Charge-transfer complexes of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone with amino molecules in polar solvents

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Charge-transfer complexes of 2,3-dichloro-5,6-dicyano-1, 4-benzoquinone with amino molecules in polar solvents

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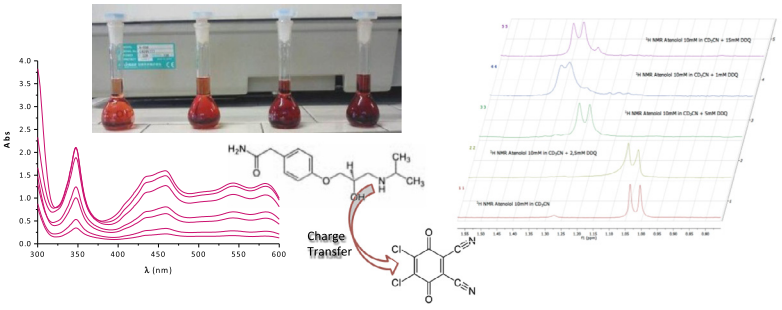
HIGHLIGHTS

- The stability of the DDQ–atenolol complex was determined in acetonitrile and ethanol.
- The stability of the DDQ–procaine complex was determined in ethanol.
- The association constants were determined by HypSpec® software.
- Only the aliphatic amino groups are involved in the charge transfer complex formation.

GRAPHICAL ABSTRACT



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ABSTRACT

The charge-transfer complexes have scientific relevance because this type of molecular interaction is at the basis of the activity of pharmacological compounds and because the absorption bands of the complexes can be used for the quantification of electron donor molecules. This work aims to assess the stability of the charge-transfer complexes between the electron acceptor 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and two drugs, procaine and atenolol, in acetonitrile and ethanol. The stability of DDQ in solution and the time required to obtain the maximum complex formation were evaluated. The stoichiometry and the stability of the complexes were determined, respectively, by Job's plot method and by the elaboration of UV–vis titrations data. The latter task was carried out by using the non-linear global analysis approach to determine the equilibrium constants. This approach to data elaboration allowed us to overcome the disadvantages of the classical linear-regression method, to obtain reliable values of the association constants and to calculate the entire spectra of the complexes. NMR spectra were recorded to identify the portion of the donor molecule that was involved in the interaction. The data support the participation of the aliphatic amino groups in complex formation and exclude the involvement of the aromatic amine present in the procaine molecule.

Introduction

The charge-transfer (CT) complexes formed from the reaction of electron acceptors with donors containing heteroatoms, such as nitrogen, sulfur or oxygen, have seen a growing importance in recent years. Some studies on acceptor–donor systems were performed to characterize the nature, the kinetic and the stability of the complexes in different organic solvents

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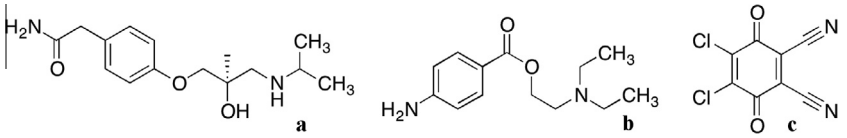

Fig. 1. Donor molecules studied: (a) atenolol, (b) procaine, (c) 2,3-dichloro-5,6-diciano-1,4-benzoquinone (DDQ).

[3,4,6,7,11,13,15–19,22]. Other works report the application of this type of interaction for the quantitative determination of the donor molecules, including the quantification of pharmaceutical products [1,2,8,9,19,21,24]. The peculiarity of the CT complexes is their elevated absorption in the visible range, where donor and acceptor usually do not absorb. Therefore, the absorbance values at the wavelengths of maximum absorption are used for the quantification of the drugs in pharmaceutical formulates. Typical electron acceptors are the 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), 2,3-dibromo-5,6-dicyano-1,4-benzoquinone (DBQ), tetracyanoquinodimethane (TCNQ), tetracyanoethylene (TCNE), 2,3,5,6-tetrabromo-1,4-benzoquinone (bromanil), 2,3,5,6-tetrachloro-1,4-benzoquinone (chloranil), dinitrobenzene (DNB) [20]. The donors are usually molecules with nitrogen or sulfur atoms, having free electron pairs or electron-rich aromatic rings.

In most literature reports, the evaluation of the stability of the complexes has been performed with linear regression methods, such as the Benesi–Hildebrand or Scott equation. However, it has long been known [10,23] that these methods: (i) may be affected by lack of linearity; (ii) can give negative intercepts that hinder the calculations; (iii) are limited by the assumption of the formation of a single complex in 1:1 stoichiometric ratio; (iv) have to respect the conditions $C_A \gg C_D$ (C_A = concentration of the acceptor, C_D = concentration of the donor), or $C_A \ll C_D$, on which the development of the entire equation is based.

