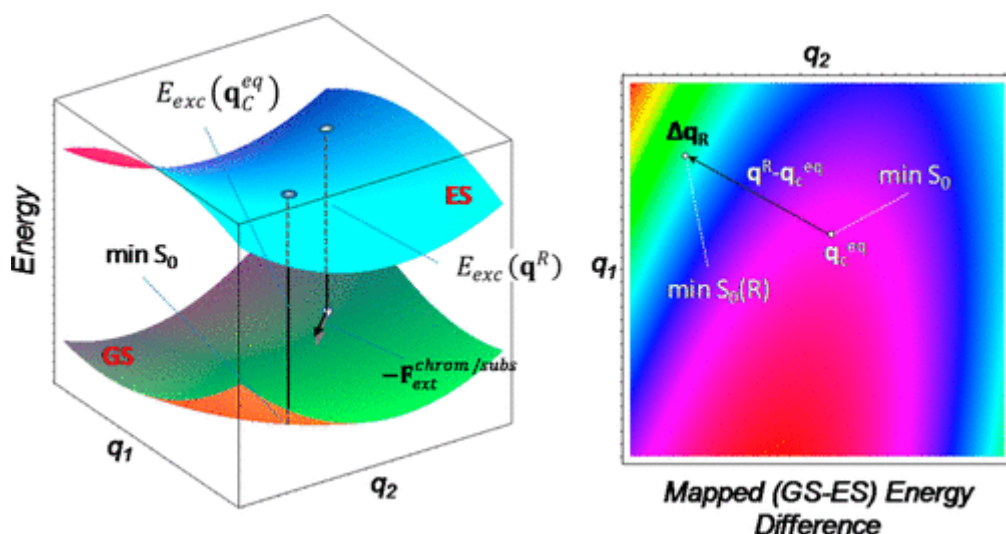


Figure 1. Left: Schematic potential energy surfaces for the ground state (GS) and excited state (ES) of an unsubstituted chromophore as a function of two of its coordinates ( $q_1$ ,  $q_2$ ). The substituent provokes a change of the molecular structure from  $\mathbf{q}_C^{eq}$  to  $\mathbf{q}^R$ , which can be explained in terms of the effect of an external force ( $\mathbf{F}_{ext}^{chrom/subs}$ ) acting on the chromophore due to the presence of the substituent. This structural change in the chromophore provokes a shift of the excitation energy from  $E_{exc}(\mathbf{q}_C^{eq})$  to  $E_{exc}(\mathbf{q}^R)$ . Right: Color-mapped excitation energy for the chromophore as a function of the same two coordinates ( $q_1$ ,  $q_2$ ). The excitation energy changes due to the substituent effect on the structure of the chromophore, from the unsubstituted chromophore geometry ( $\mathbf{q}_C^{eq}$ ) to the “R” substituted structure ( $\mathbf{q}^R$ ) corresponding to a change of the ground state equilibrium structure from  $\min S_0$  to  $\min S_0(R)$ .

#### Substituent Absorption Tuning from Chromophore Potential Energy Surfaces (PESs)

As discussed above, if the effect of the substituent in the chromophore is limited to provoke some structural changes but does not affect the nature of the electronic excitation, the electronic transition energy depends only on the new equilibrium structure of the substituted chromophore. Under this assumption, it is possible to predict, avoiding direct *ab initio* calculation, the excitation energy of the substituted chromophore just by correct knowledge of the following information: (i) the ground state structure of the substituted chromophore and (ii) to some extent the PESs (ground and excited) of the unsubstituted chromophore. Usually, the former can be easily obtained with *ab initio* calculations in the ground state; nevertheless, different approaches can be employed in order to have the ground and excited PESs of the unsubstituted chromophore. In

the current work, we have used a quadratic approximation of the PESs involved in the excitation to describe the topology of the surfaces.

By using this approximation, the energy of the ground and excited states of the unsubstituted chromophore species can be expanded taking the ground state equilibrium geometry ( $\mathbf{q}_{C^{eq}}$ ) as the origin according to eq 7 and eq 8.

$$E_{GS}(\Delta\mathbf{q}) = E_{GS}(\mathbf{q}_{C^{eq}}) + \frac{1}{2}\Delta\mathbf{q}^T\mathbf{H}_{GS}\Delta\mathbf{q} \quad (7)$$

$$E_{ES}(\Delta\mathbf{q}) = E_{ES}(\mathbf{q}_{C^{eq}}) + \Delta\mathbf{q}^T\mathbf{g}_{ES} + \frac{1}{2}\Delta\mathbf{q}^T\mathbf{H}_{ES}\Delta\mathbf{q} \quad (8)$$

where  $\Delta\mathbf{q} = \mathbf{q} - \mathbf{q}_{C^{eq}}$  is the displacement coordinate vector regarding the ground state equilibrium geometry ( $\mathbf{q}_{C^{eq}}$ ) for the unsubstituted chromophore,  $\mathbf{H}_{GS}$  and  $\mathbf{H}_{ES}$  are the Hessian matrices for both states calculated for this geometry, and  $\mathbf{g}_{ES}$  is the energy gradient vector in the excited state, also evaluated for the same geometry.

