Mendeleev Communications

Mendeleev Commun., 2025, **35**, 179–182

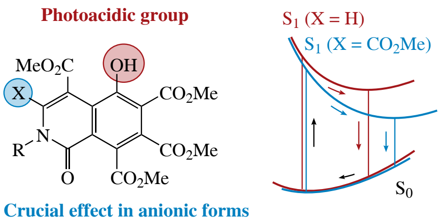
Significant impact of 3-positioned substituent on the fluorescent properties of 5-hydroxyisoquinolones

Alexander Yu. Belyy, Alena D. Sokolova, Rinat F. Salikov,* Konstantin P. Trainov, Dmitry N. Platonov and Yury V. Tomilov*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: rinosal@gmail.com, tom@ioc.ac.ru

DOI: 10.71267/mencom.7618

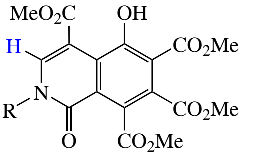
Fluorescent properties of 5-hydroxyisoquinolone-3,4,6,7,8-pentacarboxylates and their 4,6,7,8-tetracarboxylate analogs lacking a 3-positioned electron-withdrawing ester group differ substantially. The presence of an electron-withdrawing group at position 3 in the 5-hydroxyisoquinolone system was found crucial for their vibrational relaxation in the anionic forms, which highlights the importance of substitution pattern providing valuable insights for future research in this area.



Keywords: fluorescence, photoacidity, vibrational relaxation, 5-hydroxyisoquinolones, isoquinolones, Stokes shift, TD-DFT.

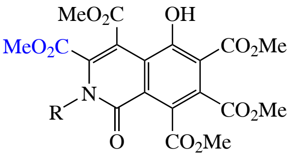
Designing an ideal fluorophore presents a significant challenge, as it must be tailored to specific applications across various fields.[1–3] For instance, the development of organic light-emitting diodes[4] necessitates materials with long-term stability, a requirement often overlooked in analytical applications. Nonetheless, a large Stokes shift remains a critical characteristic across all domains of application.[5,6] Recent studies have elucidated methods for modulating the Stokes shift thus highlighting the importance of substituents that undergo rotation in the excited state,[7,8] as well as the phenomenon of excited state proton transfer,[9] often expressed in photoacidity. Photoacidity is a phenomenon associated with an increase in acidity upon light absorption. Under irradiation, irreversible photoacids[10] can release strong acids through radical processes, while reversible photoacids exhibit changes in acidity upon excitation.[11] Common reversible photoacids belong to aromatic or heteroaromatic alcohol and amine families along with fluorene derivatives.[12–16] These compounds hold significant potential in diverse applications including biomedical research,[17] fluorescent probes,[18,19] catalysts in organic synthesis[20] and light-induced polymerization,[21] and photoresists.[22]

In previous investigations,[23,24] our team reported on the synthesis of fluorescent 5-hydroxyisoquinolone derivatives (including **1a–d** and **2a**,**b**) with four or five ester groups based on the reaction of antiaromatic cycloheptatrienyl anions[25,26] with amines. An additional investigation of compounds **2a**,**b** showcased them as some of the most potent superphotoacids known.[27] These compounds exhibit excited state $\mathrm{p}K_\mathrm{a}^*$ values up to –5.8 and can experience $\mathrm{p}K_\mathrm{a}$ shifts of up to 9.0 units upon excitation. The recent[24] synthesis of derivatives **1a–d** afforded a series of novel 5-hydroxyisoquinolones that differ from those reported earlier[23] by the absence of 3-positioned ester groups. In this study we took advantage of the opportunity to explore how this simplification of the fluorophore's structure affects its parameters. We will discuss the optical properties of fluorescent 5-hydroxyisoquinolones **1a–d** with a previously unexplored substitution pattern and compare the new data with those of compounds **2a**,**b** to find out the importance of the presence of a substituent at position 3 of the isoquinolone ring.



