Ketonization of (*Z*)-2-methoxy-1,2-diphenylvinyl alcohol. Quantitative evaluation of the remarkable kinetic stability of this enol

E.A. Jefferson, A.J. Kresge, L. Matthew, and Z. Wu

Abstract: Rates of ketonization of (*Z*)-2-methoxy-1,2-diphenylvinyl alcohol were measured in aqueous perchloric acid and sodium hydroxide solutions as well as in formic acid and ammonium ion buffers, and the results were used to construct a rate profile for this reaction. These data show this substance to be a remarkably stable enol with a lifetime of 3.6 h at the bottom of its rate profile and a hydrogen ion catalytic coefficient 660 000 times less than that for the enol of acetophenone. Comparison with simple models allows partition of this rate factor into a 440-fold retardation for the β-phenyl substituent and a 1500-fold retardation for the β-methoxy substituent. A global rate of enolization of the keto isomer producing both *Z* and *E* enol isomers was also measured, and this leads to $pK_E > 5.4$ as the lower limit of the keto–enol equilibrium constant for the *Z* enol. This result could be dissected into an enol-content enhancing effect of $\delta\ pK_E = 3.2$ for the β-phenyl group and a surprising enol-content diminishing effect of $\delta\ pK_E > 0.6$ for the β-methoxy group.

Key words: enol ketonization, enol stability, keto–enol equilibrium, β-phenyl and β-methoxy substituent effects in keto–enol systems.

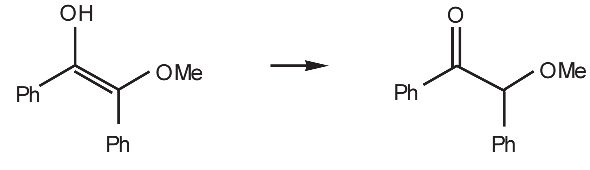
Résumé : Opérant en solutions aqueuses d'acide perchlorique et d'hydroxyde de sodium ainsi que dans l'acide formique et des tampons d'ion ammonium, on a mesuré les vitesses de cétonisation de l'alcool (*Z*)-2-méthoxy-1,2-diphénylvinylique et on a utilisé les résultats pour édifier un profil de vitesses de cette réaction. Ces données montrent que cette substance est un énol remarquablement stable dont le temps de vie est de 3,6 h au fond de son profil de vitesse et pour lequel le coefficient catalytique de l'ion hydrogène est 660 000 fois plus faible que dans le cas de l'énol de l'acétophénone. Une comparaison avec des modèles simples permet de diviser ce facteur de vitesse en un facteur retardant de 440 attribuable au substituant phényle en β et un facteur retardant de 1500 pour le substituant β-méthoxy. On a aussi mesuré une vitesse globale d'énolisation de l'isomère cétonique conduisant aux isomères *E* et *Z* de l'énol; elle permet d'établir à 5,4 la valeur inférieure limite du pK_E de la constante d'équilibre céto–énolique de l'énol *Z*. On peut disséquer ce résultat en un effet, $\delta\ pK_E > 0{,}6$ du groupe β-méthoxy, qui d'une façon surprenant diminue le contenu en énol.

Mots clés : cétonisation d'un énol, stabilité d'un énol, équilibre céto–énolique, effets des substituants β-phényle et β-méthoxy sur les systèmes céto–énoliques.

[Traduit par la Rédaction]

Most thermodynamically unstable enols are also unstable kinetically and cannot be isolated, let alone characterized by standard methods commonly used for stable substances. A notable exception is (*Z*)-2-methoxy-1,2-diphenylvinyl alcohol, **1**, which reverts to its more stable keto isomer, 2-methoxy-1,2-diphenylethanone, **2**, eq. [1], so slowly that its structure could even be determined by X-ray crystallography (1).

[1]



1 **2**

This enol was prepared (1) by treating 1,2-diphenyldiazoethanone, **3**, with sulfuric acid in methanol solution. Under these conditions, solvolysis of the diazo compound occurred through rapid pre-equilibrium protonation on carbonyl oxygen followed by rate-determining loss of nitrogen, eq. [2]; this generated a vinyl cation, **4**, which was captured by solvent on its less hindered side to give the methoxy enol, **1**, eq. [3].

