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Study of the detritylation process in the presence of acid photogenerators based on benzo[*b*]thiophene-2-carboxanilides

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New Photo-Acid Generator (PAG) based on substituted benzo[*b*]thiophene-2-carboxanilides were studied for their ability to remove the dimethoxytretyl group in the detritylation reaction of dT nucleoside in a dichloromethane solution upon excitation by the 3rd harmonic of an Nd-YAG laser.

Keywords: acid photogenerators, 6π-electrocyclization, benzo[*b*]thiophene-2-carboxanilides, laser photolysis, detritylation.

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Introduction

Photo-Acid Generator (PAG) — compounds that form an acid when irradiated by light. These compounds have been used for more than a decade and there are large review articles, starting with the review of [1], where the focus is made on ionic and nonionic PAG developed over three decades and used mainly in cationic polymerization. The paper [2] outlines the achievements in design of photoactive molecules, describes successful PAG synthesized on the basis of ionic, benzyl-ester, imido-ester, spiropyran and terarylene structures, and discusses in detail the mechanism of acid formation in each case. The development of such systems for use in lithography, surface etching, and polymer design is considered. The study [3] outlines the classification and modern use of PAG for cationic photopolymerization, photoresists, in stereolithography, two-photon recording of information, and in biochemical research. The study [4] describes the use of PAG in biomedicine.

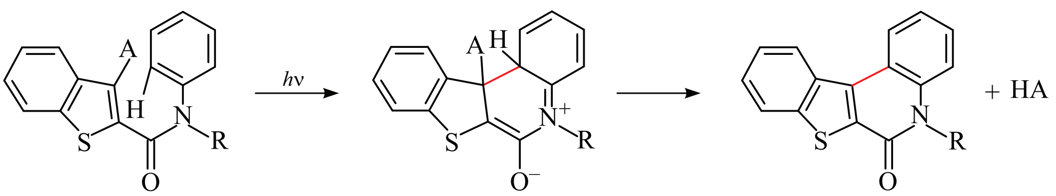
More than a dozen of PAG has been synthesized. It should be stressed that for the formation of Brensted acid, most PAGs provide an acid anion during their photolysis, whereas a proton is extracted from the proton-donor environment more often than from a solvent. If it is necessary to work in an aprotic solvent, such PAG are not functional. For this reason, the design and search for new PAG goes on. The best solution today is the design and synthesis of nonionic PAG, where 6πphotocyclization occurs in the excited state, followed by the arbitrary release of both hydrogen and acid anion [5–8]. These are the so called „self-contained“ structures.

In [9], we showed the results of photolysis in toluene of new self-contained PAG based on substituted benzo[*b*]thiophene-2-carboxanilides (Fig. 1) when excited by the third harmonic of Nd-YAG laser. Acid formation in such systems is shown in Scheme 1.

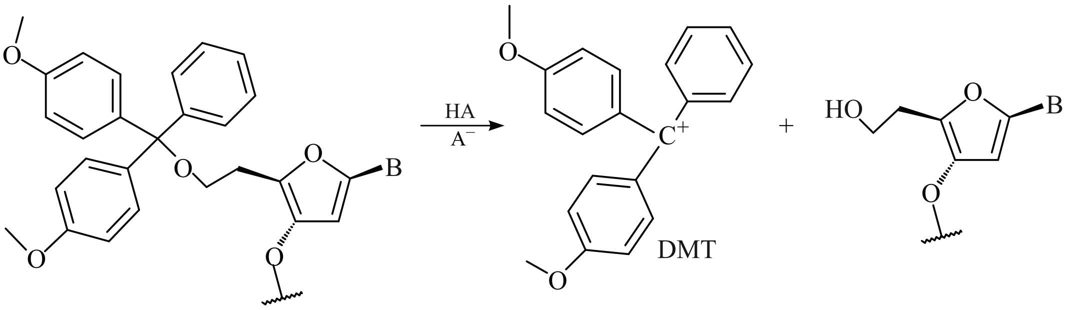
A pyrimidine derivative was used to confirm the acid formation (4,6-Bis(5-(9-ethyl-9H-carbazole-3-yl)thiophene-2-yl)pyrimidine), highly soluble in organic solvents and easily protonated in acidic environments. The absorption bands of its neutral (420nm) and protonated (530 nm) forms are spectrally well spaced, which makes it possible to reliably use this compound as an acid indicator. In addition, the protonated form of this compound gives the solution a bright crimson color. It has been shown that compounds with toluylsulfonic (DPT) and methylsulfonic (DPM) substituents form acids during photolysis in toluene, which is proved by the indicator used. Our indicator did not give a clear response to the photolysis products of a compound with a chloro-substituted (DPC) substituent: the formation of the protonated form was extremely low compared to the rest of PAGs, although the spectral pattern of photolysis of this compound was similar to compounds with DPT and DPM. It has been suggested that hydrochloric acid is formed, but in toluene it is too weak to protonate the indicator.