1a–d

a R = Me **c** R = Pr$^{\mathrm{i}}$
b R = Ph **d** R = Bn



2a,**b**

a R = Me
b R = Ph

Spectrophotometric titration of compound **1a** afforded a $\mathrm{p}K_\mathrm{a}$ value of 4.6 for this new series representing a 1.2-unit increase compared to compounds of type **2** with an additional ester group. To obtain the absorption and fluorescence spectra of compounds **1a–d** in neutral and anionic forms, we performed measurements in aqueous media at pH values of 1 and 7 (Table 1, full data are presented in Online Supplementary Materials). For comparison, we included two compounds from our previous manuscript with the same substituents at the nitrogen atom as those in **1a** and **1b** and containing an ester group at position 3 (compounds **2a**,**b**). Notably, while the influence of a substituent at the nitrogen atom appeared minimal, the absence of one ester group relative to compounds **2a**,**b** induced notable alterations in certain parameters.

The absorption in various media and fluorescence under neutral conditions are directly linked to the properties of pure neutral or pure anionic species. Our prior findings[27] demonstrated that fluorescence spectra under acidic conditions corresponded to overlapping emissions from the acid and its conjugate base due to photoacidity, although the fluorescence spectra of **1a–d** did not exhibit a minor band, unlike those of **2a**,**b** (see Table 1). To determine the fluorescence maxima of the acid forms, we employed two four-parameter lognormal functions[28] to

Table 1 Experimental and calculated optical properties of 5-hydroxyisoquinolones **1a–d** and **2a**,**b**.

Compound	λ_{abs}/nm[a]	λ_{fl}/nm[a]	$\Delta\lambda$/nm[a]	Stokes shift[a]/cm^{-1}	λ_{fl}/nm[b] (HA)	λ_{abs}^{calc}/nm (ΔE_{exp}/eV[c])		λ_{fl}^{calc}/nm (ΔE_{exp}/eV[d])	
						HA	A$^-$	HA	A$^-$
1a	351 (392)	439 (462)	88 (70)	5711 (3865)	417	357 (0.06)	376 (0.13)	410 (0.05)	449 (0.08)
1b	352 (396)	446 (462)	94 (66)	5988 (3608)	429	361 (0.09)	384 (0.10)	418 (0.08)	435 (0.17)
1c	352 (392)	439 (463)	87 (71)	5630 (3912)	419	358 (0.06)	379 (0.11)	410 (0.06)	447 (0.10)
1d	360 (391)	436 (463)	76 (72)	4842 (3977)	417	356 (0.04)	376 (0.13)	411 (0.04)	443 (0.12)
2a	366 (411)[27]	430, 524 (522)[27]	64, 158 (111)[27]	4067, 8238 (5174)[27]	430[27]	359 (0.07)	403 (0.06)	408 (0.16)	459 (0.33)
2b	368 (411)[27]	442, 525 (526)[27]	74, 157 (115)[27]	4549, 8126 (5319)[27]	442[27]	362 (0.06)	409 (0.01)	427 (0.10)	464 (0.31)

[a] At pH 1 (parentheses stand for pH 7). [b] Obtained from decomposition of fluorescence spectra at pH 1 *via* a four-parameter lognormal function. HA stands for non-deprotonated ‘acid’ such as compounds **1**, **2**. [c] Obtained *via* PBE0/def2-TZVPP//r^{2}SCAN-3c/CPCM (water) level of theory. [d] Obtained *via* PBE0/def2-TZVPP//PBE0/def2-SVP/CPCM (water) level of theory.

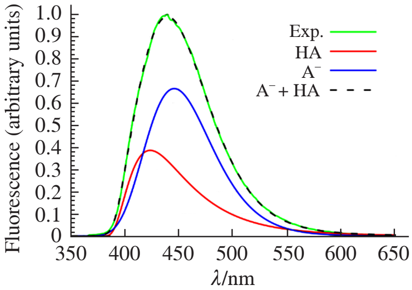


Figure 1 Decomposition of the fluorescence spectrum of compound **1a** at pH 1.

decompose the fluorescence spectra obtained at pH 1. Figure 1 illustrates the decomposition of the fluorescence spectrum of compound **1a**, revealing two lines corresponding to acid (red line) and anionic (blue line) forms, and the sum of the two components (dashed line) nearly coincides with the initial spectrum.