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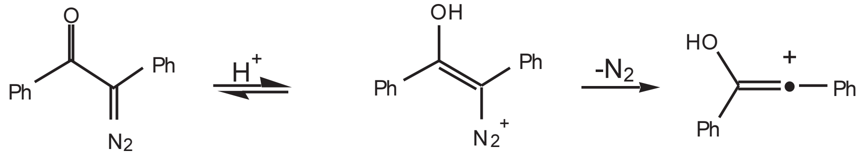
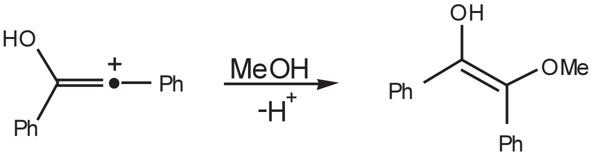
[2]



3 **4**

[3]



4 **1**

Cooling the reaction mixture caused the enol to separate in crystalline form, and this solid was then characterized by its spectra and reactions in the usual way, and its *cis*-phenyl geometry was established by X-ray diffraction.[2]

To provide a quantitative assessment of the remarkable stability of this enol we have measured rates of its ketonization in aqueous solution and have used the results to construct a reaction rate profile. We have also measured rates of enolization of the keto isomer, **2**, in order to obtain an estimate of the keto–enol equilibrium constant for this system.

Experimental section

Materials

1,2-Diphenyldiazoethanone was prepared by mercuric oxide oxidation of benzil hydrazone (3). All other materials were best available commercial grades.

Kinetics, ketonization

Rates of ketonization of (*Z*)-2-methoxy-1,2-diphenylvinyl alcohol were measured by monitoring the increase in product ketone absorbance at $\lambda = 250$ nm using a Cary 2200 spectrometer with sample compartment thermostatted at 25.0 ± 0.05°C. Reactions were initiated by adding aliquots of methanol stock solution of enol to reaction media that had come to temperature equilibrium with the spectrometer cell compartment. The enol stock solutions were made just before use by allowing 1,2-diphenyldiazoethanone to solvolyze at room temperature in methanol containing 0.1 M perchloric acid. It was found that 12 min was the optimum time for this solvolysis to take place: enol formation was nearly complete but subsequent ketonization of the enol, which was ca. 20 times slower under these conditions, had not yet occurred to any appreciable extent. Five μL aliquots of these freshly prepared enol stock solutions were then added to 3.0 mL portions of reaction media; final concentrations of enol in the solutions upon which the kinetic measurements were made were ca. 3×10^{-5} M. The enol is easily oxidized by atmospheric oxygen (1), and all solutions were therefore purged with argon. Ionic strength was maintained at 0.10 M by adding sodium perchlorate as required. The kinetic data fit the first-order rate law well, and observed first-order rate constants were obtained by least-squares fitting of an exponential function.

Kinetics, enolization

Rates of enolization of 2-methoxy-1,2-diphenylethanone were measured in aqueous sodium hydroxide solutions by using bromine to scavenge the enol as it formed. In basic solutions, bromine reacts with hydroxide ion according to eq. [4] and consequently exists as hypobromite ion; reactions were therefore followed by monitoring the absorbance of this ion at $\lambda = 330$ nm.

$$[4] \qquad Br_2 + 2HO^- \rightarrow BrO^- + H_2O + Br^-$$

Measurements were made with a Cary 2200 spectrometer whose cell compartment was thermostatted at 25.0 ± 0.05°C. In a typical experiment, 20 μL of saturated aqueous bromine solution was added to 10 mL of sodium hydroxide solution, whose ionic strength had been adjusted to 0.10 M by adding sodium bromide as required. Each of two 3.0 mL quartz cuvettes was then filled with this solution, and the absorbance of one was recorded at $\lambda = 330$ nm; this reading was later employed to calculate the hypobromite ion concentration, using $\varepsilon_{330} = 300\ M^{-1}\ cm^{-1}$ (4), in order to convert stoichiometric into actual sodium hydroxide concentrations according to the relationship of eq. [4]. The second cuvette was then placed in the reference compartment of the spectrometer and bromination was initiated by adding 5 μL of an acetonitrile stock solution of ketone to the first cuvette. Such double-beam operation minimized base-line drifting, which was prevalent without the use of a reference sample. Ketone concentrations in the reaction solutions were 4×10^{-4} M, and hypobromite concentrations were 1×10^{-3} M. The kinetic data conformed to the first-order rate law well, and observed first-order rate constants were obtained by least-squares fitting of an exponential function.

