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Thermal and photoinduced reduction of some benzyl bromides by an NAD(P)H model: the effect of electron withdrawing groups on mechanism and reactivity

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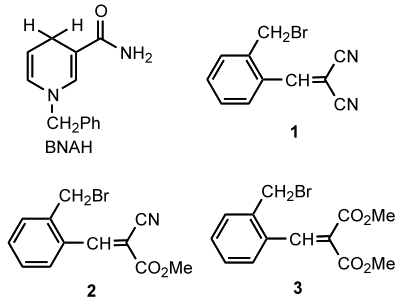
Abstract—A series of compounds, *o*-bromomethylbenzylidene-malononitrile (**1**), dimethyl *o*-bromomethyl-benzylidenemalonate (**2**) and methyl α-cyano-*o*-bromomethylcinnamate (**3**) were reduced in the dark and under irradiation by an NAD(P)H model, 1-benzyl-1,4-dihydronicotinamide (BNAH). Two different mechanisms were found, i.e. one-step hydride transfer (polar pathway) and multi-step sequence initiated by single electron transfer (SET pathway). The effect of electron-withdrawing groups on the reactivity of the substrates were discussed in terms of Hammett substituent constants, ^{13}C NMR chemical shift values and cyclic voltammetric redox potentials, and their correlations.

As an important redox coenzyme in biological reactions, NAD(P)H has attracted much interest both in its function and mechanism. Although it is believed that in real biological systems electron transfer from NAD(P)H to substrates (aldehyde, ketone, imine or ester) is rarely seen, NAD(P)H and its models have been reacted with various unsaturated substrates and the reaction mechanism has been extensively studied by chemists.[1] An issue of controversy is whether the formal hydride transfer from NAD(P)H to the substrates occurs in one-step hydride transfer (polar pathway) or in a multi-step sequence involving electron transfer as the initial step (SET pathway).[2] Numerous substrates with different features have been used as probes to react with the NAD(P)H model, 1-benzyl-1,4-dihydronicotinamide (BNAH) to distinguish the mechanisms and reveal the structure–reactivity relationship.[3]



Scheme 1.

Our group has used some probes with carbon–carbon double bonds activated by electron withdrawing groups (EWGs) and both pathways were found operating in the mechanism, depending on the substrates, NAD(P)H models, and reaction conditions.[4] We have also studied EWG activated benzyl bromides (by one or two nitro groups in the phenyl ring) and found SET pathway dominating the reaction.[5] Either thermal (dark) or photoinduced conditions were used in these studies.

In order to gain more insight into the effect of EWGs on the substrate reactivity and reaction mechanism we have designed a series of substrates combining both activated double bond and benzylic bromide in the same molecule. They are *o*-bromomethylbenzylidene-malononitrile (**1**), dimethyl *o*-bromomethylbenzylidene-malonate (**2**) and methyl α-cyano-*o*-bromomethyl-cinnamate (**3**), prepared by NBS bromination of corresponding toluenes, which were prepared from *o*-methyl-benzaldehyde and corresponding C–H acids by Knoevenagel condensation. This design would make it possible to investigate several aspects: first, the selectivity of BNAH toward the two functional groups, i.e.

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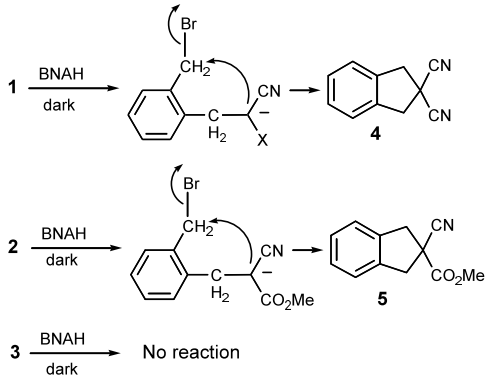
activated double bond and benzylic bromide; second, the reaction product would indicate the reaction mechanism, i.e. double bond reduction–intramolecular cyclization would indicate polar pathway while debromination would indicate SET pathway;[5,6] third, the combination patterns of EWGs (2CN, CN–CO_2Me and CO_2Me) would serve as a good model to study the effect of EWGs on reactivity. With this in mind, We studied their reactions with BNAH under both thermal and photoinduced conditions (Scheme 1).

Compound **1**, **2**, or **3** (0.5 mmol) and BNAH (0.6 mmol) were reacted in 15 mL of acetonitrile at room temperature in the dark under argon. After 4 h the reaction was quenched and worked up. The reaction of **1** and **2** gave cyclized compound **4** and **5** in yields of 90 and 80%, respectively.[7] Reaction of **3** did not give any product at all. Even heating at 60°C for 4 h or stirring at room temperature for a week did not bring about any reaction. It appears likely that the BNAH reaction takes place via hydride transfer from BNAH to **1** or **2** (polar pathway) and the resulting carbanion undergoes intramolecular nucleophilic substitution (S_Ni) to give the cyclic product (Scheme 2).