The presence of an ester group at position 3 has minimal impact on the absorption maxima, as observed in compounds **1a**,**b**. In acidic media, the absorption maxima of these compounds are shifted towards shorter wavelengths by 14–15 nm compared to their counterparts with five ester groups, and by 15–19 nm in neutral media. Conversely, the absence of a single ester group in compounds **1a**,**b** induced only a slight blueshift in the fluorescence of the acid forms (decomposed maxima) and a substantial blueshift in the fluorescence of the anions (13 nm for acids *vs*. 60–64 nm for anions). This suggests that the 3-positioned ester group primarily influences the vibrational relaxation of excited anions rather than other species (Figure 2). Therefore, the Stokes shift values of compounds **1a**,**b** are lower than those of their analogs. The experimental data also correlate with the charge redistribution diagrams[29,30] obtained upon vertical excitation of compounds **1a** and **2a** in acidic and anionic forms (Figure 3). These diagrams demonstrate isosurfaces denoting regions of electron density depletion (red) and electron density gain (blue). The ester groups at position 3 in neutral **2a** hardly participate in charge redistribution; therefore, compounds **1a** and **2a** demonstrate slightly different absorption and fluorescence in acidic media. In contrast, the 3-positioned ester group plays a significant role in charge redistribution in the anionic form of compound **2a**. This does not significantly change the absorption spectra but likely induces more significant vibrational relaxation in **2a** than in **1a**.

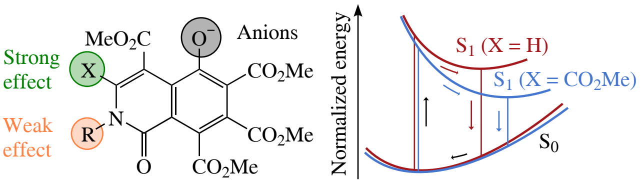


Figure 2 Schematic Jablonski diagram representing different vibrational relaxations in 5-hydroxyisoquinolone anions with (blue) and without (red) an ester group at position 3.

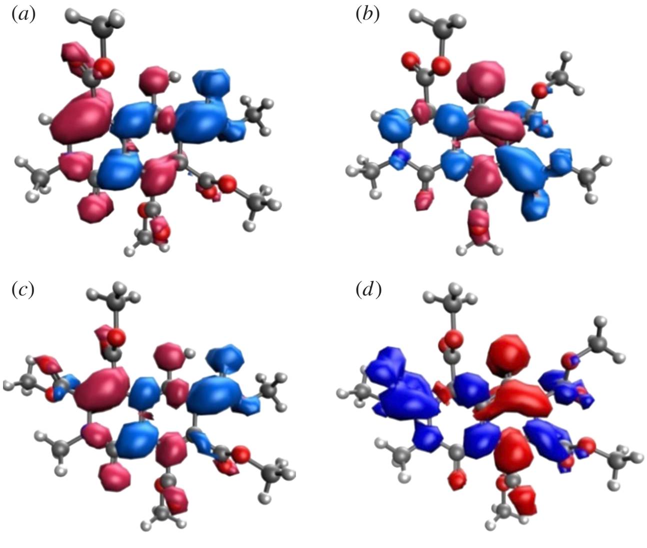
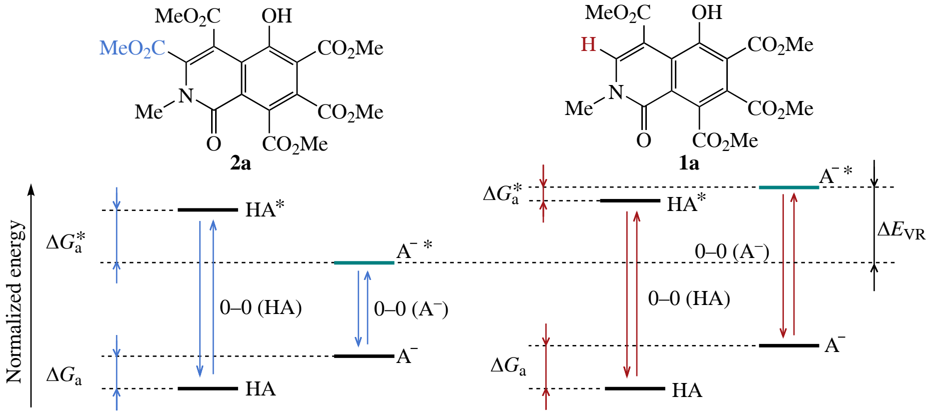


Figure 3 Difference in total density computed for the ground and excited states *via* PBE0/def2-TZVP/CPCM (water) level of theory for (*a*), (*b*) 5-hydroxyisoquinolone **1a** and (*c*), (*d*) 5-hydroxyisoquinolone **2a** in (*a*), (*c*) neutral and (*b*), (*d*) anionic forms, which represent regions with electron density depletion (red) and electron density gain (blue).

