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Persistent Radical Pairs Between *N*-Substituted Naphthalimide and Carbanion Exhibit pK$_a$-Dependent UV-vis Absorption

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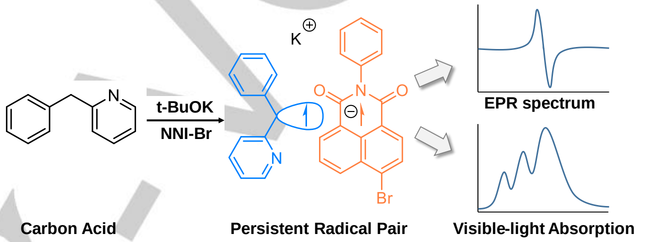
Abstract: A new strategy is devised for estimating and screening pK$_a$ values among different carbon acids under ambient conditions via the UV-vis absorption spectrum of persistent radical pairs (PRPs), which are generated from an *N*-substituted naphthalimide (NNI) derivative in the presence of various carbanions in organic solutions. The electron paramagnetic resonance (EPR) spectroscopy is used to examine the presence of radicals. Unexpectedly, it was discovered that the UV-vis spectrum of PRPs reveals a distinct linear relationship between the PRP absorption and the pK$_a$ value of a corresponding carbon acid, which is likely due to the energy difference among different RPRs. The finding may offer organic chemists an alternative reference to conduct carbanion-mediated reactions in various organic solutions.



Scheme 1. A reprehensive protocol to correlate pKa of a carbon acid with the electronic paramagnetic resonance (EPR) and the UV-vis absorption spectrum.

Knowing the pK$_a$ value of a deprotonatable carbon atom attached to a functional group (CH$_X$R$_Y$, X>0, a carbon acid, CA) is critical in organic chemistry since it foretells the reactivity and selectivity of reactions participated by the α-carbon. Over the past century, a plethora of experimental techniques, including potentiometry,[1,2] spectrometry,[3-5] conductometry,[6,7] electrophoresis,[8,9] nuclear magnetic resonance (NMR),[10,11] voltammetry,[12,13] high-performance liquid chromatography (HPLC),[14,15] fluorometry,[16-18] and more recently, theoretical calculations,[19,20] have been employed to measure or estimate the pK$_a$ values of organic compounds. Among these techniques, the UV-vis spectrometry method, similar to pH indicators, is particularly favored due to its wide accessibility, high throughput, and easy operation for non-experts.

In organic solvents, however, measuring the pK$_a$ values of CAs can be very challenging, mainly due to the complicated preparation in non-aqueous environments. Usually, a colored indicator acid (InA, e.g., fluorene anion, pK$_a$ = 22.6 in DMSO[21,22]) of known acidity is used, the pK$_a$ of which cannot differ by two units compared to that of the CA to be measured. For this specific reason, numerous InAs must be first selected and a guess must be made on the pK$_a$ value of the target CA. Furthermore, many of the InA anions readily oxidize in the presence of oxygen and quench with a trace amount of water, so that the whole experiment must be performed in a concealed environment. Consequently, a fast screening of pK$_a$ values, sufficient for most organic reactions, is not economical with this method and a more convenient one that can be operated in ambient conditions is highly desired. Here we propose a convenient method that can quickly estimate the pK$_a$ range of a CA in organic solvents with good accuracy in an open, ambient environment. Most importantly of all, the conditions are relatively mild which can dramatically speed up the screening process.

The application is based on our recent discovery that when an organic anion, such as a carbanion, comes in close contact with an electron-deficient aromatic compound, such as N-substituted naphthalimide (NNI), a persistent radical pair (PRP) forms.[23] The pair apparently lacks reactivity towards any reactions generally involving anions or radicals in the ambient condition. More interestingly, the PRP exhibits an absorption spectrum in the visible range. Based on the observation, we reason that the energy of the PRP absorption should be associated with the energy of carbanion if the aromatic acceptor is kept unchanged. As a result, it is possible that various CAs in basic condition exhibit different absorption patterns which are related to the energy difference of the PRPs formed. Since the electronic energy of the carbanion is also related to their pK$_a$ values,[24] we are tempted to explore whether a correlation could be established *between the pK$_a$ of the CA and the absorption spectrum of the PRP* (Scheme 1).