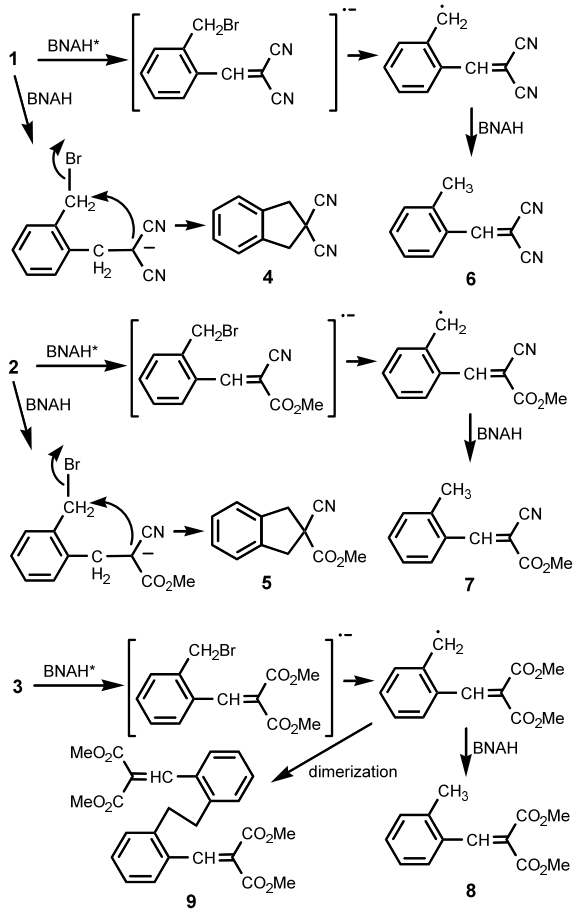
Compound **1**, **2**, or **3** (0.5 mmol) and BNAH (0.6 mmol) were also reacted in 15 mL of acetonitrile at room temperature upon irradiation with a high-pressure mercury lamp under argon. A piece of Pyrex glass was placed between the reaction vessel and the lamp to filter off UV light and give light of λ>320 nm. After 6 h the reaction was worked up and products were separated and identified. For **1**, the major product was still **4** (80%), with small amount of debrominated product **6** (<10%). In the case of **2**, however, cyclic product **5** and debrominated product **7** were obtained in comparable yields of 40 and 30%, respectively. The reaction of **3** gave debrominated product **8** and dimer **9** in yields of 30 and 40%, respectively. In the photoinduced reaction, excited BNAH*[8] ($\lambda_{max}=354$ nm) transferred an electron to the substrate, the resulting radical anion liberated the bromide anion to form a benzyl radical, the benzyl radical then abstracted a hydrogen from BNAH to give debrominated product[5,6] and the BNA· radical transferred an electron to another molecule of substrate to continue the chain reaction. In the case of **3** the benzyl radical also underwent bimolecular coupling to give the dimer **9**, strongly supporting this mechanism (Scheme 3).

From the results described above it is clearly seen that the dark reactions took 'polar' pathway and the photoinduced reactions took the 'SET' pathway. This actually reflects the selectivity of the two functional groups, i.e. activated double bond and benzylic bromide. Also the results showed the successful distinguishing of the reaction pathways as the design. Compound **1** favors the polar pathway even under photoinduced conditions, indicating its reaction rate with ground state BNAH is much faster than that with excited BNAH*. Compound **3** however, is inert to ground state BNAH and readily reacts with excited BNAH*. Compound **2** lies between these two cases. It undergoes BNAH reaction in the dark. Under photoinduced conditions, it competes with ground state BNAH and excited BNAH* in two different pathways at comparable rates. In conclusion the three compounds have the reactivity sequence as **1**>**2**>**3**. These results are apparently due to the different combinations of EWGs the compounds carry (2CN, CN–CO_2Me and 2CO_2Me for **1**, **2** and **3** respectively). The fact that the other portion of these substrates is exactly the same makes it possible to 'separately' study this 'net' EWG effect.

In linear free energy correlations the substituent constants (σ_p) represent the electron withdrawing or donat-



Scheme 2. Thermal BNAH reductions of **1**, **2** and **3**.



Scheme 3. Photoinduced BNAH reductions of **1**, **2** and **3**.

ing properties of various substituents.[9] The σ_p values are 0.70 and 0.44 for CN and CO_2Me, respectively. Since the effect of the two EWGs in the same molecule work in the same direction (actually the effect would be a little different for the two EWGs because one is *cis*- to phenyl group while the other is *trans*-) their combinative electron-withdrawing abilities could be approximately estimated as 2CN (1.40)>CN–CO_2Me (1.14)>2CO_2Me (0.88), which is consistent with the reactivity sequence of them.