In this work, we studied the interaction of the acceptor DDQ with molecules containing nitrogen atoms in acetonitrile and ethanol. The stoichiometry and the stability of the complexes were determined, respectively, by Job's plot method and by the elaboration of UV–vis titrations data. The data collection was achieved by applying the same approach used in the evaluation of the association constants in supramolecular chemistry [23]. This approach is directly derived from the chemical equilibrium theory, and the data elaboration was performed by a software, HypSpec®, dedicated to the determination of equilibrium constants from spectrophotometric data. The software can process the entire UV–vis spectrum and it calculates the stability constants with an iterative method. The single requirement is that the spectral intensity of each chemical species should be proportional to the concentration of that species in solution.

Because preliminary experiments suggested that DDQ preferentially interacts with non-aromatic amines, we chose to study the interaction of DDQ with two pharmaceuticals that contain aliphatic amino groups: a β-adrenergic blocker (atenolol) and a synthetic local anesthetic drug (procaine; see Fig. 1 for their molecular structures). Both molecules have nitrogen functions that could interact with DDQ: procaine has an aliphatic and an aromatic amine, while atenolol has an amino and an amidic nitrogen. NMR spectra were recorded to identify the portion of the donor molecule that is involved in the interaction. Optimal working conditions were assessed, evaluating the stability of DDQ in solution and the time required to obtain the maximum complex formation.

Experimental

Chemicals

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (purity 98%), atenolol (purity ⩾ 98%); procaine hydrochloride (purity 99.9%), tetrabutylammonium hydroxide solution (0.1 mol L^{-1} in organic solvent, which is a mixture of 2-propanol and methanol), ethanol (⩾99.8%) and acetonitrile (99.9%) were Sigma Aldrich products. Ethanol-d_6 (anhydrous, ⩾99%) and acetonitrile-d_3 (⩾99.8%) were Euriso-top products.

The solutions of the donors were prepared by dissolving the drugs in the solvent and were stored at 4 °C. The solutions of the acceptor molecule (DDQ) were always freshly prepared.

Procaine does not interact with DDQ if it is protonated, which is the case for the commercial (hydrochloride) form. Therefore, we used the commercial solution of tetrabutylammonium hydroxide to neutralize the procaine solutions, immediately before mixing them with DDQ.

Spectroscopic measurements

The UV–visible molecular absorption spectra (300–600 nm) of the donor–acceptor systems were recorded with a V-550 Jasco spectrophotometer, equipped with 1.000 cm or 5.00 cm quartz cells (Hellma), and working with a 200 nm/min scanning speed and 1.0 nm band width.

^{1}H NMR measurements at variable temperature were performed on a Jeol EX 400 spectrometer (B_0 = 9.4 T, work frequency ^{1}H = 399.78 MHz), in common 5 mm NMR tubes, while titrations were performed on a Bruker Avance 200 (B_0 = 4.7 T, work frequency ^{1}H = 399.78 MHz) spectrometer. In titration experiments, the drugs concentration was kept constant at 10 mmol L^{-1} while the DDQ concentration was varied from zero to 15 mmol L^{-1}.

Optimization of working conditions

In order to obtain stable and coherent results, we evaluated preliminarily the stability of the DDQ absorption spectra in the two polar solvents and the time necessary to reach the maximum complex formation. As far as the first issue is concerned, DDQ spectra change over time and show an increase of the absorbance values in the same range of the CT-complexes (400–550 nm). The spectral features are in agreement with those reported for the $DDQ^{\cdot-}$ radical ion [14].

In order to assess the sensitivity of DDQ to atmospheric exposure, we recorded the time trend of the absorbance of 5×10^{-3} mol L^{-1} DDQ in ethanol and acetonitrile under environmental atmospheric conditions, or by bubbling nitrogen into the solvent before use and in the solution after preparation. The absorbance was recorded at 460 nm, where absorption by the CT-complexes under study is maximum. To assess the complex development, the spectra of equimolar solutions of DDQ/drug were recorded during time and the absorbance at 460 nm was monitored. Both solvents were used for subsequent studies.

Job's plot method

The Job's plot method was used to evaluate the stoichiometry of the CT-complexes in the two solvents. The drug and the DDQ stock solutions (all 5×10^{-3} mol L^{-1}) were prepared in acetonitrile or ethanol. Then, for each solvent, 9 donor–acceptor solutions were prepared in 10 mL volumetric flasks. In each case, the content of acceptor and donor was chosen so as to vary their molar fractions

but not the total concentration (sum of acceptor and donor concentrations). The spectrum of each solution was recorded between 300 and 600 nm, with an optical path of 1.000 cm. The absorbance at 460 nm was reported in the Job's plot as a function of the solution molar fraction, $\chi = C_{drug}/(C_{drug} + C_{DDQ})$.

Spectrophotometric titration

Spectrophotometric titrations were conducted with the batch method to better control the atmospheric conditions and the time elapsed from the mixing of the components. The single solutions were prepared by adding an aliquot of the drug solution, different fixed volumes of the DDQ solution (increasing in different experiments, so as to carry out the titration in several single steps) and a volume of solvent, so as to reach always the same total volume (10 or 20 mL). Each solution thus prepared was maintained at 25 ± 0.1 °C and an aliquot was taken to record the UV–vis spectrum. The working concentration of the drugs ranged between 2×10^{-5} and 5×10^{-4} mol L^{-1}. The optical paths were 1.000 cm for the less diluted solutions, and 5.00 cm for the lowest concentrations. The molar ratios DDQ/drug ranged between 0 and 10.