To explore the possibility, a series of CAs with published pKa[25-28] values are first selected with photos showing various colors in DMSO solutions in the presence of NNI-Br and excess t-BuOK (Figure 1a), resulting from the formation of PRPs. The elaborate mechanism for the observed coloration is recently described by us in a previous publication.[23] The protocol for duplicate experiments is described as follows: to DMSO solution (20 mL) of CAs (2.5×10^{-4} mol/L) was added excess t-BuOK, followed by the addition of NNI-Br (equivalent molar ratio vs. CA) into the system.

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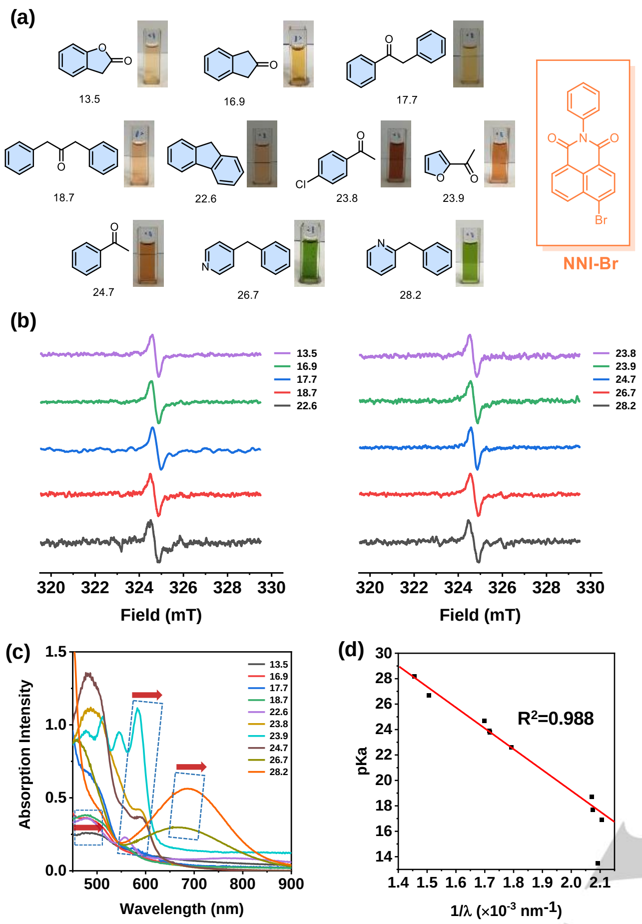

Figure 1 (a) Chemical structures of CAs and NNI-Br; the numbers below the structures is the corresponding pKa value in DMSO; inset: digital photos of CA and NNI-Br in DMSO under basic conditions. (b) Liquid-phase EPR spectra of DMSO solutions produced from CAs and NNI-Br in the presence of t-BuOK. (c) UV-vis absorption spectra of 1:1 mixture of CA and NNI-Br in the presence of excess t-BuOK; red arrow represents the shift tendency of the reddest absorption maximum. (d) Linear fitting Plot of pKa and energy in wavenumber.

The stock solutions of DMSO were then subject to EPR experiments in the open air at room temperature, which give rise to conspicuous EPR signals, confirming that all samples contain stable radical species (Figure 1b). The stability of these samples was continuously monitored after the EPR experiment and it was found that the solutions were still stable after 15 days.

As can be expected, the single-electron transfer process readily takes place between a deprotonated CA donor (or carbanion) and the NNI-Br acceptor and gives rise to a colored solution as has been recently verified in both intramolecular and intermolecular systems.[23] However, it is discovered for the first time here that the dramatic color difference among different donor CAs (in the presence of the same acceptor molecules) points to the fact that *the radical species are not contributed from the NNI-Br acceptor alone and are consistent with the radical pair model*. In addition, the ^{1}H-NMR spectra of the CA/NNI-Br mixtures under the basic condition lost nearly all of the intensity, suggesting that both organic components are paramagnetic in the presence of t-BuOK in solution (Figure S1).[23] The representative UV-vis absorption spectra of these radical pairs are shown in Figure 1c (Table S1). The result shows that more than one absorption peaks could be recorded for every different CA. We also discovered that certain CAs, such as a-cyanobenzyl derivatives, could not be used in such an experiment possibly due to active chemical reactions. For example, when 3-trifluoromethyl benzyl cyanide was tested, the color of the solution changed from green to orange over a few minutes (Figure S2), presumably due to an S_N2 reaction that replaces the -CN group with an -OR group. In this sense, the NNI-Br molecule could potentially be used to *monitor chemical transformations involving a carbanion intermediate*. While the spectra may be complex for direct interpretation, it was noted that the absorption maximum for the most red-shifted band appears to be correlated to the pK_a value of the CA used. A closer examination, shown in Figure 1d, by plotting the increasing energy of the absorption of the maximum of the reddest band (in nm^{-1}) against the descending pK_a value of the CA, reveals a roughly linear dependence within a specific range (~10 pK_a units). *The general trend is that the larger the pK_a value, the more red-shifted for the lowest absorption band*. The phenomenon is perhaps best interpreted using a simple electronic transition model, where the absorbed photon energy is related to the difference between the sp^3 orbital of the carbanion and the π^* orbital of the NNI-Br acceptor (assuming that the frontier orbitals of the PRP complex $[CA/NNI\text{-}Br]^-$ are from linear combinations of the two).