The ^{13}C NMR chemical shift values of the electro-positive β-ethylenic carbons of the substrates are a good measure of the electron deficiency nature of them caused by the EWGs.[10] The determined values (δ_C) are 156.98, 151.95, and 140.61 ppm for **1**, **2** and **3**, respectively, holding the sequence 2CN>CN–CO_2Me> 2CO_2Me, which again is in good accordance with the reactivity sequence.

In order to obtain insight into the EWG effect on the relative redox reactivity of **1**, **2** and **3** their cyclic voltammograms were measured on a CV-27 Voltamograph using Ag/AgCl electrode as reference with tetrabutylammonium perchlorate as supporting electrolyte at a scan rate of 250 mV/s. The reductive potentials (E_p) of **1**, **2** and **3** are −0.40, −0.44 and −0.48 V, respectively, again in the sequence of 2CN>CN–CO_2Me>2CO_2Me, which parallels the reactivity sequence.

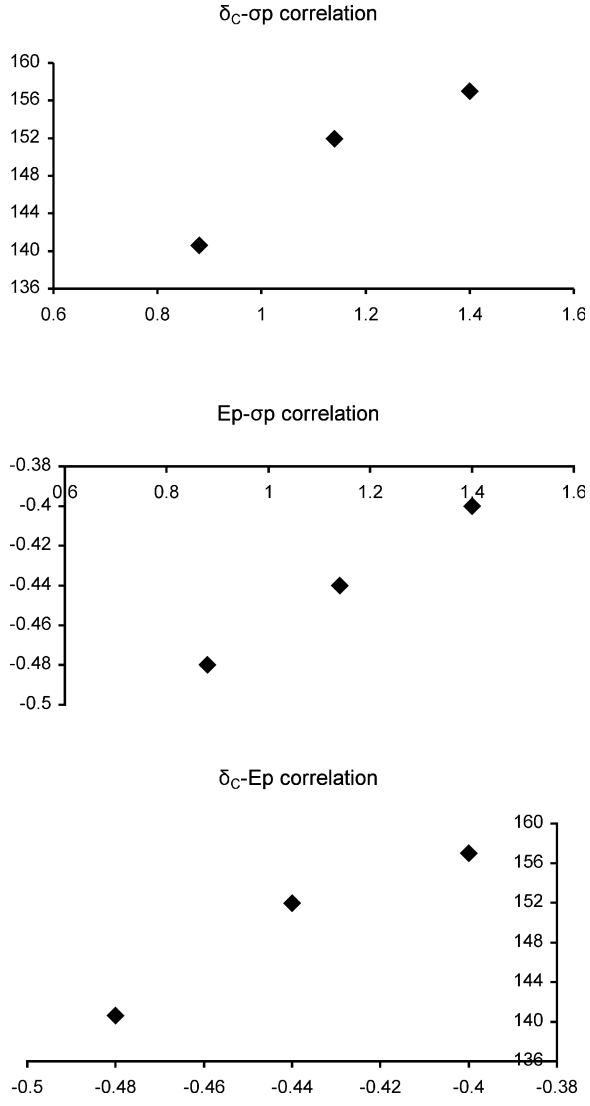


Figure 1.

The three sets of data, δ_C, σ_p and E_p were correlated by plotting them in Excel, giving curves close to straight lines (Fig. 1).

There have been some reports on the correlations of UV, IR, NMR, kinetic data, redox potential, etc., with Hammett constants to reveal the relative intrinsic reactivity of related compounds.[11] However, most of them had the substituents in the aromatic ring (or on the alkyl groups in the alkylnicotinamide models[11b]). The present study extends the substituents further to outside of the phenyl ring along conjugate system and it was proven successful. This correlation method will find more applications in the similar systems and be of value in better understanding and controlling of chemical reactivity.

Acknowledgements

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5. Presented at *Gomberg 2000: a century of organic free radical chemistry* by the International Society of Organic free radicals, University of Michigan, Ann Arbor June 25–29, 2000. Mono- and dinitrobenzyl bromides were reduced by BNAH upon irradiation and in the dark, respectively. Spin-trapping and cyclic voltammetry results support SET mechanism. Mononitrobenzyl bromides are inert in the dark.
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7. Selected physical and spectroscopic data: **4**: white solid, mp 130–131°C. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm):

3.70 (s, 4H), 7.20 (m, 4H). EI-MS m/z: 168 (100), 141 (91), 114 (7). Anal. calcd for $C_{11}H_8N_2$: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.60; H, 4.80; N, 16.61. **9**: white solid, mp 85–86°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.95 (s, 4H), 3.71 (s, 6H), 3.86 (s, 6H), 7.26 (m, 8H), 7.99 (s, 2H). EI-MS m/z: 466 (0.1), 434 (1), 311 (9), 274 (16), 255 (9), 233 (11), 143 (35), 115 (98), 59 (100). Anal. calcd for $C_{26}H_{26}NO_8$: C, 66.94; H, 5.62. Found: C, 67.02, H, 5.68.

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