Data elaboration

The titration data were elaborated with the HypSpec® software [12], to calculate the formation constants and the molar absorptivity of the CT-complexes for each system.

Results and discussion

Kinetics and stoichiometry of the CT-complexes

A detailed kinetic study was beyond the scope of this work, but a qualitative evaluation of the kinetics of formation of the complexes was attempted, since it evolves during time [16]. Moreover, to assess reliable association constants, it is necessary to identify an elapsed time from the mixing of the solutions, after which the complexes are completely formed and the measured spectra are reproducible.

A problem with DDQ is the formation of the absorbing species $DDQ^{\cdot-}$. Fig. 2 shows the absorbance trend as a function of the elapsed time, for DDQ solutions in ethanol. It is possible to observe that, when nitrogen was bubbled in the solvent, the absorbance increase was less important. A very similar behavior was obtained in acetonitrile.

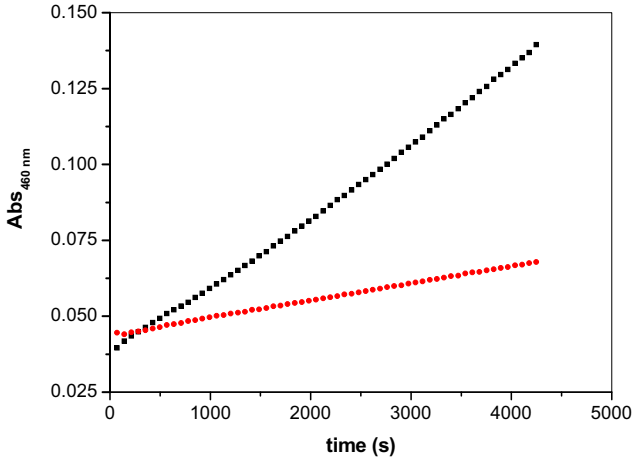

Fig. 2. Absorbance at 460 nm of a 5×10^{-3} mol L^{-1} DDQ solution in ethanol (optical path: 1.000 cm). Black points: solution prepared in atmospheric conditions. Red points: solution prepared in inert atmosphere, obtained by bubbling nitrogen in the solvent before and after the solution preparation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

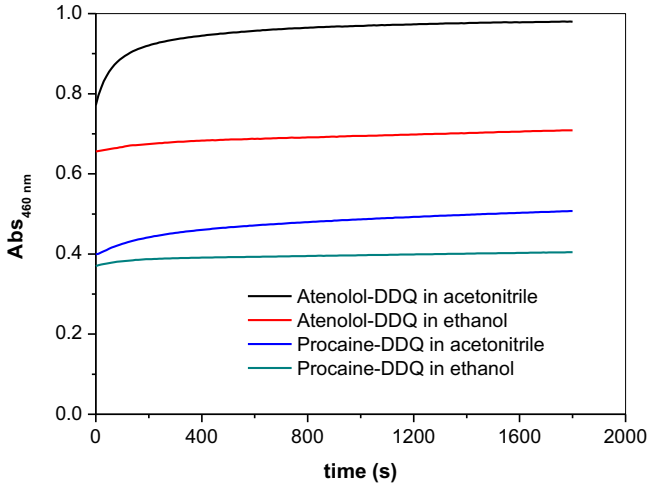

Fig. 3. Time course of CT-complex formation in ethanol and acetonitrile. The absorbance at 460 nm of 4×10^{-5} mol L^{-1} drug solutions was measured with 1 equivalent of DDQ added (optical path: 5.00 cm).

Fig. 3 shows the absorbance trend of DDQ/drug solutions as a function of the elapsed time. Stable absorbance values were reached about 15 min after solution preparation. It is also evident that the signals were lower in ethanol compared to acetonitrile, but the results in ethanol were more stable. Therefore, to allow complex formation but to minimize, at the same time, the interference of $DDQ^{\cdot-}$ on the absorption spectra, the experiments that follow were conducted with solutions prepared in inert atmosphere. The signals of the complexes were recorded after exactly 15 min from the solutions preparation.

Fig. 4 shows the Job's plots obtained for the four studied systems (DDQ–procaine and DDQ–atenolol in both solvents). All the plots have maxima at a molar fraction of 0.5, thus the stoichiometry of the CT-complexes looks to be 1:1.