Therefore, according to eqs 7 and 8, the excitation energy for any configuration of the chromophore  $E_{exc}(\Delta\mathbf{q})$  is given by eq 9.

$$E_{exc}(\Delta\mathbf{q}) = E_{ES}(\Delta\mathbf{q}) - E_{GS}(\Delta\mathbf{q}) = E_{ES}(\mathbf{q}_{C^{eq}}) - E_{GS}(\mathbf{q}_{C^{eq}}) + \Delta\mathbf{q}^T\mathbf{g}_{ES} + \frac{1}{2}\Delta\mathbf{q}^T(\mathbf{H}_{ES} - \mathbf{H}_{GS})\Delta\mathbf{q} \quad (9)$$

Finally, knowing all the parameters in eq 9 ( $E_{ES}(\mathbf{q}_{C^{eq}})$ ,  $E_{GS}(\mathbf{q}_{C^{eq}})$ ,  $\mathbf{g}_{ES}$ ,  $\mathbf{H}_{ES}$ , and  $\mathbf{H}_{GS}$ ), the ground state equilibrium structure for the “-R” substituted chromophore ( $\mathbf{q}^R$ ), and therefore the structural displacement  $\Delta\mathbf{q}^R = \mathbf{q}^R - \mathbf{q}_{C^{eq}}$ , it is possible to predict the excitation energy of the “-R” substituted chromophore ( $E_{exc}^R$ ) according to eq 10.

$$E_{exc}^R = E_{ES}(\mathbf{q}_{C^{eq}}) - E_{GS}(\mathbf{q}_{C^{eq}}) + (\Delta\mathbf{q}^R)^T\mathbf{g}_{ES} + \frac{1}{2}(\Delta\mathbf{q}^R)^T(\mathbf{H}_{ES} - \mathbf{H}_{GS})\Delta\mathbf{q}^R \quad (10)$$

Therefore, by using high-level *ab initio* derived PESs and computing ground state structures of substituted chromophores with an affordable method, it is possible to predict (applying eq 10) the excitation energy of a series of substituted chromophore derivatives.

Determination of the Coordinates Controlling the Excitation Energy

According to the discussed methodology, it is possible to have a computationally saving estimation of the excitation energy of a given substituted chromophore on the basis of quadratic ground and excited state PESs of the unsubstituted chromophore—calculation made only once for a given chromophore—and the ground state equilibrium geometry of a substituted chromophore—one calculation in the ground state for each substituent. Moreover, we can take advantage of this



situation to analyze the role of each molecular coordinate by predicting their efficiency in modulating the energy gap. According to eq 10, the first order variation of the excitation energy gap is given by the excited state gradient vector ( $\mathbf{g}_{\text{ES}}$ ), which will be predominant for small displacements of the substituted chromophore structure. Nevertheless, the second order term in the excitation energy variation (last term in eq 10) can be also relevant, especially when the substituent induces distortions in the ground state that are orthogonal to the energy gradient vector, or when the gradient vector itself ( $\mathbf{g}_{\text{ES}}$ ) tends to vanish.

In order to analyze this effect, it is useful to separate the coordinates into two subsets, one corresponding to the energy gradient vector and the rest of coordinates orthogonal to it. The energy gradient vector coordinate provides the first-order correction to the energy difference along  $\mathbf{g}_{\text{ES}}$ , while those orthogonal to  $\mathbf{g}_{\text{ES}}$  provide the second-order energy gap variation through a projected Hessian difference matrix ( $\mathbf{H} \equiv \mathbf{H}_{\text{ES}} - \mathbf{H}_{\text{GS}}$ ) which can be obtained by using a projection operator as shown in eq 11.

$$\mathbf{H}^{\text{P}} = \mathbf{P}\mathbf{H}\mathbf{P} \quad (11)$$

where  $\mathbf{P}$  is the projector operator defined by

$$\mathbf{P} = \mathbf{I} - \mathbf{g}_{\text{ES}}^N (\mathbf{g}_{\text{ES}}^N)^T \quad (12)$$

where  $\mathbf{I}$  is the identity matrix with  $N - 1$  elements,  $N$  being the number of molecular coordinates, and  $\mathbf{g}_{\text{ES}}^N$  is the normalized excited state gradient vector. The eigenvalues of the projected Hessian difference ( $\mathbf{H}^{\text{P}}$ ) provide the set of force constants difference between ground and excited states ( $k_{\text{ES}} - k_{\text{GS}}$ ). Close to zero eigenvalues denote that distortions along the corresponding eigenvectors do not provide significant change of the excitation energy (Figure 2, case a). However, negative eigenvalues are related to reduction of the excitation energy (Figure 2, cases b1 and b2) while positive eigenvalues are related to an increase of the energy gap (Figure 2, case c) when structural changes take place along the corresponding eigenvectors. With this information, it is possible to rationalize the influence of the different internal coordinates of a chromophore in tuning the excitation energy.

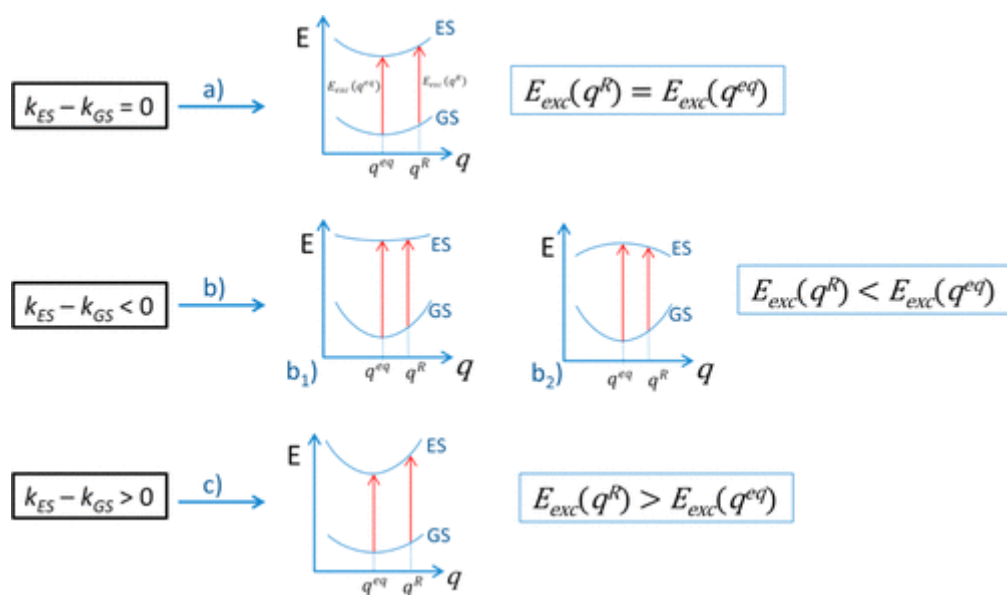


Figure 2. The possible energy difference (excited-ground) force constants ( $k$ ). Three different cases are possible when distorting the equilibrium structure ( $\mathbf{q}^{eq}$ ) along the corresponding eigenvector ( $\mathbf{q}$ ) to reach the equilibrium geometry for the substituted chromophore ( $\mathbf{q}^R$ ): the excitation energy ( $E_{exc}$ ) does not change significantly (case a); reduction of the excitation energy with positive and negative excited state curvature (cases  $b_1$  and  $b_2$ , respectively); increase of the excitation energy (case c).