Results

Ketonization

Rates of ketonization of 2-methoxy-1,2-diphenylvinyl alcohol were measured in aqueous perchloric acid solutions at 10 different concentrations over the range $[HClO_4] = 0.001$–0.1 M and in aqueous sodium hydroxide solutions at seven different concentrations over the range [NaOH] = 0.0005–0.05 M. Replicate measurements were made at each concentration. The data so obtained have been deposited and are summarized in Tables S1 and S2.[3]

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[2] Sterically hindered enols for which access to the vinyl group is inhibited by bulky substituents are also remarkably stable (2).

[3] Tables S1–S4 may be purchased from: The Depository of Unpublished Data, Document Delivery, CISTI, National Research Council of Canada, Ottawa, Canada, K1A 0S2.

Fig. 1. Rate profile for the ketonization of 2-methoxy-1,2-diphenylvinyl alcohol in aqueous solution at 25°C.

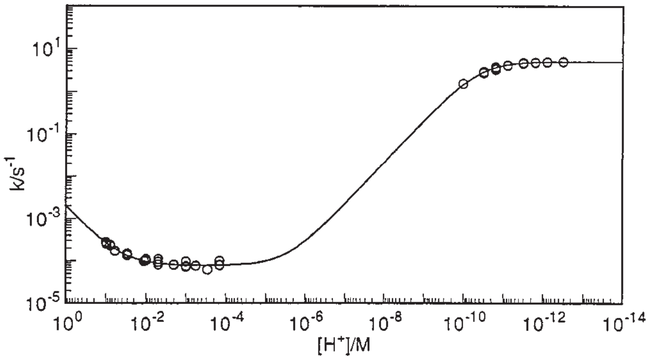
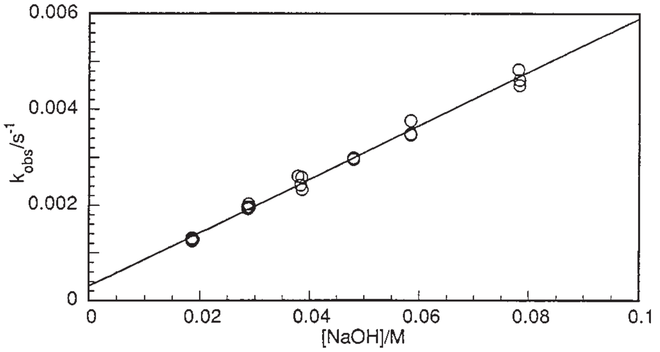


Fig. 2. Relationship between hydroxide ion concentration and observed rate constants for the enolization of 2-methoxy-1,2-diphenylethanone in aqueous solution at 25°C.



Rates of ketonization of 2-methoxy-1,2-diphenylvinyl alcohol were also measured in formic acid and ammonium ion buffers. Series of buffer solutions of constant buffer ratio and constant ionic strength (0.10 M), and therefore constant hydrogen ion concentration, but different buffer concentrations were used. Buffer concentrations were varied by a factor of five, and replicate measurements were made at each concentration. The data so obtained are summarized in Table S3 of the depository.[3]

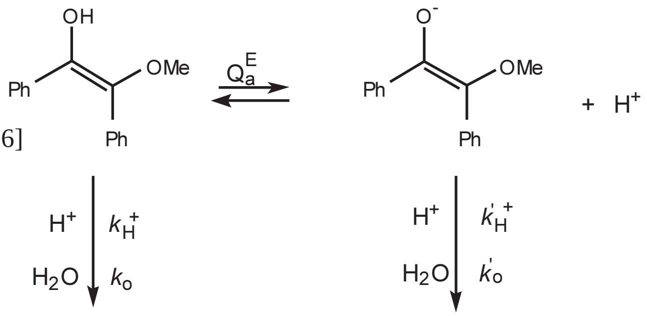
Observed first-order rate constants measured in these buffer solutions proved to be accurately proportional to buffer concentration, and the data were therefore analyzed by least-squares fitting of eq. [5].

$$[5] \qquad k_{obs} = k_o + k_{cat}[\text{buffer}]$$

The zero-buffer-concentration intercepts, k_o, obtained in this way were then used, together with the rate constants measured in perchloric acid and sodium hydroxide solutions, to construct the rate profile shown in Fig. 1. Hydrogen ion concentrations of the buffer solutions needed for this purpose were obtained by calculation, using literature values of the buffer acid dissociation constants and activity coefficients recommended by Bates (5).

