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Synthetic and Theoretical Studies on the Reduction of Electron Withdrawing Group Conjugated Olefins Using the Hantzsch 1,4-Dihydropyridine Ester

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The Hantzsch 1,4-dihydropyridine ester (**1**) has been observed to be a useful selective reducing agent for the reduction of electron-withdrawing conjugated double bonds. The rate of this reaction was observed to be dependent upon the nature of the conjugated substituents and, consequently, the electronic nature of the unsaturated double bond. Theoretical calculations confirmed the importance of the HOMO−LUMO gap for this reaction and implicated a hydride transfer, agreeing with the experimentally observed reaction rate order. The calculations also revealed the importance of a boatlike structure of the 1,4-dihydropyridine nucleus as well as a trans arrangement of the ester groups to facilitate the hydride transfer.

Introduction

The natural product enzyme cofactors NAD(P) and NAD(P)H[1−6] have been a stimulus for the investigation of the use of the Hantzsch ester (**1**) and other 1,4-dihydropyridine derivatives, including 1-benzyl-1,4-dihydronicotinamide (BNAH) and 10-methyl-9,10-dihydroacridine ($AcrH_2$), as attractive biomimetic reducing agents for application in synthetic and physical organic chemistry.[6−8] These esters are known to reduce ketones[9−13] and aldehydes[14−16] to the respective alcohols in the presence of Lewis acids, and some studies have shown promise for application in asymmetric reductions[17−23] as well as in reductive aminations[24] and the photoinduced reduction of α,β-epoxyketones.[25] In addition to the reduction of carbonyl compounds, Braude, Hannah, and Linstead first showed that **1** could be employed for the reduction of certain α,β-unsaturated compounds.[26−28] Subsequent studies have further delineated the applicability of Hantzsch esters as hydrogen equivalents in olefin reduction reactions.[29−35]

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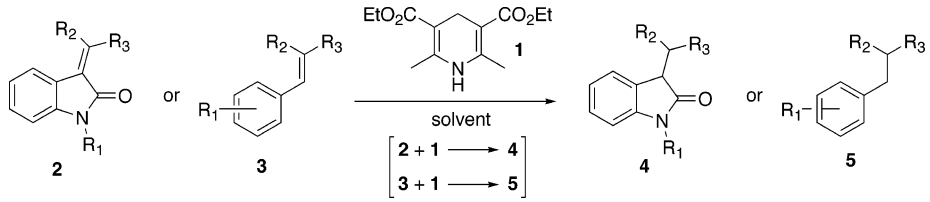
SCHEME 1



There has been considerable interest in the oxidation mechanism of **1** and analogues, and this interest stems from the biological role of NAD(P)H and the fact that these dihydropyridine derivatives are potent drugs for the treatment of hypertension.[36−39] A number of mechanisms have been proposed based upon various experimental findings. There is considerable evidence showing that NADH and its model compounds may reduce their substrates by a one-step hydride transfer or by a multistep electron-transfer-initiated hydride transfer, either as an electron−proton−electron or electron−hydrogen atom (e^-−H^+−e^- or e^-−$H^•$). Experimental studies involving strong oxidants revealed an e^-−H^+−e^- mechanism.[40,41] Nevertheless, evidence supporting a one-step hydride transfer was also reported when aldehydes and ketones were employed as substrates, as in the majority of bioreductions.[42,43]

The Hantzsch ester (**1**) and analogues have been employed as NADH models but not as frequently as BNAH or $AcrH_2$.[44−48] This is probably due to there being an additional mechanistic complexity regarding which of the two different hydrogen atoms (from the 1- or 4-positions) is first transferred in the reduction process. A number of isotope-labeling studies have pointed to initial dehydrogenation taking place at the 4-position.[30,44−46,49,50] However, there is also compelling evidence supporting the initial loss of hydrogen from the 1-nitrogen in certain oxidations of derivatives of **1**.[51,52]

TABLE 1. Identification of Substrate and Product Structures

compound	R_1	R_2	R_3
2a → **4a**	H	CO_2Et	CO_2Et
2b → **4b**	H	CN	CN
2c → **4c**	Me	CN	CN
2d → **4d**	H	CN	CO_2Me
2e → **4e**	H	CN	CO_2Et
2f → **4f**	H	CN	CO_2allyl
2g	H	CO_2Et	*N*-piperidinyl
3a → **5a**	H	CN	CN
3b → **5b**	H	CN	CO_2Et
3c	H	CO_2Et	CO_2Et
3d → **5d**	3-MeO-4-HO	CN	CN
3e → **5e**	3-MeO-4-HO	CN	CO_2Et

Recently, Zhu, Cheng, and co-workers described their findings with respect to the oxidation mechanism of **1** by ethyl α-cyanocinnamates and benzylidenemalononitriles where they concluded that the reduction of the α,*β*-unsaturated substrates was initiated by hydride transfer from C-4 of **1**.[46] A hydride transfer was further substantiated by obtaining cyclopropane products from appropriately substituted benzylidenemalononitriles[32,33] and other cyclic products from appropriate precursors.[48] Independently of these workers, we found that the Hantzsch ester was capable of reducing ethyl α-cyanocinnamates and benzylidenemalononitriles as well as isatylidenemalonyl derivatives (Scheme 1). Our experimental investigations have found **1** to be a highly selective reducing agent for the desired transformation, giving excellent yields.[53] We have observed that the velocity for the reaction between **1** and the methyleneoxindole derivatives in benzene/ethanol varies with the nature of the substituents R_2 and R_3, revealing the reactivity order CN/CN > CN/CO_2Et (diastereomeric mixture) > CO_2Et/CO_2Et, and that when R_2 and R_3 are CO_2Et and *N*-piperidinyl, no reaction with **1** was detected (Scheme 1, Tables 1 and 2). Thus, in this work, we have probed the mechanism for the reaction between **1** and the methyleneoxindole derivatives in a theoretical study of the reactivity order obtained experimentally.

