Possible electronic mechanisms of generation and quenching of luminescence of singlet oxygen in the course of photodynamic therapy: \textit{ab initio} study

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On the basis of \textit{ab initio} quantum chemical calculations the strong enhancement of the \( ^1\text{(a'}^1\text{A}\text{g',S\text{\_o}})} \rightarrow \( ^1\text{(X}'^3\text{S\text{'_g'})} \) transition in collision complex between \( \text{O}_2 \) and organic dye is predicted, where \( \text{T} \) is the triplet excited state of the dye and \( \text{S}_0 \) is its ground singlet state. The collision-induced electric dipole transition moment depends on polarizability of the dye and can be used for the estimation of energy transfer rate constant. Quantum chemical calculations can predict the most efficient dye sensitizer for photodynamic therapy of cancer, instead of the difficult experimental search. Some new ideas are proposed for additional laser simulated mechanisms of active oxygen generation.

\textit{Key words:} singlet, triplet, complex of collision, transition moment, spin-orbit coupling.

Life strongly depends on kinetic barriers to oxidation by \( \text{O}_2 \), determined by spin prohibition. In aerobic metabolism the molecular oxygen is required as the terminal electron acceptor in respiration and as a reagent for direct biochemical synthesis. Oxygen is a stable biradical with two unpaired electrons generating the electronic triplet ground state. Triplet oxygen from the air has sluggish reactivity with organic substrates in spite of the strong thermodynamic drive: oxidation to water and \( \text{CO}_2 \) is strongly exothermic. Insertion of the triplet oxygen into organic molecules with all spins paired is a spin-forbidden process [1]. Enzymes activate \( \text{O}_2 \) in order to overcome this spin-prohibition. The higher energy and greater reactivity of singlet oxygen is a major contributing factor in maintaining the constant level of triplet oxygen in the terrestrial atmosphere. In recent years the singlet oxygen, \( \text{O}_2 \, (\text{a}'\Delta\text{g}) \), is getting more and more important in biochemistry and photobiology. The \( \text{O}_2 \, (\text{a}'\Delta\text{g}) \) species has now obtained regulatory approval in most countries for the treatment of several types of tumors, most importantly, in photodynamic therapy of cancer [2, 3]. Thus a simple two-atomic molecule, \( \text{O}_2 \), provides numerous puzzles in chemistry of combustion and respiration, in photophysics of dye-containing air-saturated solvents, in photobiology and laser-induced photodynamic therapy of cancer [1]. With two singlet states lying close above its ground triplet state, the \( \text{O}_2 \) molecule possesses a unique open-shell \( \pi^2 \) configuration, which gives rise to very peculiar photochemical and photophysical processes in presence of intense laser fields. Photosensitized generation of the first excited state, \( \text{O}_2 \, (\text{a}'\Delta\text{g}) \), can be used in numerous applications, from chemical synthesis and cancer treatment to a new type of cell microscope [1—4]. The aim of the present paper is to provide theoretical arguments for a new mechanism of photosensitized generation of the excited singlet state oxygen, \( \text{O}_2 \, (\text{a}'\Delta\text{g}) \), which explain the purposeful choice of sensibilizers in photodynamic therapy of cancer.
X luminescence in photosensitization experiments in solvents [4]. He used a special phosphorescence equiped with a near-IR photomultiplier for detection of very weak emission at 1270 nm in CCl₄. This solvent is a non-efficient quencher of O₂. Later it was shown that k₋,X increase with solvent polarizability in aromatic and other nonsaturated solvents [1]. This was especially important in connection with numerous photochemical reactions. Minaev et al. [10] few years after the theoretical prediction [8]. Such prediction can explain the great enhancement of the aΔg → XΣg− transition intensity is strongly increased in solvent (ca. 10⁷ times), this means the same increase for the aΔg → XΣg− transition. The admixture coefficient (3) is a pure oxygen property and does not depend much on solvent. Thus the theory [8] explains the negligible solvent dependence of the k₋,X rate constant [5] as a principal result of a simple approach.