In addition, quantum chemical calculations were conducted to determine the absorption and fluorescence maxima of compounds **1a–d**, **2a**,**b** in both neutral and anionic forms (see Table 1). The calculated fluorescence maxima of neutral compounds **1a–d** differ by only 11 nm (0.08 eV) from those obtained through spectral decomposition at pH 1, validating the accuracy of the lognormal decomposition. Most calculated values align closely with experimental results, with differences within 0.17 eV, except for the fluorescence maxima of anions **2a**,**b**, which exhibit errors within 0.31–0.33 eV. This discrepancy highlights the failure of the chosen level of theory (see Table 1 footnotes) to adequately account for the vibrational relaxation process in the excited states of anions with an ester group at position 3 (see Figure 2). A comprehensive analysis of the accuracy of quantum chemical calculation methods for estimating the fluorescence maximum of compound **2a** in the anionic form is presented in Online Supplementary Materials.

The Förster cycle method[31] based on estimating the difference between ground-state pK_a and pK_a^* from excitation and de-excitation energies was employed to estimate excited-state pK_a^* values for compounds **1a–d**. The wavelengths corresponding to 0–0 transitions were estimated from intersections between normalized absorption and fluorescence spectra of acids and



2a

1a

Figure 4 Förster cycle representation for compounds **2a** and **1a**.

Table 2 Excited and ground state pK_a values and 0–0 transition wavelengths of 5-hydroxyisoquinolones **1a–d** and **2a**,**b**.

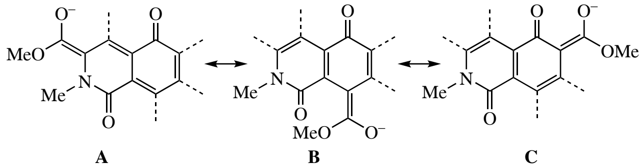
Compound	λ_{0-0}/nm		pK_a	ΔpK_a	pK_a^*
	HA^a	A$^{-\,b}$			
1a	393	422	4.6	3.6	1.0
1b	398	426	4.6^c	3.4	1.2
1c	395	422	4.6^c	3.3	1.3
1d	395	423	4.6^c	3.5	1.1
2a	395[27]	458[27]	3.4[27]	7.3[27]	–3.9[27]
2b	400[27]	458[27]	3.4[27]	6.7[27]	–3.3[27]

^{a}The intersection points between the normalized experimental absorption and decomposed fluorescence bands. ^{b}The intersection points between the normalized experimental absorption and fluorescence bands. ^{c}Interpolated from **2a**.

anions (see Table 1; for spectra, see Online Supplementary Materials). Subsequently, ΔpK_a values were calculated from the 0–0 transition wavelengths using equation (1) to derive, in turn, the pK_a^* values (Table 2). Compared with previous results for compounds **2a**,**b**, 5-hydroxyisoquinolones **1a**,**d** demonstrated drastically lower photoacidity, with their pK_a values decreasing by 3.4–3.6 units upon excitation *vs*. 6.7–7.3 units reported previously.[27] A schematic representation of the Förster cycle is shown in Figure 4. The results show that 5-hydroxyisoquinolones with a 3-positioned ester group are strong photoacids, whereas those without an ester group are weak photoacids, resulting in distinct relative positions of the excited anion at the 0-point position on the diagram. This aligns with our earlier discussion of the impact of the ester group at position 3 on the vibrational relaxation process (see Figure 2), which is notably more pronounced in anions of **2a**,**b** than in anions of **1a–d**. This influence is visualized by the quinonoid resonance structure **A** (Figure 5) which can be drawn for anion of **2a** (not of **1a** as structures **B** and **C**).

$$\Delta pK_a = 2.10\times10^4\left(\frac{1}{\lambda_{HA}}-\frac{1}{\lambda_{A^-}}\right) \qquad (1)$$

The derivatives of α- and β-naphthol are the most intensively studied analogs of our compounds. For them, the influence of substitution pattern onto photoacidity either has not been investigated or was found insignigficant.[32–34] Therefore, our identification of the most important position for substitution with an electron-withdrawing group in 5-hydroxyisoquinolones in terms of photoacidity may offer valuable insights for future research in this area.



