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On the Alcohol- and Water-Catalyzed Tautomerization of Vitamins K_1- and K_2-Derived Quinone Methide Intermediates

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Abstract: Rates of conversion of 1,3-quinone methides into the corresponding 1,2-quinone methide tautomers, formed upon laser-flash excitation of vitamins K_1 and K_2 in CH_3CN solutions, were determined in the presence of hydroxylic solvents (ROH; R = H, alkyl). In all cases, the tautomerization process is accelerated in the presence of ROH, and the corresponding observed rate constants show a cubed dependence on ROH concentration. This high-order dependency is attributed to a proton-relay transfer involving 3 equiv of ROH in each case.

The photochemistry of vitamin K compounds has received considerable attention over the course of the past thirty-five years, particularly in the cases of vitamins K_1 (2-methyl-3-phytyl-1,4-naphthoquinone) and K_3 (2-methyl-1,4-naphthoquinone). While the photochemistry of vitamin K_3 is dominated primarily by the reactivity of its quinone moiety in the triplet state,[1] vitamin K_1 photoreactions are governed by intramolecular processes involving the isoprenoid side chain.[2,3] It is well-documented that 1,2-quinone methide tautomers (1,2-QM) form as reaction intermediates in vitamin K_1 photoreactions; however, the nature of the primary processes leading to the formation of 1,2-QM has been until very recently a matter of some inconsistencies. A new report, based in part on picosecond spectroscopy of vitamin K_1 analogues, provides comprehensive evidence for the primary processes leading to the formation of 1,2-QM.[3] This study indicates that, in polar solvents, a charge transfer from the β,γ-double bond to the quinone moiety causes an intramolecular proton transfer from the side chain, yielding 1,3-quinone methides (1,3-QM) as a mixture of singlet (zwiterionic) and triplet (diradical) species that are in rapid thermal equilibrium; subsequent solvent-mediated proton transfer from the polar singlet state of 1,3-QM yields the 1,2-QM tautomers.[3]

Tautomerization processes such as those just referred to in the paragraph above are of fundamental interest, since they can reveal the role of hydrogen-bonded solvent adducts in (intramolecular) proton-transfer reactions.[4] The rate for conversion of vitamin K_1-derived 1,3-QM into 1,2-QM has been found to vary by orders of magnitude depending on the solvent and added reagents (such as protic solvents, acids, and bases);[3] however, very little quantitative reactivity data are indeed available. In the present paper we report the results of a kinetic study on the effects of hydroxylic compounds (ROH; R = H, CH_3, $(CH_3)_2CH$, $CH_3(CH_2)_3$, $(CH_3)_3C$, and $CH_3(CH_2)_7$) on the rate of tautomerization of vitamins K_1- and K_2-derived 1,3-QM into 1,2-QM (Scheme 1), in CH_3CN solutions. A cubed dependence of the rate of tautomerization on ROH concentration is observed, and catalysis is ascribed to multiple proton transfer via a hydroxylic solvent bridge comprising three ROH molecules.

Laser flash excitation (at 355 nm) of vitamins K_1 and K_2 in CH_3CN solutions leads to the instantaneous formation (i.e., within the time response of our laser system of ca. 20 ns) of a transient species that absorbs strongly in the near-UV; this signal agrees excellently with the spectral data reported for 1,3-QM.[3] As expected, the transient absorption due to 1,3-QM can be easily quenched by the addition of small amounts of water or (aliphatic) alcohols to CH_3CN solutions (Tables S1−S14).[5] Furthermore, in the presence of added hydroxylic solvents to CH_3CN solutions of vitamins K_1 and K_2, formation of a transient species absorbing in the 420−550-nm region is observed (Figure S1 is representative);[5] this transient species corresponds to 1,2-QM.[2c,3] It should also be pointed out here that the single-exponential decay of 1,3-QM (monitored at 400 nm) matches the single-exponential formation of 1,2-QM (monitored at 465 nm), as illustrated in Figure S1.[5]