In this study, we summarize the use of these PAGs for the process of deprotection (detritylation) in synthesis of oligonucleotides. The growth of the oligonucleotide chain is carried out through 5′-hydroxyl oxygen of the hydrocarbon part of nucleoside, which is protected by a dimethoxytrityl group (DMT). This group is removed using acid in the appropriate moment of time. In the classical case, dichloroacetic acid or trichloroacetic acid is used. This process is shown in Scheme 2.

The DMT cation has a well-defined absorption spectrum in the visible region with a maximum at 506 nm. In [10,11], various PAG have already been used to remove the DMT group from phosphoramidites, including in the synthesis of oligonucleotides [12–14].



Scheme 1.



Scheme 2.

In this paper, the capability of DPT, DPM, and DPC compounds to remove the DMT protective group from a phosphoramidite when irradiated with the third harmonic of an Nd-YAG laser is investigated.

Experiment

DPT, DPM and DPC compounds were synthesized at I.Ya. Postovskiy Institute of Organic Synthesis of the Ural Branch of the Russian Academy of Sciences, the synthesis is described in [9]. 2 ml DPT, DPM, and DPC solutions in dichloromethane with concentrations of 10^{-4}, $5 \cdot 10^{-4}$ and 10^{-3} M in the automated experimental setup in a standard quartz cuvette under constant stirring by anchor and magnetic agitator were fractionally irradiated by 10 pulses of the 3rd harmonic Nd-YAG laser (355 nm, 40 mJ/impulse, 200 mJ/cm^2), followed by registration of spectra. AvaLight-DH light source and AvaSpec 2048-2 spectrometer (Avantes) located perpendicular to the irradiation source were used to register the absorption spectra.

In photolysis process we used a solution of 5′-dimethoxytrityl-2′- desoxytimidine, 3′-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite (further in the text - dT) at a concentration of $5 \cdot 10^{-5}$ M. The quantum yield of the photo-transformation of compounds in dichloromethane is determined in the same way as in [9], according to the formula

$$\gamma = \frac{N_{\text{ph}}}{N_{\text{abs}}}, \tag{1}$$

where N_{ph} — number of molecules after photo-transformation at N_{abs} of the absorbed photons. The number N_{ph} was determined by a declined intensity of the main absorption band early in the photolysis, when the absorption of photoproducts in this area can still be neglected:

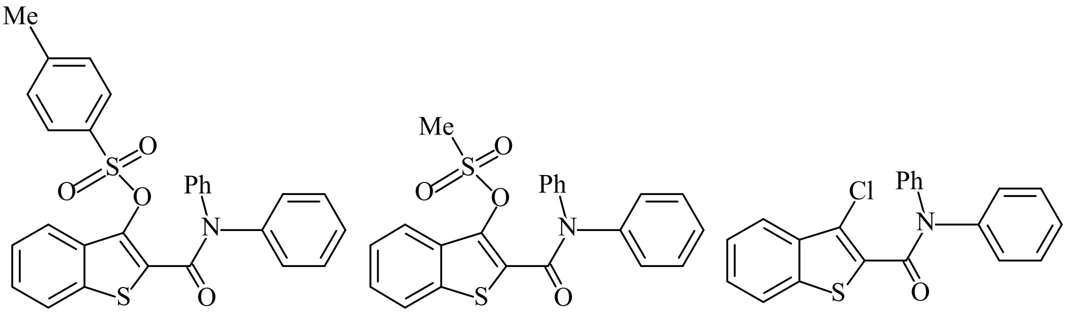
$$N_{\text{ph}} = \frac{(D_0 - D_n) \times C_0 N V}{D_0 \times 10^3}. \tag{2}$$

Here D_0 and D_n — optical densities of the solution before and after irradiation by n pulses (in our case $n = 10{-}20$), C_0 — initial concentration of compounds (in our case — $C_0 = 10^{-4}$ M), N — Avogadro's number, V — irradiated volume of (2 ml). Under laser irradiation, the pulse energy E_p (40 mJ in our case) can be easily converted into the number of photons allowing for the transmission coefficient of the solution at the excitation wavelength (T) and the photon energy $E_{h\nu} = 5.6 \cdot 10^{-19}$ J at the wavelength of 355 nm:

$$N_{\text{abs}} = \frac{nE_p \times (1 - T)}{E_{h\nu}}. \tag{3}$$

Results and discussion

It can be seen from Fig.1 that the studied compounds have the same backbone and differ only in the acid substituent. If the acids are formed according to the Scheme 1, then we must obtain toluylsulfonic, methylsulfonic or hydrochloric acids during the irradiation process. The strength of these acids can be estimated by the rate of formation of DMT cation during the detritylation reaction under identical experimental conditions. The radiation of Nd-YAG laser 355 nm falls on the very edge of the absorption bands of all compounds, where the molar extinction coefficient barely reaches 1000. However, even in this case, the bonds undergo noticeable changes. The nature of these changes is similar for all compounds, so let's look at it using the example of DPT.