#### Electronic-Structure Methods

The implementation of the methodology discussed above has been tested for the prediction of the excitation energy of a wide family of S-nitrosothiol derivatives. All S-nitrosothiol structures, except S-nitrosoglutathione, have been taken from ref [32](#), all of them being optimized on the ground state at the B3P86 level (Becke's three-parameter hybrid exchange along with Perdew's nonlocal correlation functionals) and calculating the excitation energy by time dependent treatment of the same functional (TD-DFT), as implemented in the Gaussian09 suite of programs. [\(34\)](#) In all cases, a 6-311+G(2df) basis set was applied. This method has been proven to predict excitation energies in good agreement with high-level multiconfigurational methods as Complete Active Space Perturbation Theory to Second Order (CASPT2). [\(35, 36\)](#) The analytical PESs for the ground and excited states of *syn*- and *anti*-methyl-S-nitrosothiol have been constructed from energy gradients and Hessians determined at the ground state minima. Numerical Hessians have been computed in the case of excited state, while analytical Hessians have been determined for the ground state.

### III Application to S-Nitrosothiol Derivatives

S-nitrosothiols are a family of compounds where the chromophore corresponds to the -SNO terminal fragment (see Figure 3). The partial double bond character of the S-N bond, caused by delocalization of the sulfur lone pairs in the nitroso group, makes possible the existence of two different RSNO ground state conformers: *syn* and *anti*. (37) In spite of their usual instability at room temperature, the main interest about RSNOs concerns their ability to release nitric oxide (NO), a molecule of fundamental importance in medicine and biology. (38-48) Especially, the generation of NO as a stable radical by irradiating RSNOs at a specific wavelength (i.e., photochemical rupture of the S-N bond) is of potential interest in phototherapy. (29)

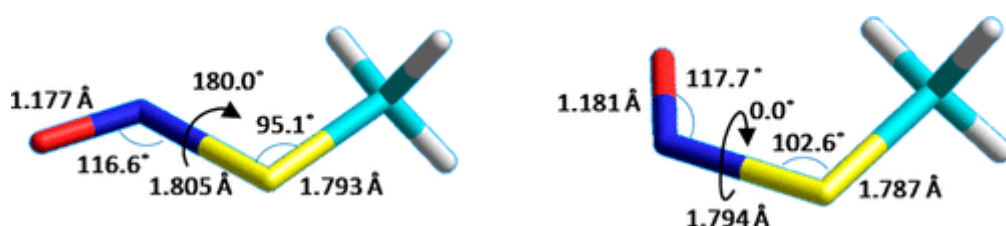


Figure 3. *Anti* (left) and *syn* (right) methyl-S-nitrosothiol ground state equilibrium structures at the B3P86/6-311+G(2df) level of theory. The main geometrical parameters are shown.

One of the simplest members of this family of molecules is methyl-S-nitrosothiol ( $\text{CH}_3\text{SNO}$ , see Figure 3), which was studied theoretically but not experimentally, because of the intrinsic instability shown by the compound. (37, 49-51) We have taken this compound as the representative model chromophore for building up the reference PESs (ground and excited state). As already described by the authors, after irradiation of  $\text{CH}_3\text{SNO}$  to the bright state ( $S_2$  corresponding to a  $^1(\pi,\pi^*)$  state), the minimum energy paths lead to a barrierless photocleavage process resulting in the formation of  $\text{CH}_3\text{S}\cdot$  and  $\cdot\text{NO}$  radicals. This implies that an ultrafast process is expected, making possible a modulation of the NO release only by modulation of the vertical excitation energy required to initiate photocleavage. (32)

In the following, the construction of the PESs for ground and excited electronic states is described, and the coordinates modulating the energy gap are identified. Finally, a series of S-nitrosothiols are studied, determining the excitation energy predicted on the basis of  $\text{CH}_3\text{SNO}$  PESs and ultimately compared with the excitation energy directly computed by the above-described TD-DFT methodology.

## The PESs of Methyl-S-nitrosothiol

CH<sub>3</sub>SNO has two conformations in the ground state, *syn* and *anti* conformers (see Figure 3), where the most relevant structural difference is related to the CSNO dihedral angle ( $\sim 0^\circ$  and  $\sim 180^\circ$  for *syn* and *anti* isomers respectively). The absorption spectra for *syn* and *anti* CH<sub>3</sub>SNO were previously reported by the authors at the MS-CASPT2/ANO-L level of theory. (32) For both conformers, the two lowest-energy vertical excitations ( $S_0 \rightarrow S_1$  and  $S_0 \rightarrow S_2$ ) correspond to optically dark  $^1(n, \pi^*)$  and bright  $^1(\pi, \pi^*)$  transitions, respectively. More in detail, the absorption spectrum of *syn* CH<sub>3</sub>SNO is characterized by a  $S_0 \rightarrow S_1$  transition at 530 nm and a  $S_0 \rightarrow S_2$  transition at 330 nm, while a red shift in *anti* CH<sub>3</sub>SNO sets the  $S_0 \rightarrow S_1$  transition at 600 nm and the  $S_0 \rightarrow S_2$  transition at 342 nm. For both conformers, the  $S_0 \rightarrow S_2$  transition is associated with a much higher oscillator strength than for  $S_0 \rightarrow S_1$  (higher by a factor 33 and 28 for *syn* and *anti* CH<sub>3</sub>SNO, respectively). The present study is focused on the prediction of the lowest-energy bright  $^1(\pi, \pi^*)$  transition of a series of differently substituted RSNOs.