Interestingly, the conversion of 1,3-QM into 1,2-QM in air-equilibrated CH_3CN solutions in the presence of water or alcohols is not first order with respect to the added hydroxylic compound, as clearly illustrated by the curved plots shown in Figure 1 (top). Excellent linear plots, however, are obtained when the observed rate constants (k_{obs}) are plotted against the cubed quencher concentration (Figure 1, bottom); this indicates that k_{obs} values may be related to [ROH] according to eq 1, where k_O is largely dominated by oxygen quenching of (triplet) 1,3-QM. The slope values for the linear plots yield the fourth-order rate constants k_{taut} summarized in Table 1; with the

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[1] The detailed literature on vitamin K_3 photochemistry is beyond the scope of this paper; only a few representative articles are listed here: (a) Werbin, H.; Strom, E. T. *J. Am. Chem. Soc.* **1968**, *90*, 7296. (b) Maruyama, K.; Otsuki, T.; Takuwa, A.; Arakawa, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2470. (c) Maruyama, K.; Arakawa, S. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1960. (d) Fisher, G. J.; Land, E. J. *Photochem. Photobiol.* **1983**, *37*, 27. (e) Sakaguchi, Y.; Hayashi, H. *J. Phys. Chem.* **1984**, *88*, 1437. (f) Amada, I.; Yamaji, M.; Sase, M.; Shizuka, H. *Res. Chem. Intermed.* **1997**, *23*, 121. (g) Chen, J. F.; Ge, X. W.; Chu, G. S.; Zhang, Z. C.; Zhang, M. W.; Yao, S. D.; Lin, N. Y. *Radiat. Phys. Chem.* **1999**, *55*, 35.

[2] The detailed literature on vitamin K_1 photochemistry cannot be covered in this report; only a few representative articles are listed here: (a) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1969**, *91*, 731. (b) Leary, G.; Porter, G. *J. Chem. Soc. A* **1970**, 2273. (c) Creed, D.; Hales, B. J.; Porter, G. *Proc. R. Soc. London A* **1973**, *334*, 505. (d) Wilson, R. M.; Walsh, T. F.; Gee, S. K. *Tetrahedron Lett.* **1980**, *21*, 3459. (e) Creed, D.; Werbin, H.; Daniel, T. *Tetrahedron Lett.* **1981**, *22*, 2039. (f) Hales, B. J.; Case, E. E. *Biochim. Biophys. Acta* **1981**, 637, 291. (g) Craw, M. T.; Depew, M. C.; Wan, J. K. S. *J. Magn. Reson.* **1985**, *65*, 339. (h) Burie, J.-R.; Boussac, A.; Boullais, C.; Berger, G.; Mattioli, T.; Mioskowski, C.; Nabedryk, E.; Breton, J. *J. Phys Chem.* **1995**, *99*, 4059. (i) Balakrishnan, G.; Umapathy, S. *J. Mol. Struct.* **1999**, *475*, 5.

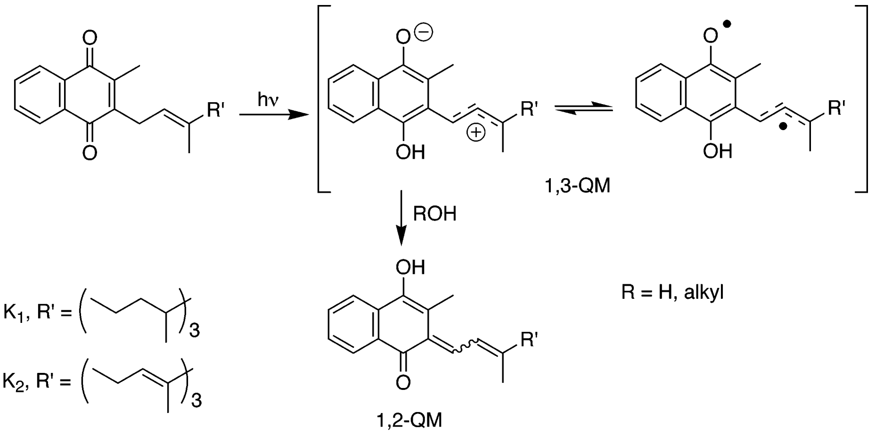
[3] Hangarter, M. A.; Hörmann, A.; Kamdzhilov, Y.; Wirz, J. *Photochem. Photobiol. Sci.* **2003**, *2*, 524.