Rate profiles such as that of Fig. 1 are a characteristic feature of enol ketonization reactions (6). They reflect a reaction mechanism consisting of rate-determining protonation on β-carbon of either the enol or the enolate ion, as shown in eq. [6].

[6]



The acid-catalyzed portion at the extreme left of the profile represents carbon protonation of the enol by hydrogen ion, and the uncatalyzed portion adjoining that represents either protonation of enol by solvent water or ionization of enol to the much more reactive enolate ion followed by carbon protonation of that by hydrogen ion. Following this uncatalyzed region is a segment of apparent hydroxide ion catalysis produced by ionization of enol to enolate followed by carbon protonation of that by water, and saturation of this catalysis, which occurs when the position of the ionization equilibrium shifts from enol to enolate, gives the second uncatalyzed region at the very right of the profile.

The rate law that describes this reaction scheme is shown in eq. [7],

$$[7] \qquad K_{obs} = k_{H^+}[H^+] + k_{UC} + k'_o\, Q_a^E/(Q_a^E + [H^+])$$

whose symbols are defined by eq. [5] with k_{UC} = either k_o or $k'_{H^+}\, Q_a^E$. Least-squares fitting of this expression gave the following results: $k_{H^+} = (1.89 \pm 0.06) \times 10^{-3}\ M^{-1}\ s^{-1}$, $k_{UC} = (7.71 \pm 0.13) \times 10^{-5}\ s^{-1}$, $k'_o = (4.99 \pm 0.10)\ s^{-1}$, and $Q_a^E = (4.22 \pm 0.34) \times 10^{-11}$ M, $pQ_a^E = 10.38 \pm 0.04$.[4]

Enolization

Rates of enolization of 2-methoxy-1,2-diphenylethanone were measured in aqueous sodium hydroxide solutions at six different concentrations over the range [NaOH] = 0.02–0.08 M. Replicate measurements were made at each concentration. The data so obtained are summarized in Table S4 of the depository.[3]

Observed first-order rate constants determined in these solutions proved to be accurately proportional to sodium hydroxide concentration (see Fig. 2), and linear least-squares analysis gave $k_{HO^-} = (5.59 \pm 0.12) \times 10^{-2}$ as the hydroxide ion catalytic coefficient for the enolization reaction.

Discussion

Reaction identification

2-Methoxy-1,2-diphenylvinyl alcohol is a vinyl ether as well as an enol, and, in view of the fact that vinyl ethers are subject to facile acid-catalyzed hydrolysis (7), this substance might have undergone that reaction, as shown in eq. [8], rather than the intended ketonization. It is known, however, that acid-catalyzed ketonization of enols is at least an order

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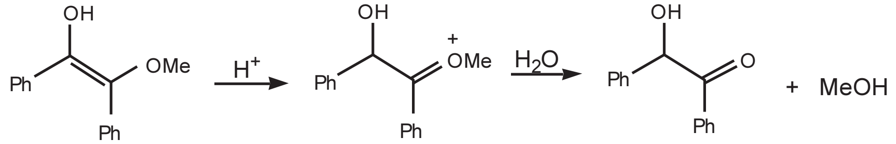
[4] This acidity constant is a concentration quotient applicable at ionic strength equal to 0.10 M.