Stability of the complexes

Spectrophotometric batch titrations were conducted to evaluate the stability of the CT-complexes. The changes in the absorbance of the prepared solutions are obviously related with the concentration of the components: DDQ, drug and CT-complex. In the cases under study, for not excessive concentration of free DDQ, the complex is the only species that absorbs in the range 400–600 nm. Therefore, in this wavelength interval, the absorbance is directly proportional to the complex concentration or to its molar fraction. An example of spectra obtained for the system DDQ–atenolol in ethanol is reported in Fig. 5. By merely looking at the data obtained from the spectrophotometric titration, it is possible to estimate the values of the association constants. As reported by [23], the binding isotherm (the diagram of the molar fraction of the complex, measured by its absorbance change, *vs.* the equivalents of titrant added, $[DDQ]_0/[drug]_0$) changes its features as a function of the ratio $[drug]_0/K_d$. Here K_d is the dissociation constant of the complex, calculated as the reciprocal of the association constant, $1/K_a$. If $[drug]_0/K_d > 100$, the trend is linear till 1 equivalent of titrant added ($[DDQ]_0/[drug]_0 = 1$), after which point the absorbance does not change any longer. In contrast, if $[drug]_0/K_d < 100$, the absorbance increases continuously also after 1 equivalent of titrant added. The latter case is preferred, because

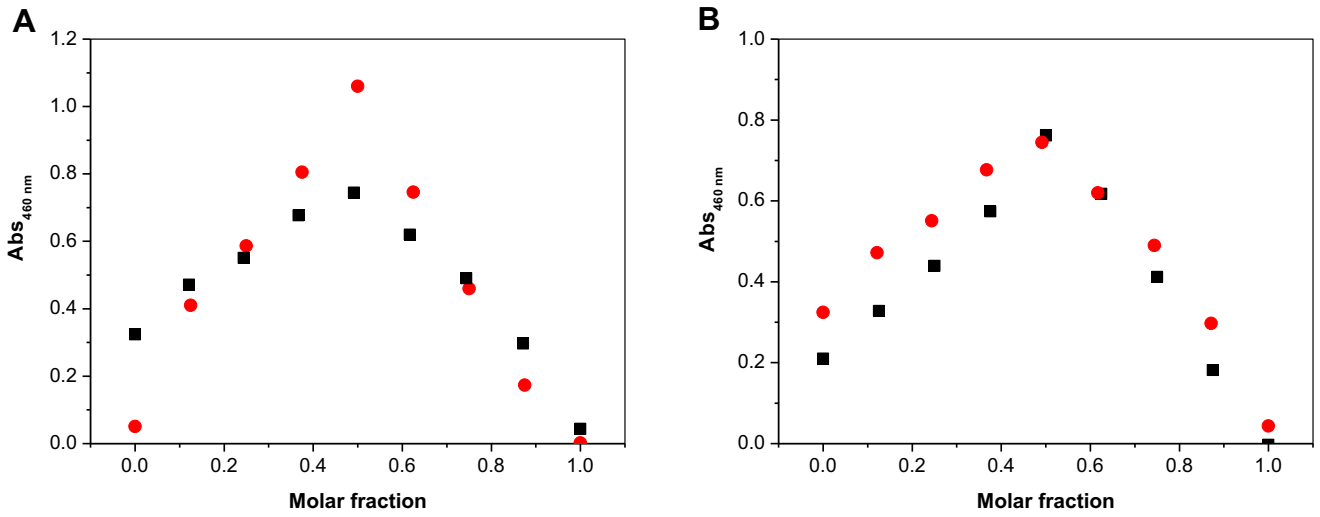

Fig. 4. Job's plots of the CT-complexes, in acetonitrile (A) and ethanol (B), for DDQ–atenolol (red) and DDQ–procaine (black) systems. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

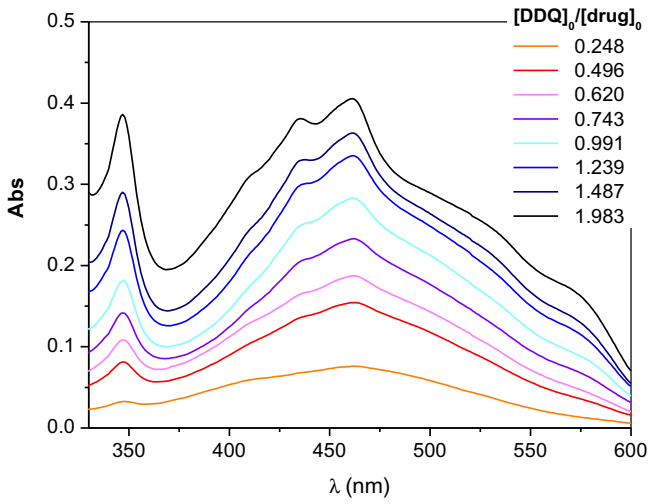

Fig. 5. UV–vis spectra recorded on solutions containing different molar ratios of DDQ and atenolol in ethanol, with $[drug]_0 = 3.9 \times 10^{-5}$ mol L^{-1} and optical path 5.0 cm.

more titration points can be used for K_a evaluation and the uncertainty on K_a gets lower.