Egorov et al. [6] first applied the single-photon counting to detect the aΔg → XΣg− luminescence in water solvent of organic dye. The sensitizer was excited by a copper vapor laser with 10-kHz repetition rate; about 10⁷ laser shots were necessary to accumulate very weak luminescence. Biexponential rise
and decay curve of the O₂ (αΔg) with time constants τa and sensitizer triplet-state lifetime τg were measured accurately varying the O₂ partial pressure from 1 to 15 bar; 1/τa was found to be proportional to [O₂], whereas τa = 3.1 μs remained constant. Two main factors contribute to the relative inefficiency of the singlet oxygen deactivation (k₁). Firstly, the O₂ (αΔg) excitation energy (0.98 eV) has to be converted into vibrational, rotational and translational energy of the solvent. This explains why the noble gases (Ne, Ar, Kr) are the weakest quenchers of O₂ (αΔg) [1]. Secondly, the αΔg → X³Σg⁻ deactivation is spin-forbidden for quenchers with singlet ground states. The CI active space includes 3Σg⁺_1, 3πu molecular orbitals of O₂ and a number of occupied and empty MO of ethane. All single and double excitations are included in our CI method: this gives 9680 configuration state functions for singlet states CI. At large distances (R > 6 Å) all states are easily interpreted as excitations inside O₂ or ethene molecules (Table). The a → b transition (3-5) is quite strong even at large distance, R = 4 Å. Only 1-5 transition (αΔg → c1Σu⁺ excitation inside O₂ perturbed by collision) is stronger. This band has been observed in emission for oxygen diluted in Ar matrix by Okada et al. [20]. In matrix the a → c transition is much stronger than in free O₂ in agreement with our results. The 1-4 transition corresponds to cooperative phosphorescence which is shifted by 0.98 eV to the red. It is getting more intense than the 1-5 transition at R = 3.2 Å. Increase of CI and basis set in our present work lead to more accurate data than before

In the present work we discuss results of our new systematic ab initio calculations of collision complexes between O₂ and dye molecules by 6-311G* CI method, based on the restricted open-shell Hartree-Fock calculation of the ground triplet state of the complex. Ethene, butadiene and hexatriene have been considered as dienes, free base porphin — as a typical porphyrin dye. A systematic increase of the a → b and a → X transitions probability with increase of π-conjugation system is confirmed. In Table the results of ethene +O₂ collision complex are presented. Only singlet (S) states given in Figure are considered. Table indicates increase of the S-S transition moments, induced by collision, with decrease of the intermolecular distance R. Two quasidegenerate aΔg states denoted as a, a correspond to A1 and B₂ states in the C₂v point group. We use the same type of collision complex as before [15]: the O=O and C=C bonds form a regular trapezium (zx plane) with z-axis (C₂ symmetry axis) being perpendicular to the ethane plane (yx). The CI active space includes 3Σg⁺_1, 3πu molecular orbitals of O₂ and a number of occupied and empty MO of ethane. All single and double excitations are included in our CI method: this gives 9680 configuration state functions for singlet states CI. At large distances (R = 3—4 Å) all states are easily interpreted as excitations inside O₂ or ethene molecules (Table). The a → b transition (2-3) is quite strong even at large distance, R = 4 Å. Only 1-5 transition (αΔg → c1Σu⁺ excitation inside O₂ perturbed by collision) is stronger. This band has been observed in emission for oxygen diluted in Ar matrix by Okada et al. [20]. In matrix the a → c transition is much stronger than in free O₂ in agreement with our results. The 1-4 transition corresponds to cooperative phosphorescence which is shifted by 0.98 eV to the red. It is getting more intense than the 1-5 transition at R = 3.2 Å. Increase of CI and basis set in our present work lead to more accurate data than before

<table>
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<th>R (Å)</th>
<th>αΔg → 1Σg⁻</th>
<th>αΔg → 3Σg⁻</th>
<th>αΔg → 5Σg⁻</th>
<th>αΔg → 7Σg⁻</th>
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<tr>
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<td>9.5599</td>
<td>5.9227</td>
</tr>
</tbody>
</table>