[4] Grunwald, E.; Eustace, D. In *Proton-Transfer Reactions*; Caldin, E., Gold, V., Eds; Chapman and Hall: London, UK, 1975; Chapter 4.

[5] Supporting Information: see paragraph at the end of this paper regarding availability.

10.1021/jo030365c CCC: $27.50

SCHEME 1



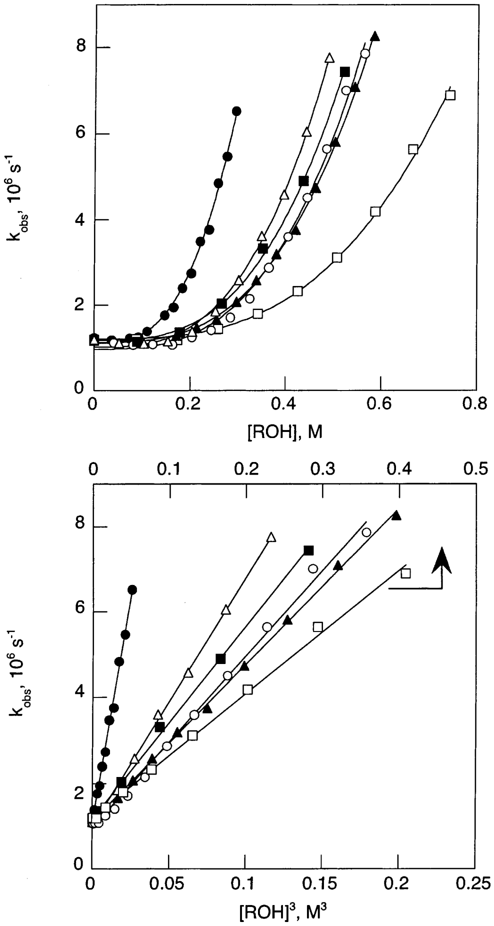


FIGURE 1. Observed rate constants for vitamin K_1-derived 1,3-quinone methide tautomerization in CH_3CN solution as a function of ROH concentration (ROH = water (●), methanol (○), 2-propanol (▲), 1-butanol (■), *tert*-butyl alcohol (□), and 1-octanol (△)).

exception perhaps of results for 1-octanol, k_{taut} values determined for vitamins K_1 and K_2 are essentially indistinguishable.

$$k_{obs} = k_O + k_{taut}[ROH]^3 \qquad (1)$$

TABLE 1. Forth-Order Rate Constants for ROH-Mediated Tautomerization of Vitamins K_1- and K_2-Derived 1,3-Quinone Methides in CH_3CN Solution[a]

	k_{taut}, 10^7 M^{-3} s^{-1}	
ROH	vitamin K_1	vitamin K_2
water	21.0 ± 0.4[b]	20.4 ± 0.5[c]
methanol	4.00 ± 0.08	3.57 ± 0.08
2-propanol	3.66 ± 0.03	3.86 ± 0.05
1-butanol	4.49 ± 0.07	4.02 ± 0.04
tert-butyl alcohol	1.44 ± 0.03	1.74 ± 0.03
1-octanol	5.79 ± 0.08	8.1 ± 0.2

[a] $T = (21 \pm 1)$ °C; air-equilibrated samples. [b] Rate constant for D_2O: $(1.12 \pm 0.02) \times 10^8$ M^{-3} s^{-1}. [c] Rate constant for D_2O: $(1.14 \pm 0.02) \times 10^8$ M^{-3} s^{-1}.

Undoubtedly, the cubed dependence observed on ROH concentration implies that 3 equiv of ROH are involved in the transition state of the rate-limiting step of the conversion of 1,3-QM into 1,2-QM. The presence of an alcohol with both hydrogen bond donating and accepting capacities is essential for this high-order dependency, since addition of 2,2,2-trifluoroethanol (i.e., compound characterized by a hydrogen bond accepting basicity value of zero)[6] to deoxygenated CH_3CN solutions of vitamin K_1 leads to weak catalysis (Table S15)[5] and k_{obs} values showing linear dependence on quencher concentration (plot not shown).[7] Interestingly, three molecules of water or methanol were also found to be involved in the excited-state intramolecular proton transfer of *m*-hydroxy-1,1-diarylalkenes yielding 1,3-quinone methides in CH_3CN solutions.[8]

The temperature dependence of the rate of conversion of 1,3-QM into 1,2-QM in three selected ROH/CH_3CN solutions of vitamin K_1 was also investigated (Table S16).[5] As shown by the Arrhenius plots in Figure 2, a *decrease* in rate with *increasing* temperature is observed. This temperature dependence indicates that the conver-

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[6] Reichardt, C. *Solvents and solvent effects in organic chemistry*; VCH: Weinheim, Germany, 1989; Chapter 7.