In order to explore the role of the internal coordinates controlling the  $S_0 \rightarrow S_2$  excitation energy, we have determined the second order approximated PESs of both conformers: the excitation energies, the energy gradient vectors, and the projected Hessian difference,  $\mathbf{H}^p$  (see eq 11), as well as its eigenvalues and eigenvectors. The later magnitudes provide the directions orthogonal to the excited state gradient vector modulating the  $S_0 \rightarrow S_2$  energy gap, while the corresponding eigenvalues quantify the extent of the energy gap variation. Negative eigenvalues of the projected Hessian difference (note that the Hessian difference matrix is defined as  $\mathbf{H} \equiv \mathbf{H}_{S_2} - \mathbf{H}_{S_0}$ , where ES stands for  $S_2$  and GS for  $S_0$  in Figure 2) are related to distortions where the force constant in  $S_0$  is larger than that of  $S_2$ , and consequently, displacements along the corresponding eigenvectors reduce the  $S_0 \rightarrow S_2$  excitation energy. On the other hand, positive eigenvalues are related to eigenvectors providing an increase of the energy gap.

Using a minimal set of internal coordinates for the chromophore, the *syn*-methyl-S-nitrosothiol  $\mathbf{H}^p$  matrix shows eigenvalues ranging from  $-0.229$  to  $0.044$  hartree·[bohr(rad)]<sup>-2</sup>, indicating that an energy gap increase and decrease can be achieved not only by distortions along the excited state energy gradient vector but also along different coordinates (see Figure 4). On one hand, the excited state energy gradient vector is mainly

associated with S–N stretching (corresponding to an eigenvector of the projected Hessian difference with zero eigenvalue). On the other hand, the eigenvectors of  $\mathbf{H}^p$  can be associated, to a large extent, with single internal coordinates. The highest eigenvalues (0.044, 0.0, and  $-0.01$ ) are related to stretching coordinates (N–O, S–N, and C–S, respectively) while the lowest eigenvalues ( $-0.068$ ,  $-0.112$ , and  $-0.229$ ) correspond to eigenvectors that are mostly related to CSN bending, CSNO torsion, and SNO bending, respectively. With these results, a clear picture of the energy gap variation can be obtained: lowering the  $S_0 \rightarrow S_2$  energy gap can be reached by increasing the S–N distance (gradient contribution) and by changing (decrease or increase) the N–O distance (second order contribution). However, an increase of the energy gap is possible by decreasing the S–N distance (gradient contribution) and mainly by varying bendings (CSN and SNO) and torsion (CSNO) and, to a lesser extent, by changing the C–S bond distance.

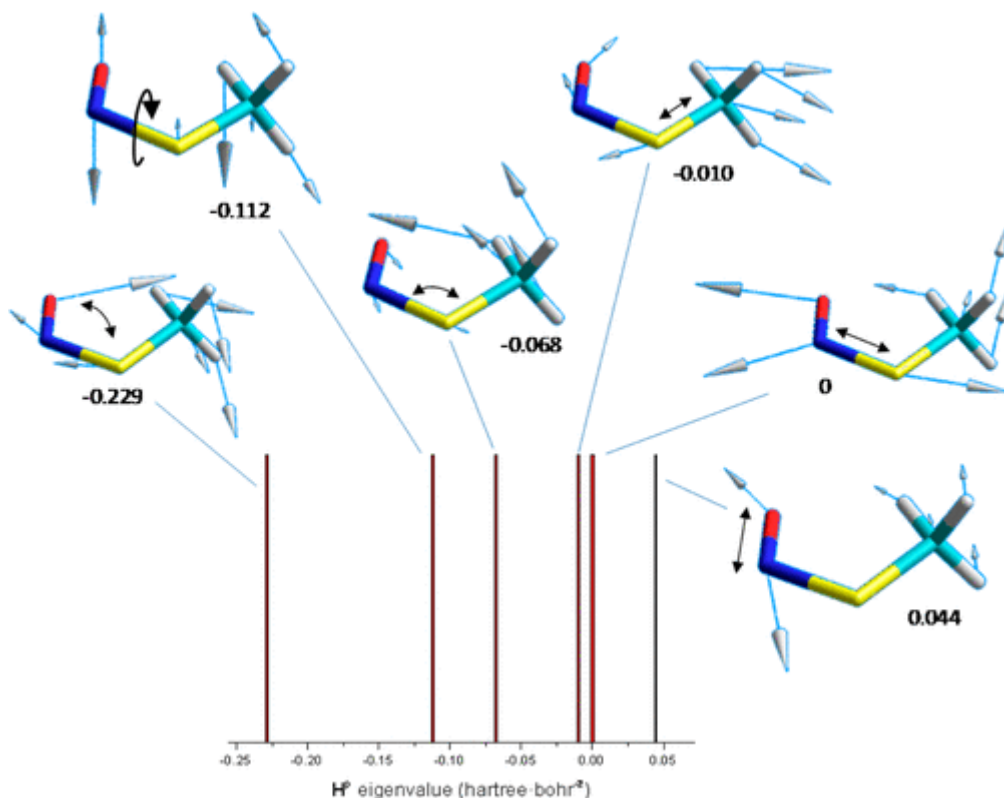


Figure 4. *Syn*-methyl-S-nitrosothiol projected Hessian difference ( $\mathbf{H}^p$ ) eigenvectors and eigenvalues in hartree-bohr<sup>-2</sup>. The eigenvalue spectrum is displayed with vertical bars, where the  $\mathbf{H}^p$  eigenvalue (x axis) indicates the different ability to modify the energy gap (positive for hypsochromic shift and negative for bathochromic shift). The main coordinates associated with each eigenvector are shown with black arrows.