Transition dipole moments (Mₗₘ₋, 10⁻² debye) induced by collision O₂ + C₃H₆ at different intermolecular distances (R)
The calculated energy levels in the complex between \( O_2 \) and dye molecules. *For porphyrins the \( E(T) \) is about 1.6 eV and is close to the energy of the \( b^1Σ_g^+ \) state. The ground \( S_0 \) state of dye is missed, only the triplet \( (T) \) state is shown. The ground state of dye is missed, the energy of the \( b^1Σ_g^+ \) state is about 1.6 eV and is close to \( E(T) \) molecules. *For porphyrins the \( (4-5) \) is phosphorescence. The other cooperative transition nature. It lies lower than the vertically excited \( c^1Σ_g^+ \) 1-4 transition can detect the presence of the \( T \) excited dye. In complex the \( 4 \rightarrow 5 \) transition has 0.86 eV energy. In other dienes it occurs in visible region. With two laser experiments it is possible to produce a pumping of the \( c^1Σ_g^+ \) state of \( O_2 \), which could be very useful for many applications. Firstly it is very reactive in respect to oxidation of organic dye, as we can see it from our computer simulation of reaction with butadiene. Secondly, it can lead to generation of the singlet \( a^1Δ_g \) state. Thus the quantum chemical calculations can predict the most efficient dye sensibilizer for photodynamic therapy of cancer, instead of the difficult experimental search. This is based on calculation of electric dipole transition moments, induced by collisions \( O_2+ \) dye; next step is the energy transfer rate estimation by dipole-dipole interaction. The second dipole transition moment corresponds to vibrational excitation which comes to the resonance with a proper energetic balance for energy transfer process.

Energy transfer from the triplet-excited dye and \( O_2 \) molecule to produce the ground \( S_0 \) state of the dye and the singlet \( a^1Δ_g \) oxygen is spin allowed and usually is explained by the so-called exchange mechanism [9, 20]. In the model developed before [14] the exchange mechanism of such energy transfer is considered by direct calculation of collision complexes between \( O_2 \) and organic dye. Forbidden \( S-T \) transitions in such complex are getting electric-dipole allowed because of exchange interactions in the open shell system \( O_2+ \) dye. Then the energy transfer is described by the usual dipole-dipole interaction model [20], where the collision-induced transition moments are taken into account for the resonance intermolecular interaction estimation [14]. Now we shall apply this model. The 1-4 transition is the most intense one (Table); it can interact with the resonance vibrational transition inside the dye molecule, which can be an overtone or combination of C–H vibrational modes. Similar results have been obtained for other dyes and the increases of the 1–4 transition moments \( M_{d-xT} \) with the size of \( π \)-conjugation chain goes in parallel with the increase of polarizability of the dye.

Thus our theory predicts that mostly the singlet \( a^1Δ_g \) oxygen can be generated during the energy transfer act, not the \( b^1Σ_g^+ \) oxygen. This is in agreement with many experimental data, though the direct measurements of the energy transfer rate constants are very difficult [1].

The large 1–4 transition moment \( M_{d-xT} \) can be used for additional generation of the triplet state using additional laser impulses with the frequency \( ν = \frac{1}{h} = E(T) - E(a^1Δ_g) \). For porphyrins it is about 0.6 eV = 4800 cm\(^{-1}\), thus it comes into IR region. Tuning such laser we can select those dyes which correspond to the resonance. It means that the singlet oxygen \( (a^1Δ_g) \) being generated in the first cycle of photodynamic therapy of cancer can produce the triplet excited state of the dye in photosensitization experiments in solvents.

Let us provide some conclusions from previous experimental studies and our new findings in the context of photodynamic therapy of cancer. Relative efficiency of the singlet \( a^1Δ_g \) oxygen generation by the dye can be predicted on the ground of quantum chemical calculation of the following factors 1) CI calculation of the 1–4 transition moment; 2) calculation of vibrational frequencies and normal modes of the dye in the singlet ground state and in the triplet excited state; 3) calculation of the dipole-dipole interaction between quantum transition moments and estimation of the energy transfer rate constants.
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Могутны электронные механизмы утворения і гасіння свічения синглетнага кисню ў фотадинамічнай тэрапіі: наслдківі методам ab initio

Разомы

На основы ab initio квантово-хімічных розрахункаў прадстаўлены існаванне синглетнага стану кисню у фотодіна́мічнай тэрапіі: даследжаньем методам ab initio. Можливы электронныя механізмы утворэння і гасіння свічэння синглетнага кисню у фотодіна́мічнай тэрапіі: даследжаньем методам ab initio. Запропанавана некаторыя новыя ідэі стаўлення на электронныя аддаленыя пераходы званісцей для оцінкі кантактных переносніцаў. Квантово-хімічнымі розрахункамі можна тачакше прадстаўляць інтэрферэнцыю барвіна-сэнсібілізацый для фотодіна́мічнай тэрапіі. Рэзюме

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