A
(**2a** only)

B
(**2a** and **1a**)

C
(**2a** and **1a**)

Figure 5 Quinonoid resonance structures with structure **A** responsible for the vibrational relaxation of anion **2a**.

To summarize, we have demonstrated that the optical properties of 5-hydroxyisoquinolones are not dependent on the substituent on the nitrogen atom; however, the presence of an ester group at position 3 of the heterocyclic ring has been found to be crucial in terms of fluorescence in neutral aqueous media, Stokes shift and photoacidity.

This work was supported by the Russian Science Foundation (grant no. 23–23–00624).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7618.

References

1 S. O. Fakayode, C. Lisse, W. Medawala, P. N. Brady, D. K. Bwambok, D. Anum, T. Alonge, M. E. Taylor, G. A. Baker, T. F. Mehari, J. D. Rodriguez, B. Elzey, N. Siraj, S. Macchi, T. Le, M. Forson, M. Bashiru, V. E. Fernand Narcisse and C. Grant, *Appl. Spectrosc. Rev.*, 2024, **59**, 1; https://doi.org/10.1080/05704928.2023.2177666.
2 J. Zhang, M. Zhou, X. Li, Y. Fan, J. Li, K. Lu, H. Wen and J. Ren, *Talanta*, 2023, **254**, 124133; https://doi.org/10.1016/j.talanta.2022.124133.
3 Q. Xu, F. Xiao and H. Xu, *TrAC Trends Anal. Chem.*, 2023, **161**, 116999; https://doi.org/10.1016/j.trac.2023.116999.
4 R. Pode, *Renewable Sustainable Energy Rev.*, 2020, **133**, 110043; https://doi.org/10.1016/j.rser.2020.110043.
5 X. Wu, X. Sun, Z. Guo, J. Tang, Y. Shen, T. D. James, H. Tian and W. Zhu, *J. Am. Chem. Soc.*, 2014, **136**, 3579; https://doi.org/10.1021/ja412380j.
6 G. Yang, J. Li, X. Deng, X. Song, M. Lu, Y. Zhu, Z. Yu, B. Xu, M.-D. Li and L. Dang, *J. Phys. Chem. Lett.*, 2023, **14**, 6927; https://doi.org/10.1021/acs.jpclett.3c01437.
7 X. Liu, Z. Xu and J. M. Cole, *J. Phys. Chem. C*, 2013, **117**, 16584; https://doi.org/10.1021/jp404170w.
8 Y. Chen, J. Zhao, H. Guo and L. Xie, *J. Org. Chem.*, 2012, **77**, 2192; https://doi.org/10.1021/jo202215x.
9 L. F. B. Fontes, J. Rocha, A. M. S. Silva and S. Guieu, *Chem. – Eur. J.*, 2023, **29**, e202301540; https://doi.org/10.1002/chem.202301540.
10 C. J. Martin, G. Rapenne, T. Nakashima and T. Kawai, *J. Photochem. Photobiol., C*, 2018, **34**, 41; https://doi.org/10.1016/j.jphotochemrev.2018.01.003.
11 J. F. Ireland and P. A. H. Wyatt, *Adv. Phys. Org. Chem.*, 1976, **12**, 131; https://doi.org/10.1016/S0065-3160(08)60331-7.
12 C. Berton and C. Pezzato, *Eur. J. Org. Chem.*, 2023, **26**, e202300070; https://doi.org/10.1002/ejoc.202300070.
13 G. R. Han, E. Lim, J. Kang, D. Hwang, J. Heo, S. K. Kim and J. W. Lee, *J. Phys. Chem. A*, 2023, **127**, 7884; https://doi.org/10.1021/acs.jpca.3c03170.

14 H. Liu, Y. Chen, D. An, X. Zhang and S. Liao, *Synlett*, 2022, **33**, 800; https://doi.org/10.1055/a-1799-7464.

15 A. O. Naumova, P. V. Melnikov, V. A. Kuzmin and N. K. Zaitsev, *Mendeleev Commun.*, 2023, **33**, 212; https://doi.org/10.1016/j.mencom.2023.02.020.