As for the observed linear relationship between the CA pK_a and the photon energy, we have a rather crude but plausible explanation. The chemical equations (1), (2), and (3) represent the ionization process of a CA in the presence of a deprotonating base in DMSO, the formation of carbanion radical pair, and the photo-absorption process of the radical pair, respectively.

$$D \leftrightharpoons D^- + H^+ \qquad (1)$$

$$D^- + A \leftrightharpoons D^{\bullet} \cdots A^{\bullet -} \qquad (2)$$

$$D^{\bullet} \cdots A^{\bullet -} + h\nu \leftrightharpoons [D^{\bullet} \cdots A^{\bullet -}]^* \qquad (3)$$

$$\Delta G_0 = -RTlnK_a = 5705.85pK_a \qquad (4)$$

Based on equation (1), the relationship between the standard Gibbs free energy change (ΔG_0) and pK_a can be deduced (equation 4). To elucidate the relation between the ground-state energy of D^- ($E(D^-)$)and that of $D^{\bullet}\cdots A^{\bullet-}$ ($E(D^{\bullet}\cdots A^{\bullet-})$), a simplified model is proposed based on the molecular orbital (MO) theory (Scheme S1). In order for the electron transfer to occur spontaneously, the energy of the carbanion HOMO must be higher than that of the NNI-Br LUMO, which is also consistent with calculations (Table S2). In a certain energy range, the ground-state energy of the radical pair is linearly proportional to that of the carbanion, according to the principle of linear orbital combination. Given that $E(HOMO_{D^-})$ is proportional to ΔG_0, the following relationship can also be established:

$$E(D^{\bullet} \cdots A^{\bullet -}) \sim E(HOMO_{D^-}) \sim \Delta G_0 \qquad (5)$$

Furthermore, based on the model (Scheme S1), the lower ground-state energy of the “bonded” state formed, the higher transition energy is needed assuming that the NNI-Br LUMO is less perturbed. It is rational to assume that the energy difference (E_{Abs}) between the ground-state $D^{\bullet}\cdots A^{\bullet-}$ HOMO energy and NNI-Br LUMO energy also exhibits an inverse linear relationship to $E(D^{\bullet}\cdots A^{\bullet})$ (equation 6).

$$E_{Abs} \sim -E(D^{\bullet} \cdots A^{\bullet -}) \qquad (6)$$

Based on equation (4), (5), and (6), we can deduce the final relationship:

$$E_{Abs} \sim -pK_a \qquad (7)$$

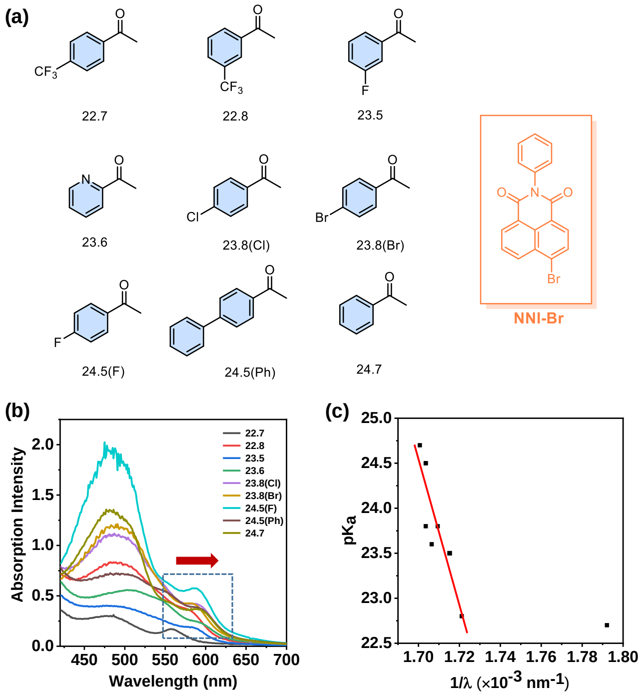

Figure 2 Chemical structures of CAs and NNI-Br; the numbers below the structures is the corresponding pKa values in DMSO; inset: digital photos of CA and NNI-Br in DMSO under basic conditions. (b) UV-vis absorption spectra of 1:1 mixture of CA and NNI-Br in the presence of excess t-BuOK; red arrow represents shift tendency of the reddest absorption maximum. (c) Linear fitting Plotting of pKa and energy in wavenumber.

According to equation (6), the linear relationship between the reddest absorption maximum and $\mathrm{p}K_\mathrm{a}$ can be explained. Nonetheless, more sophisticated and detailed analyses are required to quantitatively understand the experimental results. Incidentally, it has to be noted that there is a substantial deviation from linearity when the $\mathrm{p}K_\mathrm{a}$ value is below 16.9. Such anomaly is caused by the difficulty extracting spectral information when the absorption of CA/NNI-Br radical pair overlaps with that of the NNI-Br by itself (Figure S3), as also can be seen in the UV-vis absorption spectrum of the CA and t-BuOK in DMSO in the absence of NNI-Br (Figure S4). The results also suggest that the absorption beyond 450 nm does not solely derive from the CA carbanion, which further indicates that absorption in the visible range is contributed by the PRPs and not an individual part.

Next, to test whether such a method could exhibit any good resolution within very close $\mathrm{p}K_\mathrm{a}$ values, we then chose a series of nine well-documented aromatic α-ketones whose $\mathrm{p}K_\mathrm{a}$ values are already published in the literature (Figure 2a).[27] The ketones were subject to the same experimental condition as well: excess t-BuOK was added into a DMSO solution with the target α-aromatic ketone with a concentration of 2.5×10^{-4} mol/L and one equivalent of NNI-Br as the acceptor was added into the system. In this case, the UV-vis absorption spectra in DMSO are relatively similar to one another with one major absorption band in between 400-500 nm and a red-shifted shoulder peak beyond 550 nm (Figure 2b, Table S3), which is used as the energy value in cm^{-1} to plot against $\mathrm{p}K_\mathrm{a}$ of the aromatic ketone (Figure 2c). The correlation is also roughly linear except for an anomalous point for 4-trifluoromethyl acetophenone with a published $\mathrm{p}K_\mathrm{a}$ value of 22.7. At this point, it is not immediately obvious why this particular ketone deviates more significantly from the others. It is possible that the value is also within the error range due to very close absorption maxima between 3-trifluoromethyl acetophenone carbanion and the relevant radical pair (Figure S5).

In conclusion, the UV-Vis absorption spectrum of an NNI derivative in the presence of various carbanions in DMSO was found to be correlated with the $\mathrm{p}K_\mathrm{a}$ value of CA, which is proposed as a potentially useful method to help organic chemists estimate, compare or fast screen $\mathrm{p}K_\mathrm{a}$ values among different carbon acids under ambient conditions. This simple design method opens a new door for $\mathrm{p}K_\mathrm{a}$ measurement in organic solutions and serves as an example to systematically tune the energy of carbanion radicals.

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Keywords: carbanion • radical pairs • UV-vis Absorption • $\mathrm{p}K_\mathrm{a}$

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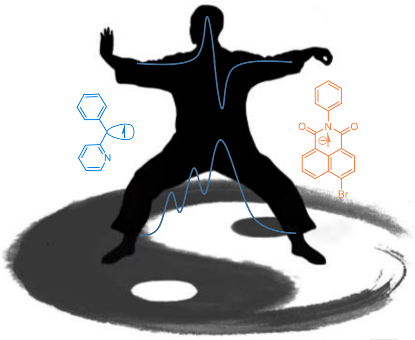

The UV absorption spectrum of carbanion radical pairs can serve as a tool to screen pKa values of various carbon acids.