[7] The resulting second-order catalytic rate coefficient is $(6.8 \pm 0.6) \times 10^4$ M^{-1} s^{-1}. This (relatively) low value is the reason quenching of triplet 1,3-QM by oxygen ($k_Q \sim 5 \times 10^8$ M^{-1} s^{-1})[3] in air-equilibrated solutions hinders the role of 2,2,2-trifluoroethanol as catalyst in the singlet 1,3-QM to 1,2-QM conversion, making it necessary to deoxygenate the CH_3CN solutions. On the contrary, the catalytic effect of water, and of the other alcohols, is significant enough to carry out experiments in air-equilibrated solutions. It is important to point out here that deoxygenation of H_2O/CH_3CN solutions of vitamin K_1 leads essentially to the same rate constant as the one reported in Table 1 for air-equilibrated solutions.

[8] Fisher, M.; Wan, P. *J. Am. Chem. Soc.* **1999**, *121*, 4555.

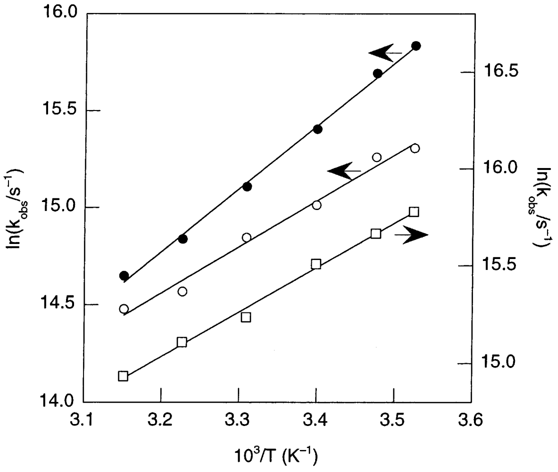

FIGURE 2. Arrhenius plots for vitamin K_1-derived 1,3-quinone methide tautomerization in CH_3CN solution, in the presence of hydroxylic solvents (0.239 M water (●), 0.405 M methanol (○), 0.587 M *tert*-butyl alcohol (□)).

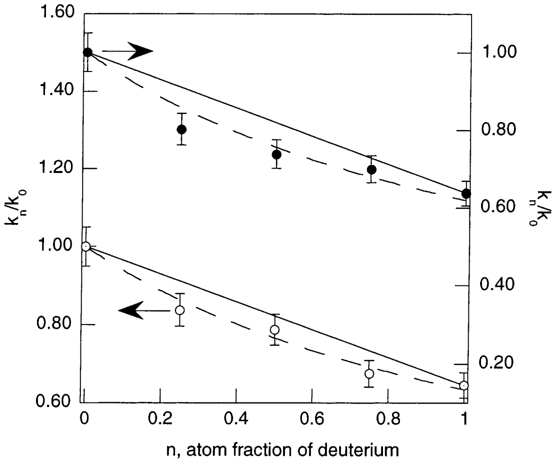

FIGURE 3. Plot of (k_n/k_o) vs n. Plot for vitamin K_1 (●) includes data for five different molarities; plot for vitamin K_2 (○) includes data for three different molarities. Solid and dashed lines are drawn to emphasize the nonlinear dependence.