Fig. 6 shows the trends of the absorbance (at the wavelength of maximum absorbance, 460 nm) *vs.* the equivalents of titrant added, $[DDQ]_0/[drug]_0$, for systems where $[drug]_0$ was about 4×10^{-5} mol L^{-1} (experimental data obtained at different concentration levels are reported in Fig. S1 of the Supplementary material file). The trends reported in Fig. 6a correspond to data obtained by waiting for 15 min after the mixing of the components, and the last data points have a little excess of DDQ added. In contrast, Fig. 6b reports points with higher concentrations of DDQ. In this case the measurements were executed immediately after the solution preparation, in order to avoid DDQ degradation. The systems DDQ–atenolol, in both solvents, show a very low increase of the absorbance of the drug solution for $[DDQ]_0/[drug]_0 > 1$. This trend is characteristic for systems that have $[drug]_0/K_d \approx 10$ [23], from which we can suppose that $\log K_a \approx 5.4$. A different behavior can be observed for procaine in ethanol, from which it is possible to suppose a lower formation constant of the CT-complex. Moreover, after 1 equivalent of DDQ added, waiting for 15 min after the solution preparation (Fig. 6a), there is a singularity in the trend which suggests that a different reaction between the components is taking place, such as a degradation or an association process. For this reason, the spectra thus obtained were not used for the K_a calculation when $[DDQ]_0/[procaine]_0 > 1$. The system with procaine in acetonitrile showed a singular behavior: replicates of the same solution showed different spectra in the same conditions of temperature, mixing order, elapsed time and freshness of the stock solutions. The reactivity of the system was not clear and, as a consequence, it was not possible to calculate the association constant and the spectral parameters of the complex in acetonitrile.

In order to measure the values of the CT-complexes association constants, the experimental spectra were elaborated with HypSpec®. For the system atenolol–DDQ in ethanol, the absorbance did not change very much with the waiting time. Therefore, also the spectra recorded with high excess of DDQ were elaborated. In the case of atenolol–DDQ in acetonitrile, only the spectra obtained by waiting for 15 min and with no more than 1.2 equivalents of DDQ were elaborated. The reason is that there was a non-negligible increase in the concentration of the complex during the waiting time. In this system, the need to wait for the complete formation of the complexes and the instability of the components provided spectra that were not consistent with one another, in the presence of an excess of DDQ.

Table 1 reports the association constants obtained for the three systems. The values are in agreement with the qualitative analysis of the diagrams Abs_{460nm} *vs.* $[DDQ]_0/[drug]_0$, already discussed. The formation percentages of the CT-complexes, calculated by the application of the association constants obtained for the system atenolol–DDQ, reach values of about 88% when 1.1 equivalents of titrant are added to 4×10^{-5} mol L^{-1} drug solutions, in agreement with the trends of the absorbance reported in Fig. 6. For concentrations of drug higher than 2×10^{4} mol L^{-1}, at the same titration point, the formation percentages of the CT-complexes reach values of about 98% and, consistently, one observes the stabilization of the experimental absorbance values (see Supplementary material). In the case of procaine, about 65% of the drug would be involved in complex formation when 1 equivalent of DDQ is added to a 4×10^{-5} mol L^{-1} drug solution.