Results and Discussion

Synthetic Application of 1 for the Reduction of α,*β*-Unsaturated Compounds. The Hantzsch ester (**1**)

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TABLE 2. Reduction of Isatylidene and Benzylidene Compounds with the Hantzsch Ester (1)

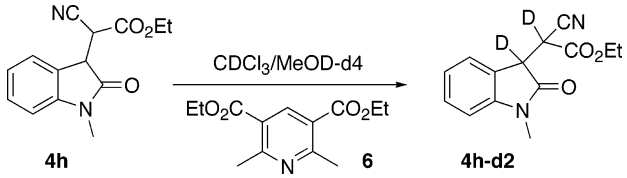
entry	substrate	product	reaction conditions	yield (%)[a]
1	**2a**	**4a**	benzene/EtOH (1:1) Δ 3hr	92
2	**2b**	**4b**	EtOH, r.t., 15 min	80
3	**2b**	**4b**	benzene/AIBN, Δ N_2	80
4	**2c**	**4c**	EtOH, r.t., 15 min	70
5	**2d**[b]	**4d**[c]	benzene/EtOH 1 h (1:1), Δ	89
6	**2e**[b]	**4e**[c]	benzene/EtOH (1:1) r.t. 3hrs	85
7	**2e**[b]	**4e**[c]	benzene/EtOH (1:1) Δ 1hr	87
8	**2f**	**4f**[c]	benzene/EtOH (1:1) r.t. 1.5 hrs	75
9	**2g**[b]		benzene/EtOH (1:1), Δ	0
10	**3a**	**5a**	benzene	84
11	**3b**	**5b**	EtOH	79
12	**3c**		benzene/EtOH (1:1)	0
13	**3d**	**5d**	EtOH	72
14	**3e**	**5e**	EtOH	75

[a] Isolated purified yield. [b] Mixture of geometric isomers. [c] Product is a 1:1 mixture of two diastereoisomers.

was employed in stoichiometric quantities for the homogeneous reduction of isatylidenemalonyl derivatives (**2a**−**g**), ethyl α-cyanocinnamates (**3b,e**), and benzylidenemalononitriles (**3a,d**) in ethanol or in benzene-ethanol (Scheme 1, Table 1). Table 2 summarizes our findings. Analysis of Table 2 readily reveals a reactivity order, which is dependent upon the nature of the substituents R_2 and R_3. Barbry and co-workers recently revealed a dependence of the electronic nature of the substituted olefin in reductions with **1** in the presence of silica under microwave irradiation as well as revealing a dependence upon the structure of analogues of **1**.[35] The malonylnitrile derivatives, **2b**,**c** (Table 2, entries 2−4), are more readily reduced, reaction occurring at room temperature or at reflux in a few minutes, than the α-cyanoacetyl esters (**2d**−**f**) which require several hours at room temperature or 1 h under reflux (Table 2, entries 5−8). The α-cyanoacetyl esters are, in turn, more reactive than the malonyl ester derivative, **2a** (Table 2, entry 1). Further, the introduction of a basic nitrogen conjugated with the α,*β*-unsaturated system (**2g**) resulted in no observed reaction even after refluxing for several hours (Table 2, entry 9). In contrast to the reaction of **2a**, compound **3c** was found to be unreactive toward **1** (Table 2, entries 1 and 12). As observed for compounds **2**, although it was necessary to perform all reactions under reflux, compounds **3** also revealed similar differences in reactivity (reactivity order, Table 2, entries 10, 13 > 11, 14 > 12). The differences observed in the reactivity indicate that the reactions are dependent upon the electronic nature of the conjugated system or, more precisely, the HOMO−LUMO gap of the reactants.

No evidence was found for the participation of a radical reduction mechanism. The reactions were performed under an air atmosphere with the exception of Table 2 entry 3 where the inclusion of AIBN and the use of an inert atmosphere made no difference to the observed reactivity or yield. The reaction of compound **2f** (Table 2, entry 8) with **1** was also used to probe for the possibility of a radical reaction though no evidence of products arising from a radical cyclization reaction was observed.[54] In a similar manner, the phenolic substrates **3d** and **3e**, which could be expected to have antioxidant

SCHEME 2



properties, also gave excellent isolated and purified yields of reduced products (Table 2, entries 13 and 14).

The structures of the oxindole products **4a**−**d** were confirmed by NMR, where the vicinal saturated methine groups gave rise to two doublets in the ^{1}H NMR (4−5 ppm) and corresponding signals for the respective carbon atoms in the proton decoupled ^{13}C PENDANT NMR spectra. Mass spectra revealed a molecular ion consistent with the incorporation of two hydrogen atoms in comparison with the respective spectra of the substrates. In addition, the products proved to be identical to the products obtained by reduction of **2** with zinc in ethyl acetate/aqueous HCl or by catalytic hydrogenation with Pd/C.

Compounds **2** (**d, e, g**) were obtained from the respective condensation reactions as mixtures of geometrical isomers. Compound **2f** was obtained as a single isomer. ^{1}H NMR was used to determine the ratio of the isomers of **2**, before reduction with **1**: **2d** (2:1), **2e** (6:1). Compounds **4** (**d**, **e**, **f**) were obtained as 1:1 mixtures of two diastereoisomeric products irrespective of the initial ratio of the substrate isomers. The obtention of 1:1 mixtures of diastereoisomeric products does not allow differentiation between the possibility of a concerted (or pseudoconcerted) transfer of hydrogen from **1** to the substrates, which would have resulted in the preservation of the initial diastereoisomeric ratios, or an initial hydride transfer followed by subsequent protonation. This is the result of the Hantzsch pyridine (**6**) being sufficiently basic so as to catalyze the epimerization of the chiral centers.[55−58] This was confirmed when **4h** was treated with **6** in $CDCl_3$ containing a couple of drops of MeOD-d_4 resulting in the product **4h**-d_2 (Scheme 2). When **4h** was solubilized in MeOD-d_4, deuterium exchange occurred even in the absence of **6**. The ^{13}C NMR revealed the disappearance of the ^{1}H decoupled signals corresponding to the methines at 37.9 (diastereoisomer, 39.2) and 44.88 ppm (44.94) and the appearance of multiplets due to coupling of the ^{13}C nuclei with the ^{2}D nuclei.

