

Isotope Effects in Photochemistry. 1. *o*-Nitrobenzyl Alcohol Derivatives

Aurélien Blanc and Christian G. Bochet*

Department of Chemistry, University of Fribourg, Chemin du Musée 9, CH-1700 Fribourg, Switzerland

Received January 17, 2004; E-mail: christian.bochet@unifr.ch

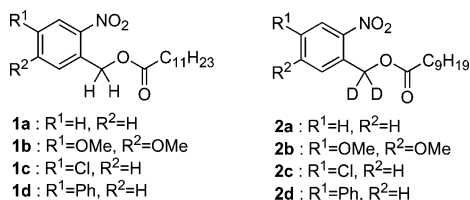
The kinetic isotope effect (KIE) has been of fundamental interest in organic chemistry for the elucidation of reaction mechanisms for several decades.¹ On the other hand, it is only recently that its potential as a synthetic tool has been exploited.² The C–D bond is slightly stronger than the C–H bond, mainly due to the difference in the zero-point energies; hence, a reaction in which a C–H(D) bond is broken in the rate-determining step will be affected by isotopic substitution. For example, it has been shown that the low-temperature deprotonation of *N*-Boc allylic amines by *n*-BuLi/sparteine is 86 times slower for the α -dideuterated derivative; similar results were found for various lithiation reactions.^{3–5} This observation led to the use of deuterium substitution to protect protons.⁶

We are interested in developing photolabile protecting groups sensitive to specific wavelengths; *o*-nitrobenzyl alcohol derivatives seemed to be promising candidates.^{7,8} They are well-known to react upon irradiation through benzylic hydrogen abstraction by the excited nitro group, followed by a subsequent cascade of reactions that result eventually in fragmentation (Scheme 1).⁹

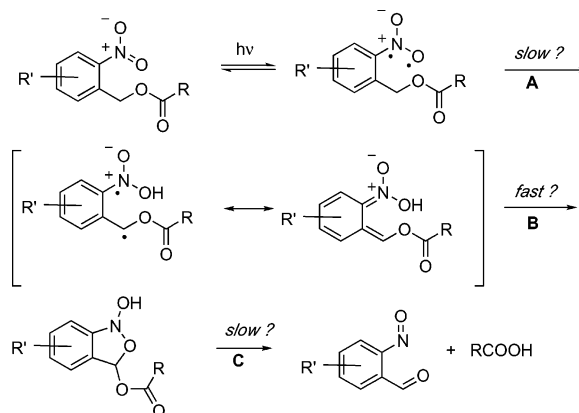
Alkyl substitution at the benzylic position was shown to significantly shorten the reaction times and increase the quantum yields.¹⁰ This suggests that the abstraction of the benzylic hydrogen is the rate-determining step or one of multiple rate-determining steps, regardless of whether the process occurs in a sigmatropic or radical fashion.¹¹ If this is the case, one should expect a significant isotope effect when substituting the two benzylic hydrogens by deuterium atoms. This opens very interesting perspectives, because it would allow the overall observed reaction rate to be tuned without changing the absorbance, as would the introduction or modification of substituents on the aromatic ring.⁷ For reactions with a low quantum yield, slowing down process **A** corresponds to a reduction in quantum yield.

To measure the isotope effects on variously substituted derivatives, we synthesized the hydrogenated and dideuterated esters **1a–d** and **2a–d**.

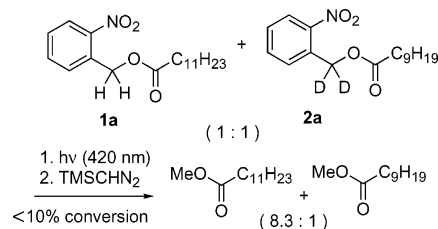
The series **1** was prepared by simple acylation of the readily available corresponding benzylic alcohols derivatives with dodecanoyl chloride. Series **2** was prepared by the reduction of acid chlorides (prepared in situ by the reaction of the carboxylic acid with thionyl chloride) with NaBD₄ in THF (65–94%, isotopic purities: 96% (**2a**), 91% (**2b**), 92% (**2c**), 92% (**2d**)), followed by acylation with decanoyl chloride (CHCl₃, Et₃N, DMAP, 84–96%). Minor side-products are the monodeuterated esters, which could not be separated. **2d** was prepared by a Suzuki coupling between phenylboronic acid and *d*₂-4-Cl-2-nitrobenzyl alcohol under palladium catalysis (71%), followed by acylation with decanoyl chloride.



Scheme 1



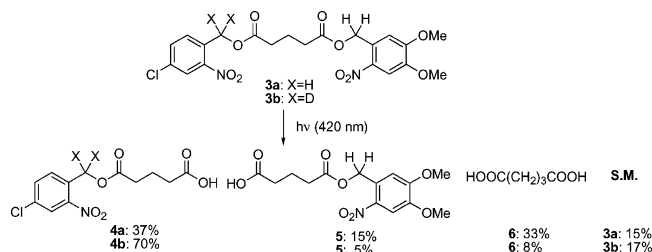
Scheme 2. Measurement of the Isotope Effect.