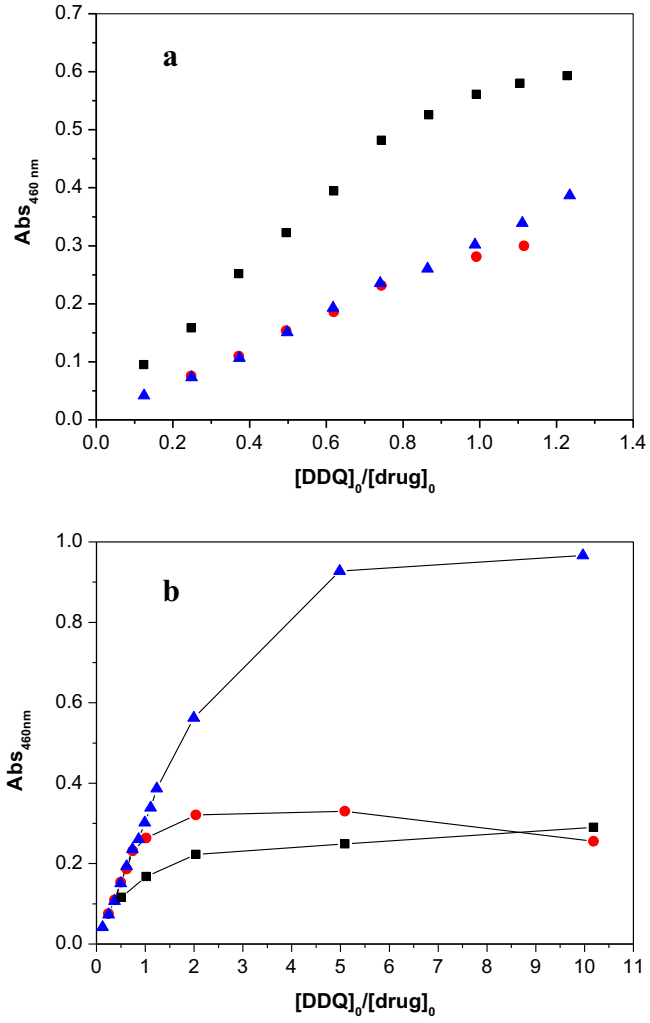

Fig. 6. Absorbance at 460 nm as a function of the equivalents of acceptor added, $[DDQ]_0/[drug]_0$, for the following systems: atenolol 3.96×10^{-5} M in acetonitrile (black), atenolol 3.95×10^{-5} M in ethanol (red), procaine 3.93×10^{-5} M in ethanol (blue). (a) The absorbance values were recorded after 15 min from the mixing of the components; (b) the absorbance values were recorded immediately after the mixing of the components and were corrected subtracting the absorbance due to the excess of DDQ in solution. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

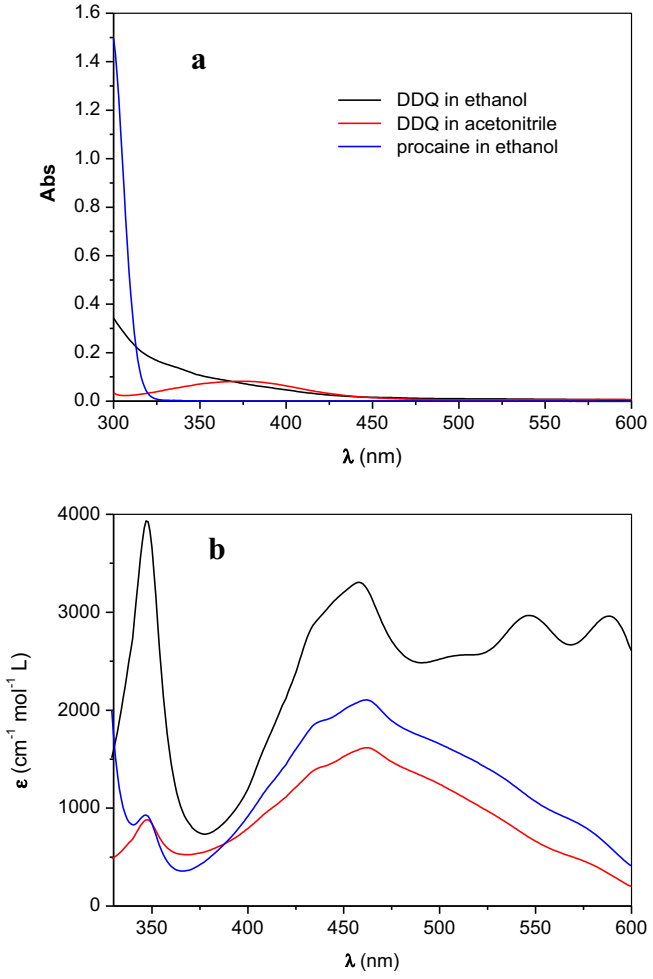

Fig. 7. (a) Spectra of the single components of the solutions 1×10^{-4} mol L^{-1}. The spectra of atenolol are not reported because it does not absorb in the range 300–600 nm. (b) Absorption spectra of the complexes DDQ–procaine (blue: in ethanol) and DDQ–atenolol (red: in ethanol; black: in acetonitrile), calculated with HypSpec®. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The values of λ_{max} are similar for all the complexes, but the complex in acetonitrile has a significantly higher value of ε_{max}. The spectra of the single complexes, also obtained with HypSpec®, are reported in Fig. 7.

NMR spectra

The ^{1}H NMR spectra of the drugs recorded at room temperature in deuterated acetonitrile and ethanol, before and after the addition of DDQ, allowed us to define the portion of the donor molecule involved in complex formation. Through NMR titration, it was also possible to support the values of the formation constants determined above. On the other hand, the spectra recorded at lower temperatures (183 K < T < 273 K) had the purpose of establishing whether the complex would be in a fast exchange regime or a stable pair.

Donor–acceptor (D–A) solutions were freshly prepared, directly in an NMR tube with a variable D/A ratio (1:0.2–1.5), they were mixed and measured after an average time of 15 min. The formation of the complexes was easily monitored in the NMR spectra by the shift of the NMR signals in the molecular region of interest.

Table 1
Association constants, wavelengths of maximum absorbance and the corresponding molar absorption coefficients of the CT-complexes of DDQ with atenolol and procaine, in acetonitrile and ethanol (t = 25 °C).

Drug	Acetonitrile				Ethanol			
	logK_a ± sd[a]	No. spectra[b]	λ_{max} (nm)	ε_{max} ± sd[a] (mol^{-1} cm^{-1} L)	logK_a ± sd	No. spectra[b]	λ_{max} (nm)	ε_{max} ± sd (mol^{-1} cm^{-1} L)
Atenolol	5.9 ± 0. 2	24	458	3306 ± 71	5.9 ± 0.3	23	462	1617 ± 53
Procaine	n.d.		n.d.	n.d.	3.9 ± 0.2	24	462	2104 ± 86

[a] Standard deviation calculated on the log$K$ obtained by the elaboration of the single titrations by HypSpec®.
[b] Number of total spectra elaborated.