The reduction of compounds **3** by **1** contrasts the results of Shinkai, where the reduction of similar benzylidene derivatives with *N*-benzyldihydronicotinamide required the presence of $Mg(ClO_4)_2$ or acetic acid thus revealing the greater reactivity of **1** for hydrogen donation.[59]

Theoretical Studies of the Reduction of the Methyleneoxindole Derivatives by 1. Two QM/MM studies verified that the reductions of pyruvate to L-

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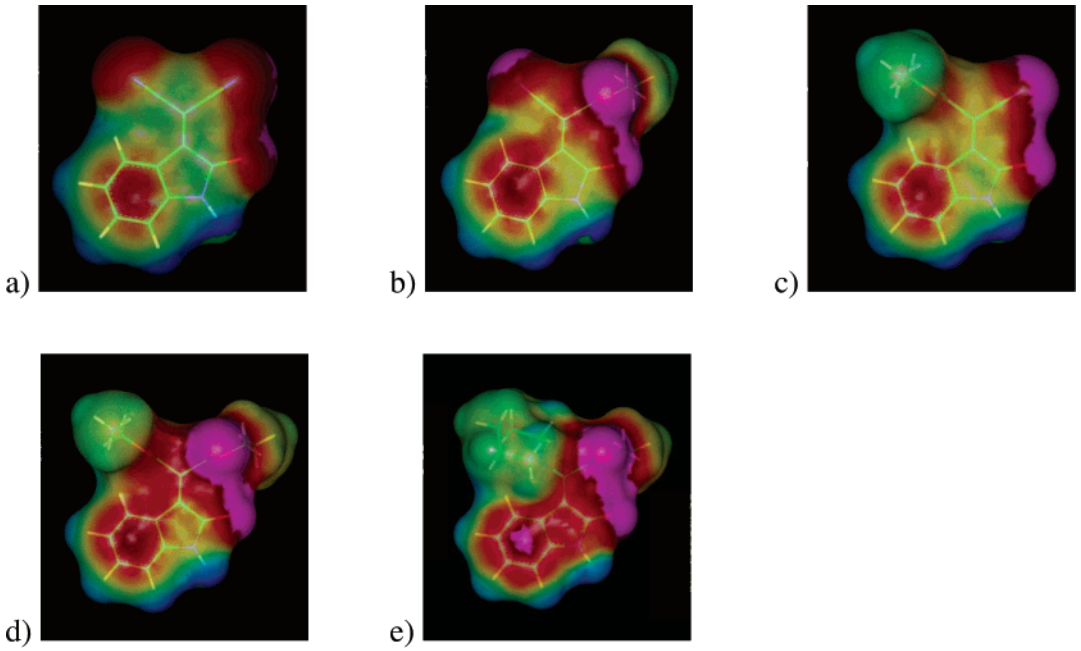

FIGURE 1. Molecular electrostatic potential maps plotted at the Connolly surface: (a) **2b** (R_2 = CN, R_3 = CN); (b) **2e** (R_2 = CN, R_3 = CO_2Et); (c) **2e′** (R_2 = CO_2Et, R_3 = CN); (d) **2a** (R_2 = CO_2Et, R_3 = CO_2Et); (e) **2g′** (R_2 = *N*-piperidinyl, R_3 = CO_2Et).

lactate in L-lactate dehydrogenase and oxaloacetate to malate in malate dehydrogenase occur by a sequential reaction of hydride transfer from NADH preceding a proton transfer from a His residue, and the rate-limiting step is the hydride transfer.[2,5] Kinetic and thermodynamic studies of the reduction of ethyl α-cyanocinnamates and benzylidenemalononitriles by **1** have shown positive ρ values of 1.78 and 1.67, respectively, demonstrating the electrophilic nature of the substrates and, consequently, that the hydrogen lost from **1** must be a hydride-like species.[46] In addition, replacement of **1** by **1**-4,4-d_2 and **1**-*N*-*d* in these reductions gave the observed kinetic isotope effects of 5.3−6.0 and 1.2−1.3, respectively.[46] Using a different substrate, (*Z*)-ethyl α-cyano-β-bromomethylcinnamate, Zhu and co-workers observed similar kinetic isotope effects.[45] These results suggest that direct hydride transfer from the C4-position is the rate-limiting step, followed by rapid proton transfer from the nitrogen.[44−46]

In a first step to probe the mechanism of the reaction between **1** and the methyleneoxindole derivatives, we analyzed the energies of the HOMO and the LUMO for each compound involved in the reaction (Table 3). The calculated energy gaps between the LUMO of the methyleneoxindole derivatives (**2a**, **b**, **e**, **e′**, and **g′**) and the HOMO of **1** are smaller than the energy gaps between the LUMO of **1** and the HOMO of the methyleneoxindole derivatives. This result suggests that a hydride transfer precedes a proton transfer from HEH, in agreement with the previously cited literature. Moreover, the energy gaps between the LUMO of **2a**, **b**, **e**, **e′**, and **g′** and the HOMO of **1** agree with the experimental reactivity order, indicating that the hydride transfer is the rate-limiting step.

To further support the hydride transfer as the rate-limiting step, we derived molecular electrostatic potential (MEP) maps plotted at the Connolly surface of each methyleneoxindole derivative (Figure 1).[60] Blue and red colors represent the most repulsive and attractive interactions with a positive probe charge, respectively. Figure 1 shows that while the most reactive compound (**2b**, R_2 = R_3 = CN) and the diasteromeric mixture (compounds **2e**, **e′**) have predominant green and yellow colors, respectively, at the exocyclic double bond, the least reactive of those substrates that react (**2a**, R_2 = R_3 = CO_2-Et) and the unreactive derivative (**2g′**) have a highly negative region (red color) at the exocyclic double bond. The color gradation suggests that if the methyleneoxindole derivatives are attacked by a hydride ion, compound **2b** would be the most reactive, followed by the diasteromeric mixture, compounds **2e** and **2e′**. This reactivity order agrees with the experimental order and, again, indicates that the hydride transfer precedes the proton transfer and is the rate-limiting step.