DPT **DPM** **DPC**

Figure 1. Studied PAG.

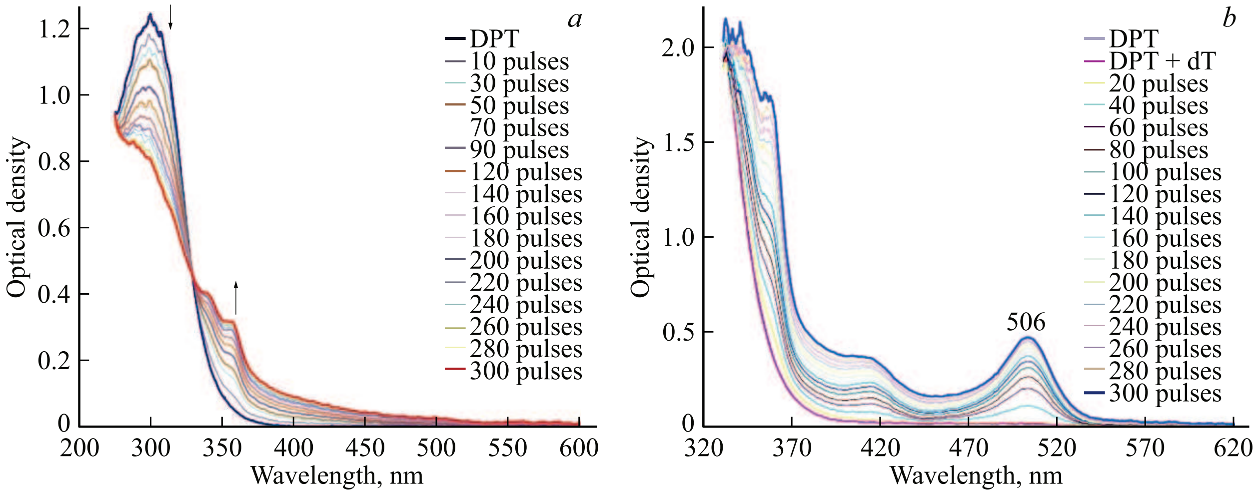


Figure 2. Photolysis of DPT (10^{-4} M) in dichloromethane (*a*), when mixed with dT ($5 \cdot 10^{-5}$ M) (*b*).

Fig. 2, *a* illustrates the photolysis of DPT concentration 10^{-4} M in dichloromethane. During the irradiation process, the intensity of the main band decreases with a simultaneous increase in absorption in the long-wavelength region of 320–450 nm. There is an isobestic point at 320 nm region, indicating the registration of a two-component solution: the initial structure and the photo-transformation product. It is clear that we will not detect the formation of the third product — acid — spectrally. But as mentioned above, we recorded it using an indicator even in toluene solutions [9].

Photolysis of compounds when dT added into solution is accompanied by appearance of a new band at 506 nm (Fig. 2, *b*). It is well known [14] that this band belongs to the DMT cation, and it is also easily detectable when a small amount, for example, dichloroacetic acid, is added to the dT solution. It should be noted that acid photo-generation by these compounds also occurs in toluene, which is confirmed by the indicator, but there was no detritylation process in toluene. It is possible that the strength of the acids formed in toluene is significantly lower than in dichloromethane. The quantum yields of the photo-transformation of these compounds found by the formula (1) in toluene and dichloromethane, are given in the table below. It can be seen that the values of γ in dichloromethane are even slightly lower than in toluene. That is, the absence of detritylation in toluene solutions, all other things being equal, is most likely due to a noticeable difference in the strength of the acids formed in these solvents rather than the rate of their formation.