The kinetic isotope effect was measured by the photolysis of an equimolar mixture of esters **1** and **2** for various irradiation times, followed by GC determination (using tetradecane as an internal standard) of the C₁₁H₂₃CO₂Me/C₉H₁₉CO₂Me ratio after derivatization with TMSCHN₂. A modified version of a known equation was used to extrapolate the isotope effect as the ratio at zero-conversion.¹² Since the reactivity of the monodeuterated ester contaminant is unknown, we must consider our measurements as lower limits of the true isotope effects. We also ruled out deceptive analytical effects by performing the reverse experiment, with deuterated **1b** and protiated **2b**. Irradiation at 420 nm of acetonitrile solutions at room temperature gave KIEs of 8.3 (**1a/2a**), 3.3 (**1b/2b**), 4.3 (**1c/2c**), and 4.1 (**1d/2d**) (Scheme 2). The KIE for the **1a/2a** pair is very high (in fact higher than the maximal value of 7.5 calculated at 25 °C for cases without tunneling).¹³ This confirms the hypothesis that the benzylic hydrogen abstraction is the rate-determining step.¹⁴ However, the significant variation in the magnitude of the KIE with different aromatic substituents suggests a displacement of the position of the transition state along the reaction coordinate and/or a change in the relative rates of the individual steps.¹⁵

We have previously demonstrated a strong dependence of the overall reaction rate on the wavelength.⁷ Hence, we measured the KIE at the wavelengths of 254, 350, and 420 nm (Table 1).

To our surprise, a very strong dependence was observed for the **1a/2a** pair. The same trend was also found for **1c/2c**, albeit to a smaller extent. On the other hand, it was almost absent for **1b/2b**

Scheme 3. Site Differentiation Using the Isotope Effect.**Table 1.** Wavelength-Dependence of the Isotope Effect

λ	k_H/k_D 1a/2a	k_H/k_D 1b/2b	k_H/k_D 1c/2c	k_H/k_D 1d/2d
254	3.8	3.0	3.1	3.6
350	5.8	3.0	4.2	4.2
420	8.3	3.3	4.3	4.1

and **1d/2d**. A comparison of superimposable UV–vis spectra for the protic and deuterated series rules out differential absorption.¹⁶

These results could suggest that the position of the transition state or the conical intersection along the reaction coordinates and/or the activation energy is wavelength-dependent. This explanation is not reasonable, since the wavelength of the incident light is an external factor, which should alter neither the molecular shape nor the properties. On the other hand, one could consider that several energy surfaces are involved. However, photochemical and photophysical (e.g., fluorescence) processes usually occur from the first excited state (either singlet S_1 or triplet T_1), regardless of the initial excitation. This is known as the *Kasha* rule and is the consequence of very fast internal conversion. The implication of a higher excited state would represent a violation of this rule.¹⁷

Irradiation at 420 nm furnishes just enough energy to reach the S_1 state, from which the reaction occurs with an intrinsically large kinetic isotope effect. Excitation at 254 nm populates a higher energy surface (S_2), where the shape of the energy surface state is different and shows a smaller KIE. This would be possible only if the chemical reaction is faster than the relaxation. This hypothesis is in agreement with the quasi-absence of wavelength-dependence for the series b, where excited states are significantly lower (as shown by the UV–vis spectra, **1a** λ_{\max} = 258 nm and **1b** λ_{\max} = 346 nm) and that the S_2 state (with low KIE) can be reached even at 420 nm. The implication of the S_2 state is also compatible with a triplet-based scheme, where the S_2 – T_1 intersystem crossing is much faster than the S_1 – T_1 transition, according to the El-Sayed selection rules.¹⁸ If this mechanism operates, our experimental evidence suggests that the singlet-based transition state presents a large KIE, whereas the triplet-based transition state shows a smaller one.

This particularly strong isotope effect opens new perspectives in wavelength-based protecting group differentiation. To verify this, we prepared diesters **3a** and **3b**, where both termini are protected by *ortho*-nitrobenzyl alcohol derivatives. Chromatic orthogonality was shown earlier to be rather poor (3.8:1 at 254 nm and 1:1.5 at 420 nm) for the hydrogen-substituted variant.⁷ Upon isotopic substitution at the benzylic center, we expected the differentiation to be significantly higher on the basis of the above results.

Hence, as a negative control, the photolysis of **3a** at 420 nm gave only a 2.4:1 ratio of monoesters **4a** and **5a** (37 and 15% yields, respectively), together with 33% yield of totally deprotected pentanedioic acid **6** and 15% yield of starting material (Scheme 3). On the other hand, in the isotopically substituted substrate, the selectivity was raised to 14:1 (70% yield of **4b** and 5% yield of **5b**), with only 8% yield of totally deprotected **6** and 17% yield of starting material. Subsequent photolysis of **4b** at a shorter wavelength would continue the deprotection to **6**. A wavelength-based,

modulated lability has already been successfully applied in solid-phase peptide synthesis.^{19,20}

These experiments show unambiguously that the successful use of the KIE in classical organic synthesis can also be extended to photochemical reactions and that careful selection of the irradiation wavelength is an additional handle to control the outcome of a reaction. We also established experimental evidence for the importance of higher excited states in an apparently well-understood reaction. This is of highest importance for the development of wavelength-selective photochemical reactions, where the kinetic and spectroscopic parameters need to be optimized separately. Further studies in the exact mechanism by flash photolysis and in the synthetic applications are currently underway.

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Supporting Information Available: Selected experimental procedures and isotope effect measurements, equations used to calculate the KIE, and UV spectra of **1a/2a** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (16) Temperature of the reaction mixture increases slightly over the time, but measurements between 5 and 30 min showed no variation in the KIE.
- (17) Only in rare cases, when the higher excited states (S_2 , S_3 , ...) are sufficiently distant from S_1 , is internal conversion inefficient and do reactions from these states occur (among the famous examples are the naphthalene fluorescence and the Norrish type I reaction of thioketones). For a discussion, see: Turro, N. J.; Ramamurthy, V.; Cherry, W.; Farneth W. *Chem. Rev.* **1978**, *78*, 125–145.
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