16 N. Sülzner and C. Hättig, *J. Phys. Chem. A*, 2022, **126**, 5911; https://doi.org/10.1021/acs.jpca.2c04436.

17 T. Sun, L. Kang, H. Zhao, Y. Zhao and Y. Gu, *Adv. Sci.*, 2024, **11**, 2302875; https://doi.org/10.1002/advs.202302875.

18 R. Nandi and N. Amdursky, *Acc. Chem. Res.*, 2022, **55**, 2728; https://doi.org/10.1021/acs.accounts.2c00458.

19 Y. Cheng, X. Ma, J. Zhai and X. Xie, *Chem. Commun.*, 2023, **59**, 1805; https://doi.org/10.1039/D2CC06816H.

20 J. Saway, Z. M. Salem and J. J. Badillo, *Synthesis*, 2021, **53**, 489; https://doi.org/10.1055/s-0040-1705952.

21 P. Sun, Z. Li, X. Zhang, Y. Liao and S. Liao, *Macromol. Rapid Commun.*, 2024, **45**, 2400054; https://doi.org/10.1002/marc.202400054.

22 H.-W. Pei, K. Ye, Y. Shao, D. Chen, Z.-Y. Sun, T. Gong, D. Liu and K. Sun, *Polym. Chem.*, 2024, **15**, 248; https://doi.org/10.1039/D3PY00992K.

23 A. Y. Belyy, D. N. Platonov, R. F. Salikov, K. P. Trainov, M. G. Medvedev, Y. N. Luponosov, E. A. Svidchenko and Y. V. Tomilov, *Dyes Pigm.*, 2021, **187**, 109107; https://doi.org/10.1016/j.dyepig.2020.109107.

24 A. Yu. Belyy, A. D. Sokolova, R. F. Salikov, V. V. Litvinenko, D. N. Platonov and Yu. V. Tomilov, *Mendeleev Commun.*, 2025, **35**, 162; https://doi.org/10.71267/mencom.7616.

25 M. K. Ilyushchenko, R. F. Salikov, A. D. Sokolova, V. V. Litvinenko, A. Y. Belyy, D. N. Platonov and Y. V. Tomilov, *J. Org. Chem.*, 2023, **88**, 5661; https://doi.org/10.1021/acs.joc.3c00142.

26 R. F. Salikov, A. Y. Belyy, M. K. Ilyushchenko, D. N. Platonov, A. D. Sokolova and Y. V. Tomilov, *Chem. – Eur. J.*, 2024, **30**, e202401041; https://doi.org/10.1002/chem.202401041.

27 R. F. Salikov, A. Y. Belyy, K. P. Trainov, J. A. Velmiskina, M. G. Medvedev, V. M. Korshunov, I. V. Taydakov, D. N. Platonov and Y. V. Tomilov, *J. Photochem. Photobiol., A*, 2022, **427**, 113808; https://doi.org/10.1016/j.jphotochem.2022.113808.

28 D. B. Siano and D. E. Metzler, *J. Chem. Phys.*, 1969, **51**, 1856; https://doi.org/10.1063/1.1672270.

29 T. Le Bahers, C. Adamo and I. Ciofini, *J. Chem. Theory Comput.*, 2011, **7**, 2498; https://doi.org/10.1021/ct200308m.

30 C. Adamo and D. Jacquemin, *Chem. Soc. Rev.*, 2013, **42**, 845; https://doi.org/10.1039/C2CS35394F.

31 L. M. Tolbert and K. M. Solntsev, *Acc. Chem. Res.*, 2002, **35**, 19; https://doi.org/10.1021/ar990109f.

32 J. Xie, R. E. Nealon, Z. T. Egan and K. Takematsu, *Phys. Chem. Chem. Phys.*, 2023, **25**, 33184; https://doi.org/10.1039/D3CP04845D.

33 F. Wendler, M. Sittig, J. C. Tom, B. Dietzek and F. H. Schacher, *Chem. – Eur. J.*, 2020, **26**, 2365; https://doi.org/10.1002/chem.201903819.

34 M. Prémont-Schwarz, T. Barak, D. Pines, E. T. J. Nibbering and E. Pines, *J. Phys. Chem. B*, 2013, **117**, 4594; https://doi.org/10.1021/jp308746x.

Received: 16th September 2024; Com. 24/7618