Values of the quantum yield of photo-transformation of compounds in toluene and dichloromethane

Solvent	γ		
	DPT	DPM	DPC
Toluene	0.072	0.06	0.024
Dichloromethane	0.021	0.016	0.016

The detritylation process was carried out for three concentrations of compounds: 10^{-4}, $5 \cdot 10^{-4}$ and 10^{-3} M. Concentration of dT remained constant, $5 \cdot 10^{-5}$ M. DMT cation absorption growth at 506 nm versus number of irradiation pulses is given in Fig. 3, *a*–*c*. An increase in the amount of DMT cation during photolysis is expected with higher concentration of PAG. A compari-

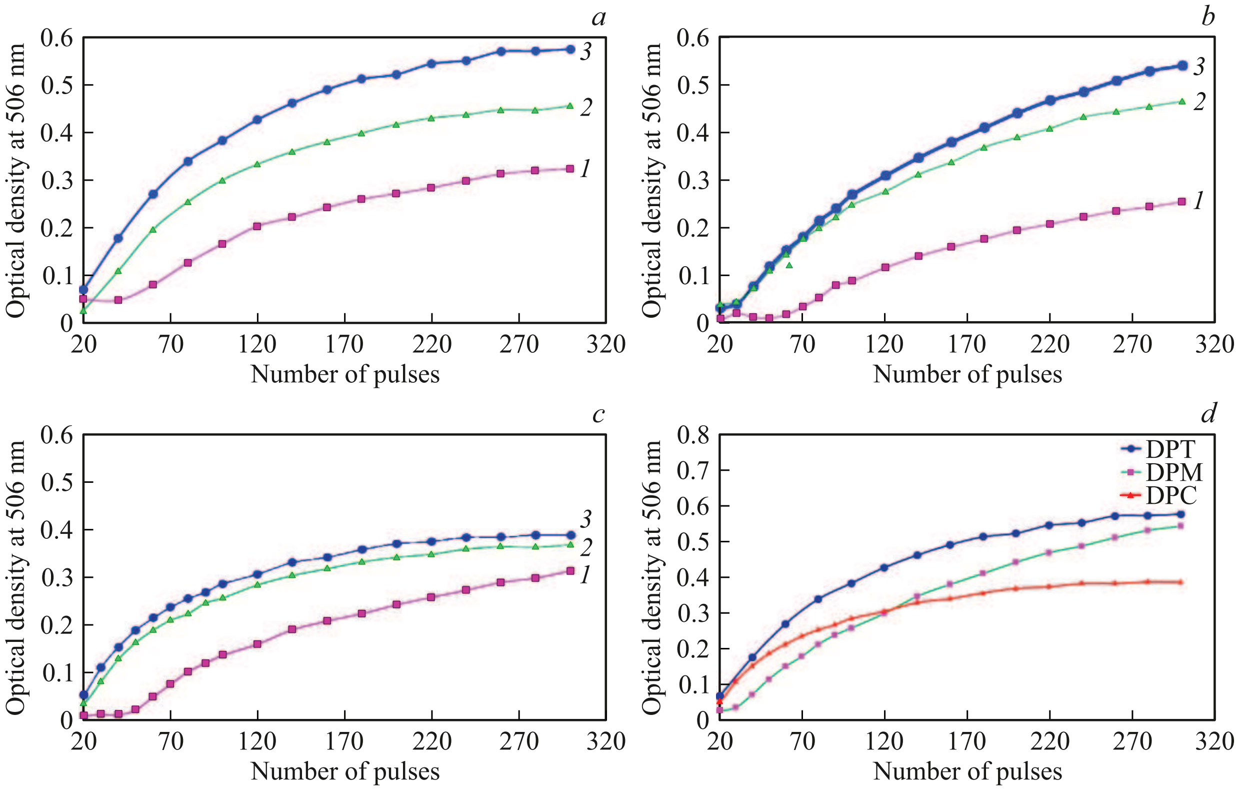


Figure 3. DMT cation optical density growth at $\lambda = 506$ nm versus PAG concentration: *1* — 10^{-4}, *2* — $5 \cdot 10^{-4}$, *3* — 10^{-3} M for DPT (*a*), DPM (*b*), DPC (*c*); comparison between PAGs in the process of detritylation for the concentration 10^{-3} M (*d*).

son of the compounds can be seen in Fig. 3, *d*, which illustrates the same dependence for the concentration of compounds 10^{-3} M.

If we compare DPT and DPM, it can be seen that the process of detritylation with DPT is more efficient. For this compound, the values of γ are higher in both toluene and dichloromethane (see the table). It can be concluded that both the rate of acid formation and its nature affect the detritylation process, but to a different extent. The DPC compound is ahead of the DPM at the first stage of irradiation, but after 100 pulses it begins to lag behind noticeably.

Conclusion

The studied toluylsulfo-, methylsulfo-, and chloro-substituted benzo[*b*]thiophene-2-carboxanilides are quite effective acid photo-generators. The detritylation process for three concentrations of PAG has been studied in dichloromethane when excited by the third harmonic of Nd-YAG laser. It has been shown that compounds with sulfonic acid substituents are more effective than those with chloro-substituted ones.

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Conflict of interest

The authors declare that they have no conflict of interest.

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