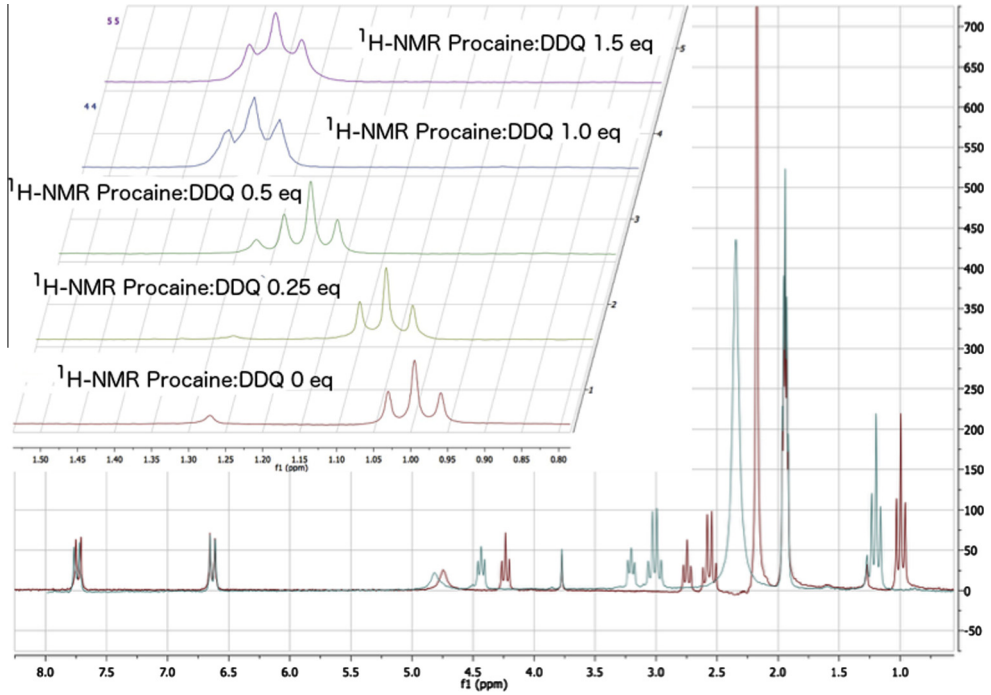

Fig. 8. ^{1}H NMR spectra of the drug in acetonitrile-d_3, before and after the addition of 0.5 equivalents of DDQ: procaine 10.0 mmol L^{-1} (red), procaine 10.0 mmol L^{-1} and DDQ 5.0 mmol L^{-1} (blue); nested graph: ^{1}H NMR CH_3-region shift observed during titration. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