Similar behavior is observed for the *anti* isomer (see Figure 5). The energy gradient vector is also dominated by the S–N stretching, and the ordering of the corresponding eigenvalues of the projected Hessian difference is equivalent: bendings, torsions, and stretchings in ascending order of the corresponding eigenvalue. Therefore, in order to increase the excitation energy, the coordinates that are able to modulate the energy are the energy gradient vector, mainly described by S–N stretching (by decreasing the S–N distance), while N–O distance variation (increase or decrease) also permits the  $S_0 \rightarrow S_2$  energy gap increase. On the other hand, in order to reduce the energy gap, different coordinates can contribute: the increase of the S–N distance (gradient contribution) and the variation of SNO and CSN bendings as well as CSNO torsion and C–S stretching. Of course, the eigenvalues of the diagonal  $\mathbf{H}^p$  matrix provide just the excitation energy modulation efficiency of each coordinate per unit displacement. Nevertheless, in order to understand the specific effect of a given substituent, the amplitude of the distortion induced by this substituent has to be taken into account explicitly, obtaining the concrete energy gap variation due to each coordinate.

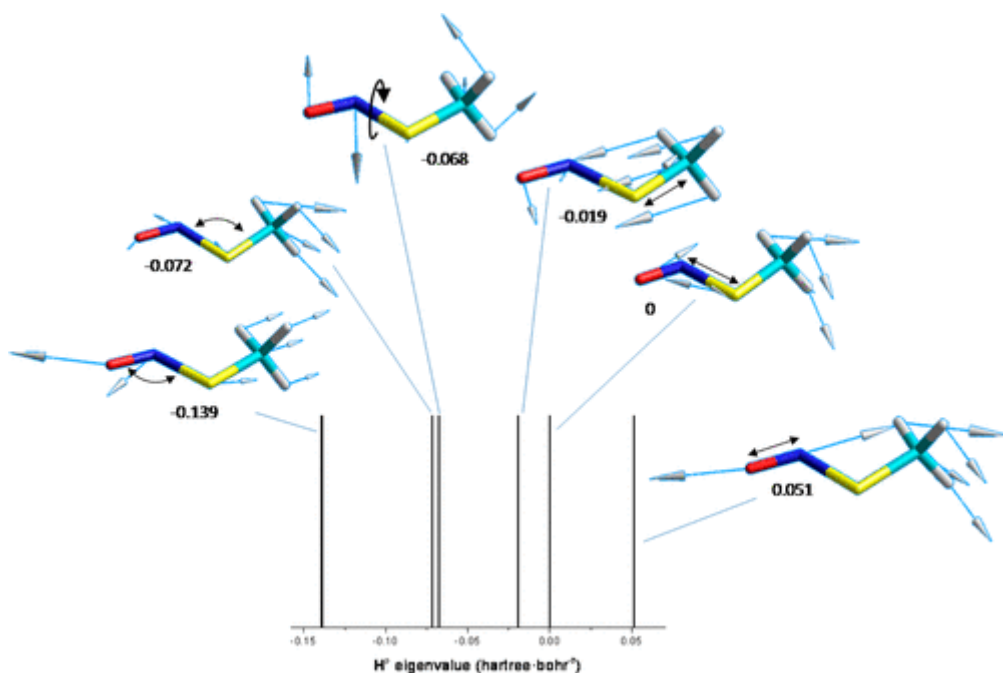


Figure 5. *Anti*-methyl-S-nitrosothiol projected Hessian difference ( $\mathbf{H}^p$ ) eigenvectors and eigenvalues in hartree-bohr<sup>-2</sup>. The eigenvalue spectrum is displayed with vertical bars, where the  $\mathbf{H}^p$  eigenvalue (x axis) indicates the different ability to modify the energy gap (positive for hypsochromic shift and negative for bathochromic shift). The main coordinates associated with each eigenvector are shown with black arrows.



It is therefore concluded that the energy gradient has the same nature for both conformers and is described mainly by C–S stretching. The variation of this coordinate provides a first-order variation of the energy gap, making possible to decrease (or increase) this gap by shortening (enlarging) the C–S distance. Analyzing the second order energy variation, bendings are effective in decreasing the  $S_0 \rightarrow S_2$  excitation energy, as well as torsion and, to a lesser extent, the C–S distance. However, the N–O distance variation provokes an increase of the energy gap for both isomers. Finally, the *syn* conformer shows a higher capacity to decrease the energy gap by structural distortions in comparison to the *anti* conformer (as is evident from the higher negative eigenvalues of  $\Delta H^p$  for the *syn* conformation) while the *anti* conformers show a slightly higher capacity to increase the energy gap.

#### Excitation Energy Prediction for Substituted S-Nitrosothiols

In order to study the substituent effect on the  $S_0 \rightarrow S_2$  energy gap for S-nitrosothiols, we have previously determined the excitation energy for a wide variety of substituted RSNOs: primary, secondary, and tertiary substituted (i.e., alkyl); vinyl; and aryl RSNOs. (32) In Figure 6, the ground state minima (B3P86/6-311+G(2df) level of theory) of different S-nitrosothiols are shown. All kinds of substitution do not affect the nature of the excitation, therefore making it possible to use the developed formalism to study the excitation energy tuning on the basis of structural distortions of the chromophore. Moreover, it was previously shown that aryl substituents do not expand the  $\pi$ -conjugation of the –SNO chromophore, since the aryl group and the –SNO moiety always form a dihedral angle between them ranging from 50 to 90°. (32) Nevertheless, in order to minimize the aryl  $\pi$ -conjugation and being able to measure the structural effect of the substituent, we have restrained to 90° the torsion of those derivatives which are not completely orthogonal. Therefore, these minimum energy conformations completely out of planarity keep the –SNO fragment as the unique chromophore, ranging the absorption maxima for the different substituted derivatives from 350 to 290 nm. (32)

The optimized structures on the ground state have been compared with the reference chromophore ( $\text{CH}_3\text{SNO}$ ) and the corresponding structural changes interpreted in terms of the coordinates controlling the excitation energy variation. Finally, on the basis of the ground state optimized structures for the different derivatives, the excitation energies are predicted by using the information of the  $\text{CH}_3\text{SNO}$  PESs.