sion of 1,3-QM into 1,2-QM is at least a two-step process, i.e., the reaction must involve a preequilibrium between two species (A and B), in which B is more stable than A, and only B reacts further to the final product (1,2-QM in this case). Since the formation of a hydrogen bond is an exothermic process, it is reasonable to think of B as representing a hydrogen-bonded cluster. The activation energies corresponding to the linear plots shown in Figure 2 (i.e., (−6.5 ± 0.2), (−4.7 ± 0.3), and (−4.5 ± 0.2) kcal/mol, for 0.239 M water, 0.405 M methanol, and 0.587 M *tert*-butyl alcohol, respectively) are indeed of the order of hydrogen bond energies.[9,10] Bearing in mind the third-order dependency observed on ROH concentration, one of the simplest conceivable mechanisms for the system described in this study would be one involving a preequilibrium between monomeric ROH molecules and trimeric ROH aggregates (i.e., $B = (ROH)_3$); these preformed trimers would subsequently react with 1,3-QM to yield 1,2-QM. Hydroxylic solvents do tend to self-aggregate in aprotic media, and since the corresponding association energies are negative,[9,10] the concentration of these aggregates is expected to decrease with increasing temperature. However, X-ray diffraction and IR spectroscopic studies on the structure of acetonitrile−water mixtures indicate that at the concentration level of this study (i.e. mole fraction of water <0.02) only water monomers are present;[11−13] likewise, self-aggregation of alcohols is essentially negligible at the mole fraction (x_{ROH}) employed in this study ($x_{ROH} < 0.04$). Another possibility is to think of B as corresponding to a solvation complex in which the acidic and basic sites of the zwitterionic singlet state of 1,3-QM are strongly solvated (hydrogen-bonded) by monomeric ROH molecules, i.e., most of the participating hydroxylic solvent molecules are found in the inner solvation shell of the singlet 1,3-QM intermediate. This interpretation is fully consistent with the increase in stability observed for the singlet state of 1,3-QM (relative to that of the triplet state) in polar media as a result of preferential solvation.[3] Although our data do not allow one to determine if the rate-limiting step involves the encounter of a (di)solvated complex with a (third) ROH molecule, or rather solvent reorganization within a (tri)-solvated complex, evidence for a concerted multiple proton transfer was obtained from kinetic isotope effects (Tables S17 and S18)[5] by using mixed H_2O/D_2O solvents (i.e., the proton inventory technique).[14] Plots of k_n/k_0 (i.e., the ratio between the observed rate constant at an atom fraction of deuterium n and the observed rate constant at $n = 0$) against n are nonlinear and bowl-shaped (Figure 3); such a dependence is typical for a concerted multiple proton transfer.[14] Furthermore, it should be noted here that while protons tend to move by quantum-mechanical tunneling, which in turn yields large kinetic isotope effects in single proton transfers, "anomalously" small kinetic isotope effects can be expected in concerted multiple proton transfers, as shown for a model of the enzyme carbonic anhydrase II,[15] in agreement with the results presented here (Table 1, $k_H/k_D \sim 1.8$). Thus, the high-order dependency on ROH concentration observed in the conversion of 1,3-QM into 1,2-QM can be interpreted in terms of a proton-relay transfer,[16] whereby the ROH molecules create a bridge between the (remote) acidic and basic sites of 1,3-QM, as shown in Scheme 2. It has been suggested that the "highest probability for intramolecular proton transfer will occur when the cyclic transition state formed can accommodate a linear arrangement of donor-proton-acceptor of appropriate length".[17] The cubed dependence observed experimentally

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[9] Landeck, H.; Wolff, H.; Götz, R., *J. Phys. Chem.* **1977**, *81*, 718.

[10] Holmes, J. R.; Kivelson, D.; Drinkard, W. C. *J. Am. Chem. Soc.* **1962**, *84*, 4677.

[11] Jamroz, D.; Stangret, J.; Lindgren, J. *J. Am. Chem. Soc.* **1993**, *115*, 6165.

[12] Takamuku, T.; Tabata, M.; Yamaguchi, A.; Nishimoto, J.; Kumamoto, M.; Wakita, H.; Tamaguchi, T. *J. Phys. Chem. B* **1998**, *102*, 8880.

[13] Sirotkin, V. A.; Solomonov, B. N.; Faizullin, D. A.; Fedotov, V. D. *J. Struct. Chem.* **2000**, *41*, 997.

[14] Isaacs, N. *Physical Organic Chemistry*; Longman Scientific: Essex, UK, 1995; Chapter 7.

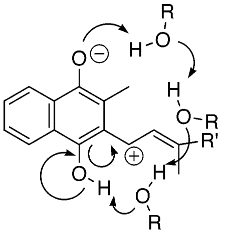
[15] Smedarchina, Z.; Siebrand, W.; Fernández-Ramos, A.; Cui, Q. *J. Am. Chem. Soc.* **2003**, *125*, 243.