TABLE 3. HOMO and LUMO Energies of 1 and Disubstituted 3-Methyleneoxindoles and HOMO/LUMO Energy Gaps[a]

compound[b]	HOMO energy	LUMO energy	ΔE (LUMO − HOMO)[c]	ΔE (LUMO − HOMO)[d]
1	−8.460	−0.353		
2b	−9.281	−2.039	6.421	8.928
2e′	−9.175	−1.718	6.742	8.822
2e	−9.159	−1.688	6.772	8.806
2a	−9.059	−1.349	7.111	8.706
2g	−8.662	−0.936	7.524	8.309

[a] Values in eV. [b] **2b** (R_2 = CN, R_3 = CN), **2e** (R_2 = CN, R_3 = CO_2Et), **2e′** (R_2 = CO_2Et, R_3 = CN), **2a** (R_2 = CO_2Et, R_3 = CO_2Et), **2g′** (R_2 = *N*-piperidinyl, R_3 = CO_2Et). [c] LUMO of disubstituted 3-methyleneoxindoles and HOMO of 1. [d] HOMO of disubstituted 3-methyleneoxindoles and LUMO of 1.

To determine whether the hydride is transferred from the 4-position (H*a*) or the 1-position (H*b*), we analyzed the HOMO eigenvector of the hydride donor, **1**, and the charges derived from the MEP, Figure 2. Table 4 shows

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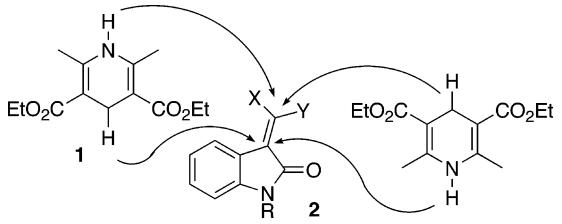

FIGURE 2. Schematic representation of the possible reactions of **1** with compounds **2**.

TABLE 4. HOMO Coefficients of 1 (H*a* and H*b*), LUMO Coefficients of the Disubstituted 3-Methyleneoxindoles (C2 and C3), and Charges Derived from the Molecular Electrostatic Potential

compound[a]	atom	coefficients	charges
1	H*a*	0.2325	0.06
	H*b*	−0.0001	0.25
2b	C3	0.5145	−0.18
	C2	0.4913	0.06
2e′	C3	0.5336	−0.28
	C2	0.4721	0.16
2e	C3	0.5387	−0.26
	C2	0.4697	0.15
2a	C3	0.5593	−0.31
	C2	0.4414	0.14
2g′	C3	0.5663	0.06
	C2	0.3974	−0.16

[a] **2b** (R_2 = CN, R_3 = CN), **2e** (R_2 = CN, R_3 = CO_2Et), **2e′** (R_2 = CO_2Et, R_3 = CN), **2a** (R_2 = CO_2Et, R_3 = CO_2Et), **2g′** (R_2 = *N*-piperidinyl, R_3 = CO_2Et).

that H*a* has a significant HOMO component, while H*b* has a negligible one. Moreover, H*a* has a less positive MEP-derived charge than H*b*. These results indicate that the disubstituted 3-methyleneoxindoles are reduced by a hydride ion from the 4-position of **1**. To determine which carbon atom (C2 or C3) of the exocyclic double bond is attacked by the hydride ion of **1**, we analyzed the LUMO eigenvector of the methyleneoxindole derivatives and, again, the charges derived from the MEP, Figure 2. The results show that, except for the unreactive derivative (compound **2g′**), it was not possible to determine precisely which carbon atom would be attacked by the hydride ion, since despite having a greater LUMO component than C2, C3 has a more negative MEP-derived charge for all the reactive compounds (Table 4).

To distinguish which carbon atom is attacked by the hydride ion and evaluate the influence of the substituents on the reactivity, we built three-dimensional models for the reactants before the hydride transfer to C2 and C3 and for the intermediates generated after the reaction. The reason for using intermediate structures instead of transition structures (TS) was due to nonconvergence in the calculations performed to obtain the TS. However, our theoretical results for the hydride transfer to both C2 and C3 indicated endothermic reactions for all derivatives. Thus, we can safely assume by using the Hammond postulate that the TS in each case is closer in energy, and in structure, to the respective intermediate than to the reactants. This supports the hydride transfer from the 4-position of **1** relative to the 1-position, as it generates an aromatic compound as an intermediate, the protonated Hantszch pyridine. As the hydride transfer from **1** is an endothermic reaction, we can expect that the TS for the reaction will also be stabilized by the conjugative effects observed in the respective intermediate.

The mechanism and TS features of hydride transfer mediated by NAD^+ and NADH have been extensively investigated using theoretical methods.[61−66] Several important conclusions from these previous calculations, that have implications in this present study, can be summarized as follows: (1) the 1,4-dihydronicotinamide ring is slightly puckered in a boatlike conformation, but the ring is quite flexible with small barriers to inversion;[62,66] (2) for hydride transfer from 1,4-dihydronicotinamide to protonated nicotinamide, there is a strong preference for a syn or stacking arrangement for the two pyridine rings in TSs.[61] The same arrangement was observed for other hydride-transfer TSs of molecules with extended unsaturation.[63,64] The syn preference can be attributed to the maximized overlap between the LUMOs of hydride acceptor and hydride donor; (3) the 3-amide group of 1,4-dihydronicotinamide activates the hydride transfer when it is in a trans conformation in transition structures.[61,65]

The three-dimensional models for the reactants and for the intermediates were constructed. These consisted of HEH, one of the disubstituted 3-methyleneoxindoles (**2a**, **b**, **e**, **e′**, or **g**), and three ethanol molecules. Besides simulating part of the solvent effects in the reaction, the ethanol molecules were included so as to avoid undesirable intermolecular hydrogen bonds between HEH and the substrates, which hindered an adequate geometry for the hydride transfer. Basically, two ethanol molecules are hydrogen bonded to the ester groups of the Hantzsch ester and one ethanol molecule is hydrogen bonded to the carbonyl of the amide group of the disubstituted 3-methyleneoxindoles. The complexes were constructed in such a manner so that **1** was always oriented in a syn arrangement with respect to the exocyclic double bond of the derivatives, for studies of hydride transfer to C2 or C3 (Figure 3). It can be noted that after the hydride transfer to one of the carbon atoms of the exocyclic double bond, the syn arrangement also facilitates the proton transfer from the 1-position of **1** to the other carbon in the second step of the reduction, without the need for major structural rearrangement. The energy of the complexes and intermediates, and consequently the relative rate constants, is highly dependent on the conformation and orientation of the ethanol molecules. Therefore, we tried to obtain energy-minimized structures for all reactants and intermediates with equivalent orientation and conformation for the solvent molecules regardless of the substituents. As in previous theoretical studies,[61,65] where it was found that the hydride transfer from 1,4-dihydronicotinamide was activated by a trans conformation of the 3-amide group, we also found in this study that the trans ester configuration was essential for hydride transfer (Figure 3). The trans ester conformation