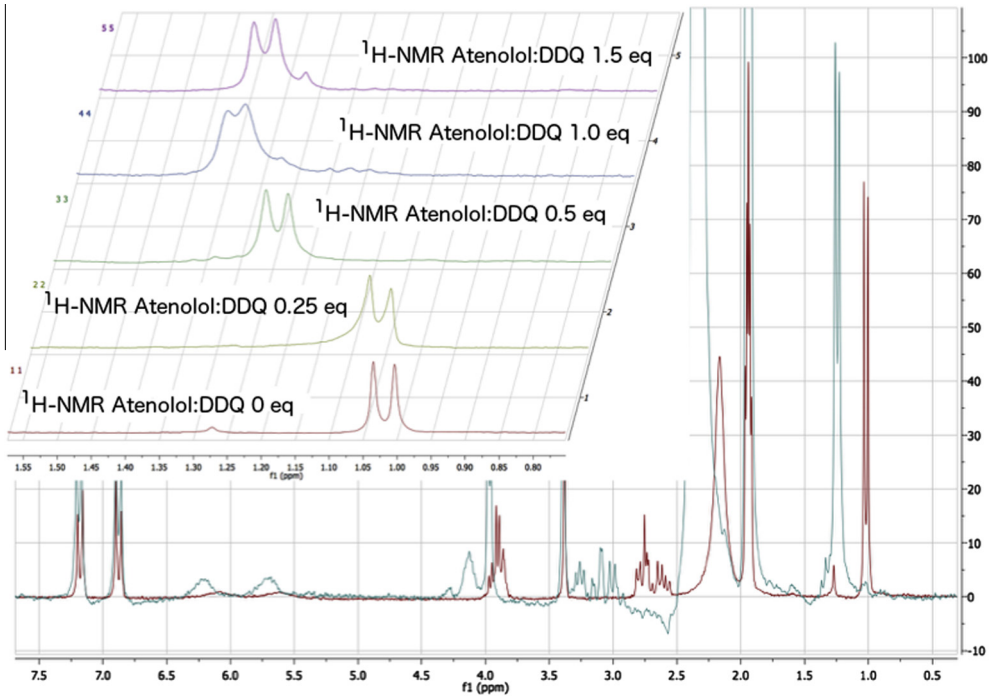

Fig. 9. ^{1}H NMR spectra of the drug in acetonitrile-d_3, before and after the addition of 0.5 equivalents of DDQ: atenolol 10.0 mmol L^{-1} (red), atenolol 10.0 mmol L^{-1} and DDQ 5.0 mmol L^{-1} (blue); nested graph: ^{1}H NMR CH_3-region shift observed during titration. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In both drugs the complex formation appears as a continuous shift of the proton signals adjacent to the nitrogen donor (Figs. 8 and 9): ^{1}H NMR of procaine in CD_3CN ∂ CH_3 3H(t) 1.03 ppm, 1.33 ppm before and after equimolar addition of DDQ; ^{1}H NMR of atenolol in CD_3CN ∂ CH_3 3H(d) 1.02 ppm, 1.35 ppm before and after equimolar addition of DDQ. Similarly, ^{1}H NMR of procaine in CD_3CD_2OD ∂ CH_3 3H(t) 1.01 ppm, 1.31 ppm before and after equimolar addition of DDQ; ^{1}H NMR of atenolol in CD_3CD_2OD ∂ CH_3 3H(d) 1.01 ppm, 1.37 ppm before and after equimolar addition of DDQ (spectra not shown). The drift stopped after the addition of

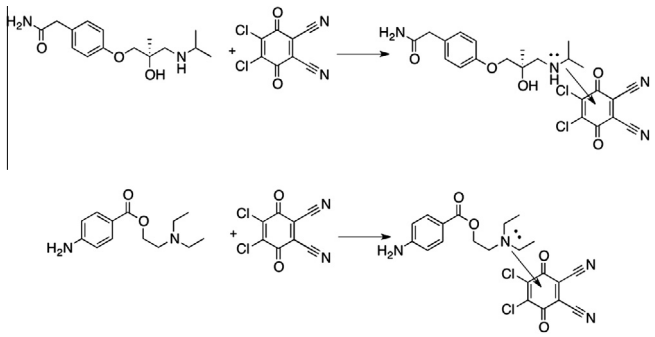

Fig. 10. Molecular structures of compounds and their correspondent charge transfer complexes.

an equimolar quantity of DDQ (nested graphs in Figs. 8 and 9). Note that, due to the relatively low sensitivity of the NMR technique, the relevant experiments were carried out at quite elevated drug concentration ($[drug]_0 = 10$ mmol L^{-1}) compared to the spectrophotometric runs. The reported behavior is in good agreement with the spectrophotometric data that were obtained on solutions with the most elevated values of $[drug]_0$ (2×10^{-4} or 5×10^{-4} mol L^{-1}, see Supplementary material). For both drugs, the NMR data support the participation of the aliphatic amine to complex formation and exclude the involvement of the aromatic amine present in the procaine molecule (see Fig. 10). In a similar case [5], the literature reports the formation of the D–A complex as a dative bond between the involved molecular regions, with the successive formation of a couple of radicals anion and cation.

The spectra recorded at low temperature in ethanol-d_6, and even at 183 K (data not shown), did not display any effect of separation between the signal of the unbound drug and that of the formed complex. The reason of this behavior could be either a very fast ligand exchange or a temperature-independent process.

Conclusion

The approach used here for the evaluation of the association constants allowed us to overcome the disadvantages of the classical linear-regression methods. Therefore, the present values of the stability constants should be more reliable than those previously evaluated, by using Benesi–Hildebrand plots, for the complex atenolol–DDQ in acetonitrile [21] and for atenolol–DDQ in 2-methyl-2-propanol [16] (although in the latter case a different solvent was used compared to the present work). The association constants obtained in this work are significantly higher than those reported in previous papers, but the values obtained here are in close agreement with the experimental trends of the spectrophotometric titrations. In contrast, such trends would not be consistent with significantly lower values of the association constants. Therefore, the application of traditional methods seems to provide underestimated values for these systems. Moreover the use of a non-linear global analysis, allowing the elaboration of the entire spectra and not only of a few absorbance values, has some additional advantages: it is possible to elaborate a data matrix, and one can calculate the spectrum of the complex and control its coherence with the experimental spectra profiles. The latter opportunity was useful in the present case, because the tendency of DDQ to be transformed into the radical $DDQ^{\cdot-}$ can affect the repeatability of the spectral measurements. Although we tried to minimize the $DDQ^{\cdot-}$ formation by maintaining the solutions under inert atmosphere and by executing batch titrations, the occurrence of the radical was found to disturb the measurements, especially on solutions containing excess DDQ. This problem was found to be minor when using ethanol as solvent (in agreement with the results shown in Fig. 2). Only the spectra that were coherent with each other were used for the association constant elaboration. The anomalous spectra could be easily found with the software application. Despite this possibility, the uncertainty on the values of the association constants remains high, as reported in Table 1.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.saa.2015.04.044.

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