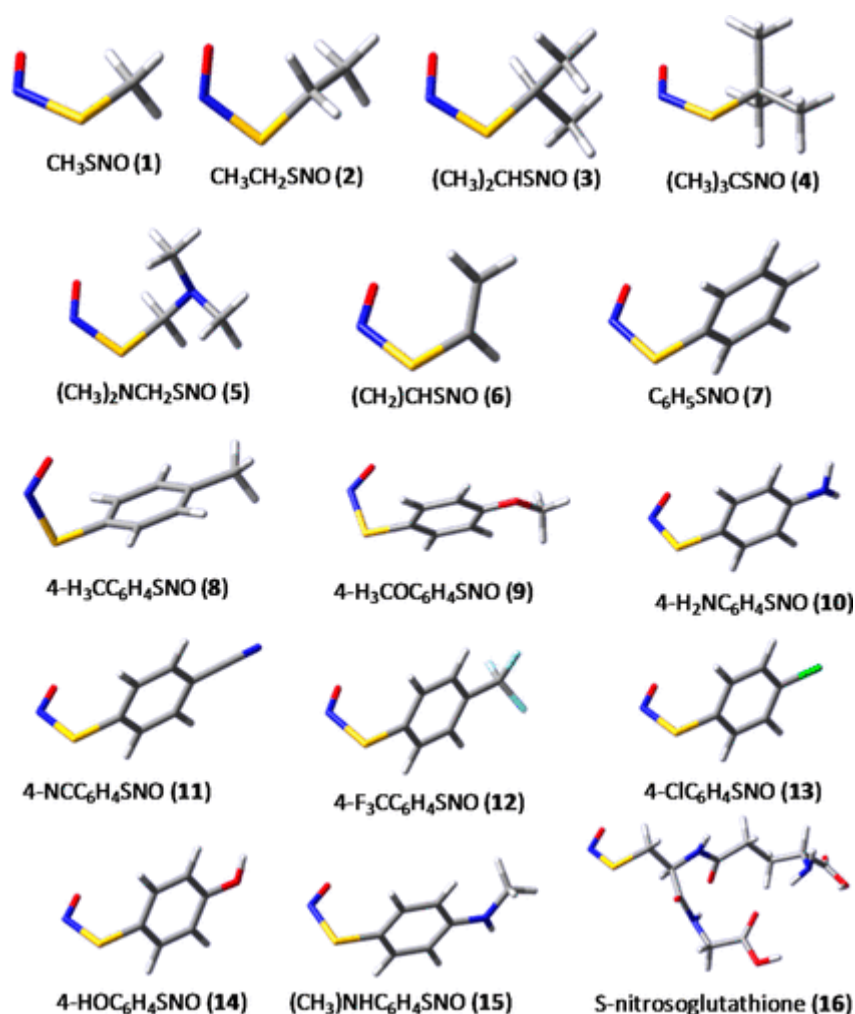


Figure 6. *syn*-S-nitrosothiol derivatives studied (same derivatives for *anti* conformers).

Before doing the analysis of the structural effect on the excitation energy, the second order approximation made for ground and excited states of the  $\text{CH}_3\text{SNO}$  reference compound has been tested. In this regard, the ground state equilibrium structure coordinates of each derivative have been transferred to  $\text{CH}_3\text{SNO}$  PESs, resulting in a differently distorted  $\text{CH}_3\text{SNO}$  structure for each  $\text{RSNO}$ . The excitation energy of each “distorted”  $\text{CH}_3\text{SNO}$  was calculated and compared to that obtained from analytical PESs according to the procedure developed in this work (see Figure 7). The correlation between both magnitudes is quantitative, showing the predictive quality of the second order approximation of the PESs employed.