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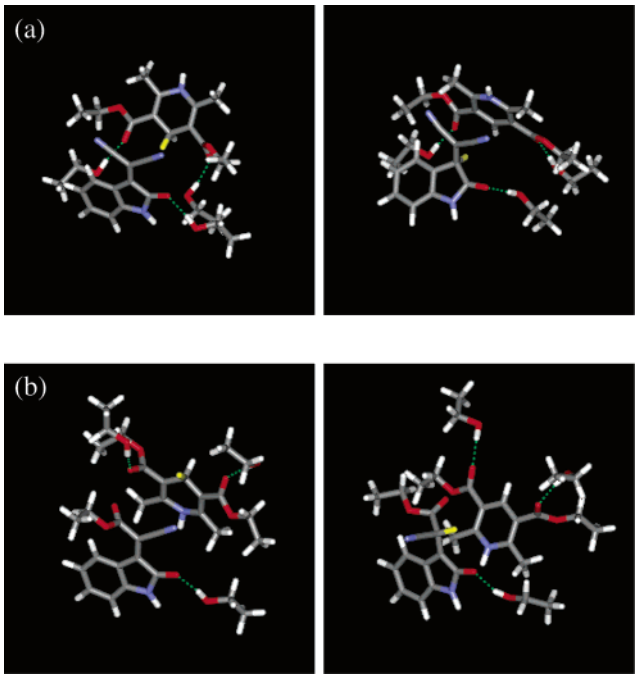

FIGURE 3. Selected PM3 energy-optimized three-dimensional models of reactants and intermediates: (a) hydride transfer from **1** to C2 of **2b** ($R_2 = R_3 = CN$); (b) hydride transfer from **1** to C3 of **2e′** ($R_2 = CO_2Et$, $R_3 = CN$). The hydrogen atom that is transferred to the exocyclic double bond is colored in yellow.

activated the hydride by orienting it in the proper configuration for attack at either C2 or C3, depending upon the model, of the exocyclic double bond.

The intermediates were obtained through the transfer of one of the H*a* hydrogens of **1** to the carbon atoms C2 and C3. Parts a and b of Figure 3 show the three-dimensional structures of the PM3 energy-optimized models of reactants and intermediates for the hydride transfer to C2 when $R_2 = R_3 = CN$ and for the hydride transfer to C3 when $R_2 = CO_2Et$ and $R_3 = CN$, respectively. The hydrogen atom that is transferred to the exocyclic double bond is colored yellow. Figure 3 reveals that the six-membered ring of **1** is slightly boatlike in the reactants, as was previously found in other theoretical studies.[61,63,66] The same observation was made for the other substituents.

As reliable theoretical entropies are unlikely to be obtainied by the PM3 method, we assumed that the entropic variation for the formation of the TS is similar for all substituents. Thus, the relative rate constant may be written as shown in eq 1 where k_a is the rate constant for the fastest reaction ($R_2 = R_3 = CN$), k_x is the rate constant for the reactions with the other substituents, R is the gas constant, T is the absolute temperature, $\Delta H_f°$int x is the standard enthalpy of formation of the intermediate x and ΔH_f °x is the standard enthalpy of formation of the reactants x.

$$\ln \frac{k_a}{k_x} \cong \frac{1}{RT}(\Delta H_f°\text{int } x - \Delta H_f°x - \Delta H_f°\text{int } a + \Delta H_f°a) \quad (1)$$

Tables 5 and 6 show the calculated values of the enthalpies of formation of each reactant and intermediate model for the hydride transfer to C2 and C3, respectively, and the relative rate constant with respect to the fastest reaction, calculated using eq 1. The theoretical reactivity order was found to be the same as the experimentally observed order for both mechanisms. Table 5 shows that the hydride transfer to C2 of compound **2b** is approximately 7×10^3 times more reactive than that of compound **2e′** ($R_2 = CO_2Et$, $R_3 = CN$) and approximately 15×10^3 times more reactive than that of compound **2e** ($R_2 = CN$, $R_3 = CO_2Et$). Thus, as shown experimentally, compound **2b** is more reactive than the diastereomeric mixture. Compound **2b** is also approximately 1×10^6 times more reactive than compound **2a** and 36×10^6 times more reactive than compound **2g′**, which is unreactive. This last result does not justify the nonreactivity of **2g′**, as it is only 36 times less reactive than **2a**. On the other hand, Table 6 shows that for the hydride transfer to C3, **2b** is roughly 60 and 45 times more reactive than compounds **2e′** and **2e** and 4×10^3 times more reactive than **2a**. Furthermore, compound **2b** is 3×10^{10} times more reactive than compound **2g′**, which does not react. The theoretical reactivity order for the hydride transfer to C3 is more in line with the experimental reactivity order, as it explains the nonreactivity of compound **2g′**. Moreover, considering only the enthalpy contribution involved in achieving the TS and, as we discussed before, that the structure and energy of the TS resemble that of the intermediate, the difference in enthalpy of formation between reactants and intermediates suggests that the hydride transfer to C3 is faster than the hydride transfer to C2 regardless of the substituents. This should be expected due to the strong stabilization by delocalizing excess electronic charge over the oxindol ring; the intermediate generated by the hydride transfer to C3 is more stable than the one

TABLE 5. Enthalpy of Formation of the Reactant and Intermediate Models for the Hydride Transfer to C2, and Relative Reactivity to the Fastest Reaction[a]

complex[c]	$\Delta H_f°$ (reactants)	$\Delta H_f°$ (intermediates)	$\Delta\Delta H_f°$	$\ln(ka/kx)$[b]
1 and **2b**	−263.32	−229.30	34.02	0
1 and **2e′**	−390.64	−351.38	39.26	8.85
1 and **2e**	−392.72	−353.01	39.71	9.61
1 and **2a**	−511.30	−469.07	42.23	13.86
1 and **2g′**	−437.89	−393.56	44.33	17.41

[a] Values in kcal/mol. [b] See equation in the text for details. [c] Complex between **1** and **2b** ($R_2 = CN$, $R_3 = CN$), **2e′** ($R_2 = CO_2Et$, $R_3 = CN$), **2e** ($R_2 = CN$, $R_3 = CO_2Et$), **2a** ($R_2 = CO_2Et$, $R_3 = CO_2Et$), **2g′** ($R_2 = N$-piperidinyl, $R_3 = CO_2Et$).