[16] Kasha, M. *J. Chem. Soc., Faraday Trans. 2* **1986**, *82*, 2379.

[17] Gandour, R. D. *Tetrahedron Lett.* **1974**, 295.

[18] Karl−Fisher titrations rendered a maximum concentration of 10 mM.

SCHEME 2



with ROH (R = H, alkyl) would indicate that, for vitamins K_1- and K_2-derived 1,3-QM, such an optimal arrangement is attained with a bridge of three ROH molecules.

It is clear that both kinetic and thermodynamic parameters would need to be accounted for to interpret the reactivity order observed for conversion of 1,3-QM into 1,2-QM in CH_3CN solutions (Table 1). For both vitamins K_1 and K_2 the reactivity order is water $\gg$ 1-octanol > 1-butanol ≥ methanol ∼ 2-propanol > *tert*-butyl alcohol. In the alcoholic series, the decrease in reactivity on going from primary alcohol to 2-propanol to *tert*-butyl alcohol could reflect the effects of steric hindrance on formation of the hydroxylic solvent bridge, whereas the increase in reactivity with chain length (if at all significant) may reflect the influence of London dispersion forces in binding ROH molecules to the hydrogen-bonding sites.[4]

In summary, we have investigated the effects of hydroxylic compounds on the rate of conversion of vitamins K_1- and K_2-derived 1,3-QM into 1,2-QM in CH_3CN solutions. Provided the hydroxylic compound has both hydrogen bond donating and accepting capacities, a cubed dependence of the rate on quencher concentration is observed. Such a high-order dependency is attributed to a proton-relay transfer whereby three hydroxylic molecules create an optimum hydrogen-bonded bridge between the acidic and basic sites of the 1,3-quinone methide intermediates.

Experimental Section

Vitamins K_1 (Aldrich) and K_2 (Sigma), acetonitrile, methanol, and 2-propanol (Omnisolv grade, EM Science), 1-butanol (ACS grade, EM Science), *tert*-butyl alcohol (HPLC grade, Aldrich), and 2,2,2-trifluoroethanol (NMR grade, Aldrich) were used as received. 1-Octanol (Baker Chemical Co.) was distilled before use. Deuterium oxide (99.96%) was purchased from Cambridge Isotope Laboratories. Water was purified by passage through a Millipore apparatus before use. The concentration of residual water in CH_3CN, as indicated in the corresponding certificate of analysis, was less than 5 mM. This value, together with the water accompanying 1-butanol (the wettest alcohol of the series), would make a maximum concentration of water of 8 mM at the highest concentration of alcohol used, i.e., catalysis by residual water is negligible in all cases.[18]

Laser experiments were carried out with a Q-switched Nd:YAG laser (Continuum, Surelite I) operated at 355 nm (4−6 ns pulses, <15 mJ/pulse) for excitation. Samples were contained in quartz cells constructed of 7 mm × 7 mm Suprasil tubing. Further details on the time-resolved laser-flash photolysis system employed in this study are reported elsewhere.[19] Experiments were carried out at room temperature (i.e., 20−22 °C), in air-equilibrated solutions, unless stated otherwise. Values for the observed rate constants were obtained by fitting the kinetic traces to a single-exponential function by using the general curve fitting procedure of Kaleidagraph software (version 3.0.5) from Abelbeck Software. Reported values correspond to the average of at least two independent kinetic runs.

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Supporting Information Available: Transient absorption spectra for vitamin K_1 in the presence of 0.352 M 1-butanol in CH_3CN solution, kinetic traces recorded at 400 and 465 nm for vitamin K_1 in the presence of 0.147 M water in CH_3CN solution, and observed rate constants for vitamins K_1- and K_2-derived 1,3-quinone methide tautomerization in CH_3CN solutions as a function of hydroxylic quenchers concentration and temperature. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) (a) Sanchez, A. M.; Barra, M.; de Rossi, R. H. *J. Org. Chem.* **1999**, *64*, 1604. (b) Barra, M.; Agha, K. A. *J. Photochem. Photobiol. A: Chem.* **1997**, *109*, 293.