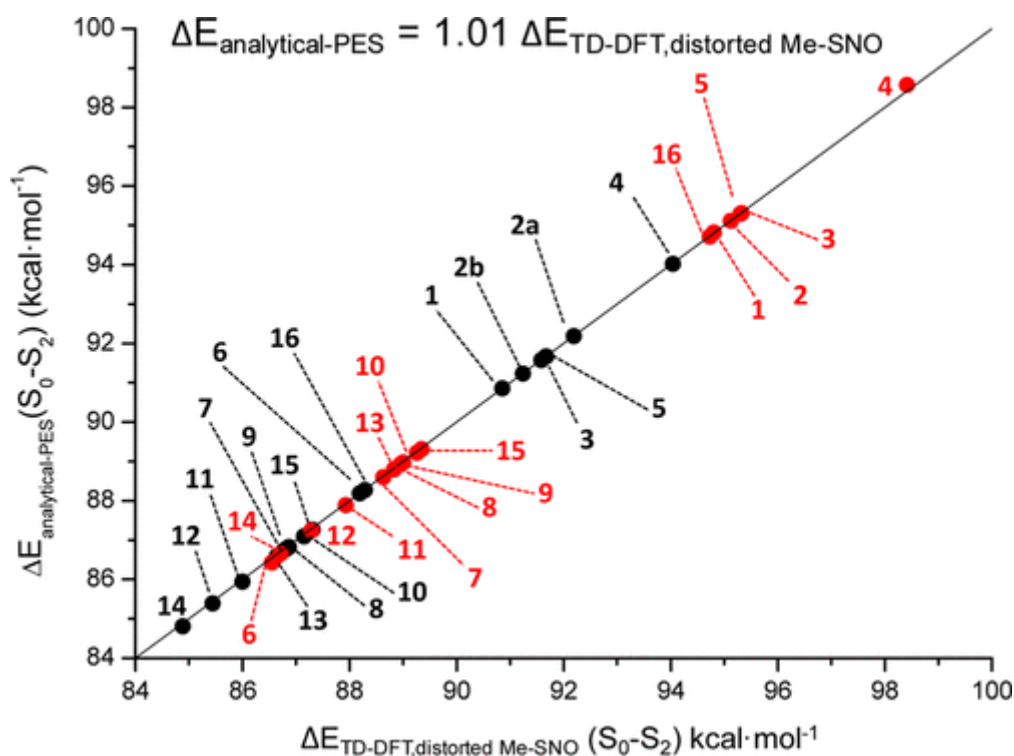


Figure 7. TD-DFT excitation energies of the different distorted Me-SNO (1) structures (fitting the corresponding optimized RSNO structures), versus the predicted excitation energies obtained from analytical PESs (black dots, *anti* derivatives; red dots, *syn* derivatives). The correlation shows quantitative agreement in the predictions made on the basis of analytical PESs for Me-SNO (see Figure 6 for numbering).

Finally, the excitation energies of the R-SNO derivatives have been predicted by using the corresponding optimized structures in the ground-state, applying the developed formalism, and then compared with those directly determined with TD-DFT calculations. The excitation energies obtained from analytical PES render exclusively the structural effect of the substituent (i.e., the chromophore structural change induced by the substituent) in the excitation energy. Therefore, the comparison of this energy with that obtained from TD-DFT calculations provides the quantification of the structural role of the substituent in tuning the excitation energy. The correlation between both energies is remarkable, indicating the principal role of the structural substituent effect in tuning S-nitrosothiol excitation energy. In fact, linear regression of these data (see Figure 8) gives a suitable correlation between predicted and TD-DFT computed excitation energies. Since both correlation lines cross the  $\text{CH}_3\text{SNO}$  reference, the slope of the correlation can be easily interpreted as the contribution of the structural substituent effect to the excitation energy variation. In this way, for *syn* derivatives the linear regression provides a slope equal to 0.82, indicating that, on average, 82% of the

excitation energy variation is due to the effect of the substituent in the structure of the CSNO chromophore. In the case of *anti* derivatives, this effect rises to 89%.

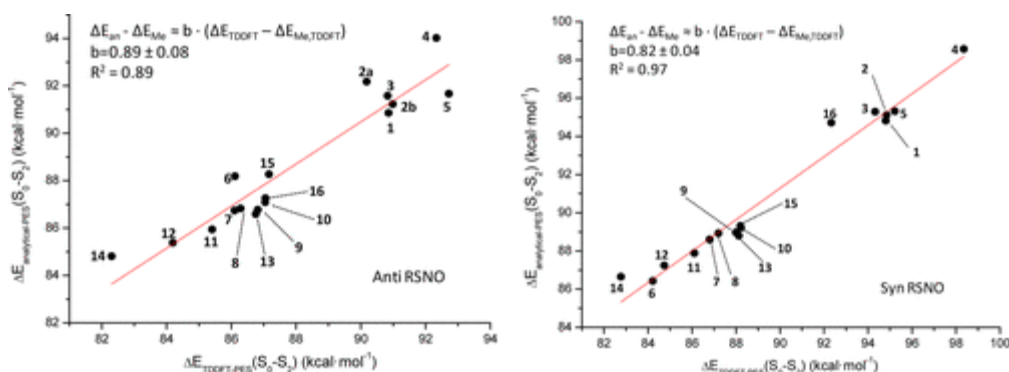


Figure 8. *Anti* (left) and *syn* (right) S-nitrosothiol excitation ( $S_0 \rightarrow S_2$ ) energies obtained from analytical PESs of  $\text{CH}_3\text{SNO}$  versus the computed excitation energies of each S-nitrosothiol derivative (see Figure 6 for numbering).

As previously described, the developed methodology is useful not only to predict the role of the structural effect of a substituent on the excitation energy but also to identify and quantify the role of each coordinate of the chromophore in tuning the transition energy. In this regard, from methyl-S-nitrosothiol PESs analysis, we have obtained the potential role of each internal coordinate of the chromophore in tuning the  $S_0 \rightarrow S_2$  excitation energy (*vide supra*). It has to be noted that, at second order, all the coordinates except one (N–O stretching) provide a reduction of the energy gap. Therefore, it is not odd to find that most of the derivatives reduce the energy gap.

We have analyzed the role of each internal coordinate of the chromophore in controlling the excitation energy for all the substituted S-nitrosothiols. The energy gradient component, related mainly to the S–N stretching, is the most important coordinate in tuning the energy gap of S-nitrosothiols (see Figure 9), representing 86% to 99% of the total excitation energy variation, second order contributions being less important (see Figure 10).

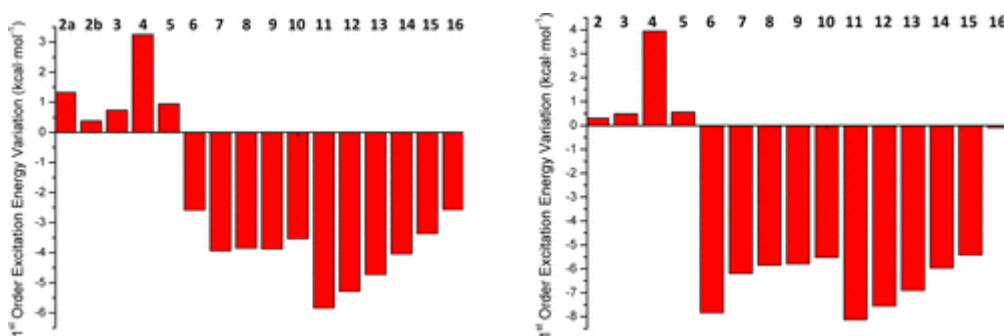


Figure 9. *Anti* (left) and *syn* (right) S-nitrosothiol excitation energy variation with respect to CH<sub>3</sub>SNO due to first order (energy gradient component) contribution.