TABLE 6. Enthalpy of Formation of the Reactant and Intermediate Models for the Hydride Transfer to C3 and Relative Reactivity to the Fastest Reaction[a]

complex[c]	$\Delta H_f°$ (reactants)	$\Delta H_f°$ (intermediates)	$\Delta\Delta H_f°$	$\ln(ka/kx)$[b]
1 and **2b**	−261.48	−238.04	23.44	0
1 and **2e′**	−386.18	−360.28	25.90	4.15
1 and **2e**	−382.27	−356.57	25.70	3.82
1 and **2a**	−508.41	−480.07	28.34	8.27
1 and **2g′**	−435.49	−397.68	37.81	24.27

[a] Values in kcal/mol. [b] See equation in the text for details. [c] Complex between **1** and **2b** ($R_2 = CN$, $R_3 = CN$), **2e′** ($R_2 = CO_2Et$, $R_3 = CN$), **2e** ($R_2 = CN$, $R_3 = CO_2Et$), **2a** ($R_2 = CO_2Et$, $R_3 = CO_2Et$), **2g′** ($R_2 = N$-piperidinyl, $R_3 = CO_2Et$).

generated by the hydride transfer to C2. The same argument follows for the TS of both mechanisms due to the Hammond postulate. Finally, we may conclude that the experimental reactivity order is affected by electronic effects of the substituents in the exocyclic double bond, as characterized by the HOMO−LUMO gaps and the MEP maps. However, steric effects probably play a significant role in the hydride transfer as the reactivity of the disubstituted 3-methyleneoxindoles decreases with the size of the substituents.

Conclusions

The Hantzsch 1,4-dihydropyridine ester (**1**) has proved to be a versatile reducing agent for the reduction of ethyl α-cyanocinnamates, benzylidenemalononitriles, and malonylisatylidene derivatives. Experimentally, no evidence was found for reactions involving radical intermediates and the rates of reaction were observed to be dependent upon the nature of the conjugated substituents. The mechanism for oxidation of **1** by disubstituted 3-methyleneoxindoles (**2**) was clarified by semiempirical calculations employing the PM3 Hamiltonian. In agreement with other studies,[2,5,44−46,61] we verified through comparison of the experimental and theoretical reactivity orders that the reduction of the methyleneoxindole derivatives occurs via a hydride transfer from the C4-position of **1** to the C3 carbon atom of the exocyclic double bond, followed by a proton transfer from the protonated pyridine intermediate to C2. The calculated energy differences between HOMO (**1**) and LUMO (**2**) molecular orbitals were found to be consistent with the observed reaction rate order, which are in turn correlated with the nature of the substituents in compounds **2**.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using 300- and 200-MHz (^{1}H) spectrometers and are referenced to $CHCl_3$. Coupling constants are quoted in Hz. Assignments in ^{13}C spectra were based upon analysis of PENDANT spectra. Mass spectra were recorded by GC-MS or by direct insertion. IR spectra were recorded using either KBr or KCl disks. Melting points were recorded using a capillary melting point aparatus and are reported as uncorrected values.

The Hantzsch ester (**1**) was prepared using a literature procedure.[67]

Preparation of the Malonylisatinylidene Derivatives. The isatinylidene derivatives (**2a**−**c, e**) were prepared by condensing diethyl malonate, malononitrile, or ethyl cyanoacetate with isatin or *N*-methylisatin in ethanol.[68,69] Compound **2d** was obtained when isatin and ethylcyanoacetate were combined in MeOH in the presence of a catalytic quantity of piperidine. Compound **2f** was obtained in a manner similar to compound **2e** except that allyl alcohol was used as the solvent for condensing allyl cyanoacetate with isatin in the presence of a catalytic quantity of piperidine. Compound **2g** was obtained when isatin was treated with ethyl nitroacetate in the presence of an excess of piperidine in refluxing ethanol.

Preparation of the Benzylidene Derivatives. The benzylidene derivatives **3**(**a**, **b**, **d**, and **e**) were prepared by condensing stoichiometric quantities of benzaldehyde or vanilin with malononitrile or ethyl cyanoacetate and basic alumina (Merck cat. 1097).[70] Benzaldehyde was condensed with diethyl malonate in ethanol in the presence of a catalytic quantity of piperidine to give **3c**.

General Procedure for Reduction with the Hantzsch Ester. Unsaturated substrate (1.00 mmol) and Hantzsch ester (1.05 mmol) were combined in EtOH or EtOH/benzene (15 mL) and left stirring at room temperature or heated to reflux as indicated in Table 2.

The reaction products were isolated by evaporating the solvent, taking up the residue in ethyl acetate, and extracting with aqueous HCl (1.0 mol L^{-1}). The crude product after drying over Na_2SO_4, filtration, and evaporation of the solvent was filtered through a short column of silica eluting with hexane/ethyl acetate (1:1 v/v).

Computational Details. All calculations were performed with the PM3 Hamiltonian[71,72] within the MOPAC 93 program[73] on a Silicon Graphics O_2 R10000 workstation under an IRIX operational system. All structures were fully optimized in the gas phase using the keywords GNORM=0.1 and PRECISE. The InsightII program was employed as a graphic interface for the construction and visualization of molecular structures.