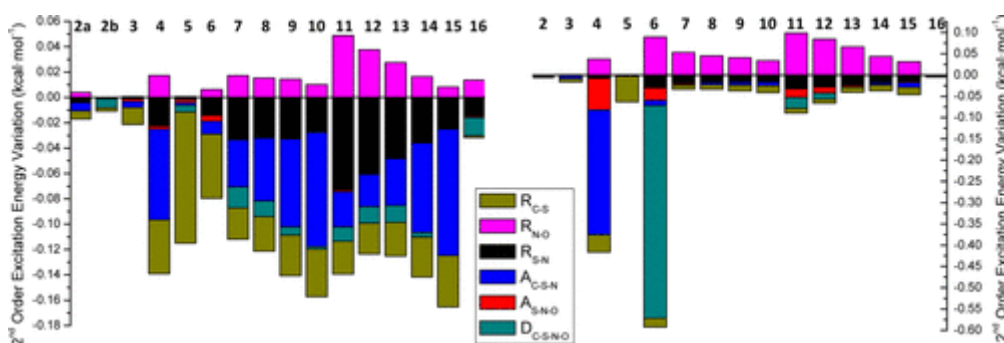


Figure 10. *Anti* (left) and *syn* (right) S-nitrosothiol excitation energy variations due to the second order terms. The individual contribution of each eigenvector of the projected energy Hessian difference ( $\mathbf{H}^P$ ) is shown (the eigenvectors are confidently assigned to distances “R” C–S, N–O, and S–N; to bond angles “A” C–S–N and S–N–O; and to the dihedral angle “D” C–S–N–O).

The energy gap variation due to the energy gradient ranges from ca.  $-6$  to  $3$  kcal·mol<sup>-1</sup> in the case of *anti*-S-nitrosothiols, and from ca.  $-8$  to  $4$  kcal·mol<sup>-1</sup> in the case of *syn*-S-nitrosothiols. Moreover, only alkyl derivatives show an energy gap increase, while for vinyl and aryl derivatives the excitation energy is reduced as compared to that of methyl-S-nitrosothiol. Interestingly, for *anti*-S-nitrosoglutathione, which should be more similar to alkyl-derivatives, the energy gap is significantly reduced, indicating an increase of the S–N distance.

Although second order terms in eq [10](#) are significantly lower than first order contributions, it can be realized that the N–O bond length is the only coordinate able to increase the energy gap (see Figure [10](#)) in both *syn*- and *anti*-S-nitrosothiols, the effect of this coordinate being minimal for alkyl-S-nitrosothiols and small but similar for the rest of substituents. On the other hand, *syn* derivatives show a slightly lower capacity of energy gap reduction in comparison to *anti* derivatives. This is the general rule,

except in the case of the *tert*-butyl substituent (compound **4**) where the steric hindrance should be responsible for the large participation of the C–S–N bond angle. Also, compound **6** (vinyl substituent, see Figure 6) exhibits a large participation of the C–S–N–O dihedral angle in energy gap modulation of the *syn* conformer. This contribution highlights the different effects of substituents in the chromophore structure, where a vinyl moiety activates the C–S–N–O dihedral angle while aryl derivatives do not provoke such a change in this coordinate. However, *anti* derivatives show an opposite behavior regarding this coordinate (aryl derivatives are C–S–N bond angle sensitive while vinyl derivative is not). For *anti* isomers, N–O, C–S, and S–N bond lengths contribute in a similar way, taking into account that the former coordinate increases the gap and the rest decrease it. Again, alkyl-S-nitrosothiols are the most energy-gap-insensitive derivatives. The most important coordinate for the decrease of the energy gap is the C–S–N bond angle, showing more pronounced response than *syn* derivatives to this coordinate.

## IV Conclusions

Here, we present a methodology to easily predict the excitation energy shift (bathochromic or hypsochromic) of substituted chromophores. The formalism is valid for substituted chromophores when the substituent fulfills the following conditions: (i) It does not change the excitation character of the electronic excited state under consideration. (ii) It does not participate directly in the excitation (no molecular orbitals with a significant contribution of the substituent are involved in the excitation process). This methodology only permits one to take into account the structural effect of the substituent in the chromophore excitation energy; therefore, no explicit through-space interaction is considered.

We show that from second-order term PESs for both ground and excited electronic states, it is possible to analyze the role of each molecular coordinate in the excitation energy tuning of the chromophore, being able to identify the ability of each coordinate in the modulation of the gap. The analysis is made on the basis of first- and second-order contributions.

This formalism has been applied to the prediction of excitation energy in a large family of substituted S-nitrosothiols. For these derivatives, 80% to 90% of the total excitation energy shift is due to structural effects induced by the substituent in the chromophore, the gradient vector being the main coordinate controlling the excitation energy variation.



This methodology offers a simple and fast procedure to obtain information regarding the substituent effect in the excitation of a chromophore, permitting the determination of the capability of the chromophore in the excitation energy tuning as well as the identification of the coordinates responsible for such a behavior, which eventually would permit the rational design of substituted derivatives with desired batho- or hypsochromic shifts. Moreover, once the ground and excited PESs (e.g., up to second order) of a chromophore are characterized, only ground-state calculations are needed in order to predict the excitation energy of a substituted derivative, being also possible to use different levels of theory for the prediction of the ground-state structures. Therefore, this methodology could be used for high-level *ab initio* excitation energy prediction where the excited-state calculations are in general computationally expensive, eventually permitting the fast prediction of excitation energies for a large number of substituted chromophores with simple ground state optimizations. Furthermore, the reference compound can be chosen as the simplest possible chromophore, in order to save computational time in the construction of the analytical PESs.

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#### Notes

The authors declare no competing financial interest.

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