Characterization of the Reduced Products. Diethyl-2-(2-oxo-2,3-dihydro-1*H*-3-indolyl)malonate (4a). Mp: 128−130 °C. IR ($\nu \pm 4$ cm^{-1}): 3386, 2984, 1736, 1616, 1474, 749. ^{1}H NMR ($CDCl_3$): δ 1.01 [3H, t, J 7.0]; 1.26 [3H, t, J 7.0]; 4.07 [2H, m]; 4.07 [1H, d, J 3.6]; 4.23 [1H, d, J 3.6]; 6.89 [1H, d, J 7.5]; 4.26 [2H, m]; 6.99 [1H, td, J 7.5; J 0.9]; 7.21 [1H, td, J 7.5, J 0.9]; 7.37 [1H, d, J 7.5]; 8.99[NH, bs]. ^{13}C NMR: 13.8 [CH_3]; 14.1 [CH_3]; 45.4 [CH]; 52.4 [CH]; 61.9 [CH_2]; 62.1 [CH_2]; 110.0 [CH]; 122.6 [CH]; 125.3 [CH]; 126.4 [C]; 128.8 [CH]; 142.2 [C]; 167.2 [C=O ester]; 168.2 [C=O, ester]; 178.0 [C=O, amide]. Mass $C_{15}H_{17}NO_5$ (*m*/*z* [% abundance]): 291 [20]; 245 [15]; 218 [28]; 172 [100].

2-(2-Oxo-2,3-dihydro-1*H*-3-indolyl)malononitrile (4b). Mp: 189−200 °C. IR ($\nu \pm 4$ cm^{-1}): 3202, 2893, 2219, 1702, 1618, 1473, 754. ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 4.00 [1H, d, J 4.3]; 5.20 [1H, d, J 4.3]; 6.98 [1H, d, J 7.8]; 7.08 [1H, t, J 7.6]; 7.32 [1H, t, J 7.7]; 7.53 [1H, d, J 7.5]; 10.79 [1H, s]. ^{13}C NMR: 24.1 [CH]; 44.6 [CH]; 110.5 [CH]; 111.4 [CN]; 112.2 [CN]; 122.4 [CH]; 123.0 [C]; 124.5 [CH]; 129.9 [CH]; 143.1 [C]; 173.2 [C=O, amide]. Mass $C_{11}H_7N_3O$ (*m*/*z* [% abundance]): 197 [22], 132 [100].

2-(1-Methyl-2-oxo-2,3-dihydro-1*H*-3-indolyl)malononitrile (4c). Mp: 138−139 °C. IR ($\nu \pm 4$ cm^{-1}): 3065, 2865, 1694, 1613, 759. ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 3.28 [3H, s]; 3.96 [1H, d, J 3.7]; 4.57 [1H, d, J 3.7]; 6.96 [1H, d, J 7.5]; 7.22 [1H, t, J 7.5]; 7.47 [1H, t, J 7.5]; 7.66 [1H, d, J 7.5]. ^{13}C NMR: 24.7 [CH]; 27.0 [CH_3]; 45.1 [CH]; 109.5 [CH]; 109.7 [CN]; 111.7 [CN]; 121.6 [C]; 124.0 [CH]; 124.8 [CH]; 130.9 [CH]; 144.9 [C]; 171.0 [C=O, amide]. Mass $C_{12}H_9N_3O$ (*m*/*z* [% abundance]): 211 [18], 146 [100].

Methyl-2-cyano-2(2-oxo-2,3-dihydro-1*H*-3-indolyl)acetate (4d). (Diastereoisomeric mixture, ratio 1:1.) Mp: 128−129 °C. IR ($\nu \pm 4$ cm^{-1}): 3286, 3095, 3027, 2958, 2900, 2253, 1749, 1720, 753. ^{1}H NMR ($CDCl_3$): δ 3.66, 3.94 [2 × 3H, s]; 3.99, 4.15, 4.38, 4.45 [4 × 1H, d, J 3.8]; 6.92, 6.94 [2 × 1H, d, J 7.5]; 7.05, 7.06 [2 × 1H, t, J 7.5]; 7.19 [1H, d, 7.5]; 7.26 [2 × 1H, t, J 7.5]; 7.48 [1H, 1d, J 7.5]; 9.19 and 9.23 [2 × NH, bs]. ^{13}C NMR: 37.7, 38.8 [CH]; 45.3, 45.5 [CH]; 54.0, 54.3 [CH_3]; 110.7, 110.9 [CH]; 113.6, 115.3 [CN]; 123.1, 123.3 [CH]; 124.2 [CH]; 124.4 [C]; 124.8 [CH]; 129.7, 129.9 [CH]; 142.0, 142.1 [C]; 164.1, 165.3 [C=O, ester]; 175.9 [C=O, amide]. Mass $C_{12}H_{10}N_2O_3$ (*m*/*z* [% abundance]): 230 [20]; 171 [100]; 132 [30].

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Ethyl 2-Cyano-2-(2-oxo-2,3-dihydro-1*H*-3-indolyl)acetate (4e).[74] (Diastereoisomeric mixture, ratio 1:1.) Mp: 105−110 °C. IR ($\nu \pm 4$ cm^{-1}): 3280, 2986, 2905, 2256, 1724, 1621, 1472, 754. ^{1}H NMR ($CDCl_3$): δ 1.07, 1.38 [2 × 3H, t, J 7.1]; 3.98 [1H, d, J 2.5]; 4.14 and 4.35 [1H, d, J 3.8], 4.08 [2H, m]; 4.15 [1H, d, J 3.5]; 4.37 [3H, m]; 4.45 [1H, d, J 3.2]; 6.94 [2 × 1H, m]; 7.05 [2 × 1H, m]; 7.24 [3 × 1H, m]; 7.49 [1H, d, J 7.4]; 9.41, 9.44 [2 × NH, bs]. ^{13}C NMR: 13.6, 14.0 [CH_3]; 37.8, 38.9 [CH]; 45.4 [CH]; 63.4, 63.8 [CH_2]; 110.6, 110.8 [CH]; 113.7, 115.5 [CN]; 122.9, 123.1 [CH]; 124.1 [CH]; 124.2, 124.4 [C]; 124.7 [CH]; 129.6, 129.7 [CH]; 142.1, 142.2 [C]; 163.5, 164.7 [C═O ester]; 176.0 [C═O amide]. Mass $C_{13}H_{12}N_2O_3$ (*m*/*z* [% abundance]): 244 [32], 171 [100], 132 [30].

Allyl-2-cyano-2-(2-oxo-2,3-dihydro-1*H*-3-indolyl)acetate (4f). (Diastereoisomeric mixture, ratio 1:1.) Oil. IR ($\nu \pm 4$ cm^{-1}): 3265, 3093, 2896, 2255, 1747, 1721, 1621, 1472, 753, 733. ^{1}H NMR ($CDCl_3$):δ 3.99 [1H, d, J 3.1]; 4.18 [1H, d, J 3.7]; 4.37 [1H, d, J 3.8]; 4.44 [1H, d, J 3.2]; 4.53 [2H, d, J 5.8]; 4.83 [2H, d, J 5.8]; 5.16−5.47 [4H, m]; 5.65 [1H,m]; 5.97 [1H,m]; 6.92 [1H, d, J 8.3]; 6.95 [1H, d, J 8.6]; 7.06 [1H, t, J 7.5]; 7.08 [1H, t, J 7.3]; 7.22 [1H, d, J 7.4]; 7.29 [1H, t, J 7.8]; 7.30 [1H, t, J 7.7]; 7.51 [1H, d, J 7.5]; 8.76 [1H, bs]; 8.81 [1H, bs]. ^{13}C NMR: 37.9, 39.1 [CH]; 45.4, 45.5 [CH]; 67.8, 68.1 [CH_2]; 110.7, 110.8 [CH]; 113.5, 115.3 [CN]; 120.0, 120.5 [C], 123.3, 123.4 [CH], 124.2 [C], 124.4, 125.1 [CH], 129.8, 130.0 [CH], 130.4, 130.6 [CH], 141.9, 142.1 [C], 163.3, 164.6 [C═O], 175.6 [C═O]. Mass $C_{14}H_{12}N_2O_3$ (*m*/*z* [% abundance]): 256 [10], 171 [100], 132 [20].

2-Benzylmalononitrile (5a).[46] Mp: 80−81. IR ($\nu \pm 4$ cm^{-1}): 3067, 3030, 2914, 2258, 1496, 1454, 749, 701. ^{1}H NMR ($CDCl_3$):δ 3.28 [2H, d, J 6.9]; 3.91 [1H, d, J 6.9]; 7.32 [2H, m]; 7.42 [3H, m]. ^{13}C NMR: 25.2 [CH]; 36.8 [CH_2]; 112.4 [CN]; 129.0 [CH]; 129.3 [CH]; 129.5 [CH]; 133.1 [C]. Mass $C_{10}H_8N_2$ (*m*/*z* [% abundance]): 156 [15], 91 [100].

Ethyl 2-Cyano-3-phenylpropanoate (5b).[46] Oil. IR ($\nu \pm 4$ cm^{-1}): 3089, 3065, 3032, 2984, 2939, 2908, 2251, 1745, 1259. ^{1}H NMR ($CDCl_3$): δ 1.28 [3H, t, J 7.1]; 3.25 [2H, m]; 3.73 [1H, m]; 4.24 [2H, q, J 7.1]; 7.32 [5H, m]. ^{13}C NMR: 14.2 [CH_3]; 35.9 [CH_2], 39.8 [CH], 63.0 [CH_2], 116.3 [CN], 127.9 [CH], 129.0 [CH], 129.2 [CH], 135.4 [C], 141.13 [CH], 165.6 [C═O]. Mass $C_{12}H_{13}NO_2$ (*m*/*z* [% abundance]): 203 [15], 130 [20], 91 [100].

2-(4-Hydroxy-3-methoxybenzyl)malononitrile (5d). Mp: 86−87. IR ($\nu \pm 4$ cm^{-1}): 3450, 3057, 3000, 2948, 2259, 1626, 1576, 1447, 960, 757, 689. ^{1}H NMR ($CDCl_3$/DMSO-*d*6): δ 3.19 [2H, d J 6.8]; 3.88 [3H, s]; 4.41 [1H, t, J 6.8]; 4.77 [1H, bs]; 6.78 [1H, dd, J 8.0, 2.0], 6.85 [1H, d, J 2.0], 6.87 [1H, d, J 8.0]. ^{13}C NMR: 24.7 [CH]; 35.8 [CH_2]; 55.5 [CH_3]; 112.1 [CH]; 112.7 [CN]; 115.2 [CH]; 121.6 [CH]; 124.2 [C]; 146.2 [C]; 147.3 [C]. Mass $C_{11}H_{10}N_2O_2$ (*m*/*z* [% abundance]): 202 [15], 137 [100], 122 [10].

Ethyl-2-cyano-3-(4-hydroxy-3-methoxyhenyl)propanoate (5e). Oil. IR ($\nu \pm 4$ cm^{-1}): 3440, 2983, 2940, 2844, 2252, 1743, 1602, 1518, 1273, 1033. ^{1}H NMR ($CDCl_3$): δ 1.28 [3H, t, J 7.1]; 3.12 [1H, dd, J 13.9, 8.2]; 3.20 [1H, dd, J 13.9, 5.7]; 3.69 [1H, dd, J 8.2, 5.7]; 3.88 [3H, s]; 4.23 [2H, q, J 7.1]; 5.77 [1H, s]; 6.74 [1H, dd, 8.0, 1.8]; 6.79 [1H, d, J 1.8]; 6.86 [1H, d, J 8.0]. ^{13}C NMR: 14.1 [CH_3]; 35.8 [CH_2]; 40.2 [CH]; 56.1 [CH_3]; 63.1 [CH_2]; 109.0 [CH]; 111.8 [CH]; 114.8 [CH]; 116.5 [CN]; 122.1 [CH]; 127.3 [C]; 145.5 [C]; 146.8 [C]; 165.8 [C═O]. Mass $C_{13}H_{15}NO_4$ (*m*/*z* [% abundance]): 249 [12], 206 [14], 151 [26], 137 [100].

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Supporting Information Available: Tables of atomic coordinates for key calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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