[8]



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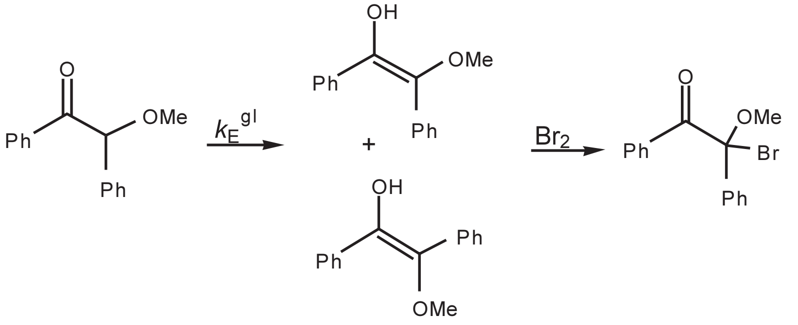

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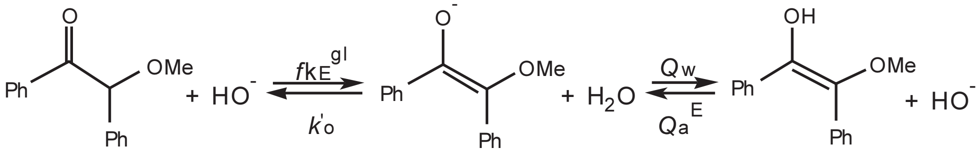
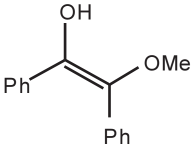


of magnitude more rapid than the hydrolysis of the corresponding methyl vinyl ethers (6). The ketonization of enols, moreover, is strongly catalyzed by bases as well as by acids, whereas the hydrolysis of vinyl ethers is catalyzed only by acids. This, plus the fact that 2-methoxy-1,2-diphenylethanone, **2**, is the only product formed (1), would appear to make it safe to conclude that the process under observation here is in fact the intended ketonization reaction.



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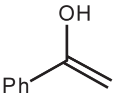

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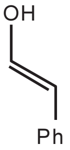

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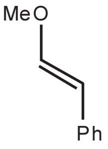
Reactivity

The lifetime of 2-methoxy-1,2-diphenylvinyl alcohol, **1**, at the bottom of its rate profile (Fig. 1) is $\tau = 3.6$ h. This contrasts sharply with the lifetime of the enol of acetophenone, **5**, in the corresponding region, $\tau = 6$ s (8), and shows that the additional β-methoxy and β-phenyl substituents in **1** have a very strong stabilizing effect.

Because the ketonization of enols at the bottom of their rate profiles can occur by either of two mechanisms (vide supra), a better assessment of the β-methoxy and β-phenyl group effects may be made using rate constants from a different region of the profile. Use of the acid-catalyzed region, moreover, allows comparison with vinyl ether hydrolysis; this is useful because acid catalysis of both ketonization and vinyl ether hydrolysis occurs by the same reaction mechanism, i.e., simple rate-determining proton transfer to the substrates's β-carbon atom. Combination of $k_{\mathrm{H}^+} = 1.25 \times 10^3$ $\mathrm{M}^{-1}\ \mathrm{s}^{-1}$ for acetophenone enol (9) with the presently determined value for 2-methoxy-1,2-diphenylvinyl alcohol then gives a rate factor of 660 000, which is equivalent to a difference in free energy of activation of $\delta\Delta G^{\ddagger} = 7.9$ kcal mol^{-1}.

This rate factor may be separated into effects of β-phenyl and β-methoxy by using rates of ketonization of the *trans*-enol of phenylacetaldehyde, **6**, $k_{\mathrm{H}^+} = 7.45 \times 10^{-2}\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ (10), and of vinyl alcohol, **7**, $k_{\mathrm{H}^+} = 3.30 \times 10^{1}\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ (11), to estimate retardation by a β-phenyl group. The result, a factor of 440, then leaves 1500 as the β-methoxy group effect. Similarly large rate retardations by β-phenyl and β-methoxy groups occur in vinyl ether hyrolysis; for example, k_{H^+} for *trans*-β-methoxystyrene (12), **8**, is 1100 times less than that for methyl vinyl ether (13), **9**, and k_{H^+} for *cis*-1,2-dimethoxyethene (14), **10**, is 13 000 times less than that for methyl vinyl ether. These retardations in rates of vinyl ether hydrolysis are believed to be the result of initial-state free-energy lowering by the well-known double-bond stabilizing effects of phenyl and methoxyl groups (15), which are partially lost in the reactions' transition states. A similar explanation can be advanced for the effect of these groups on enol ketonization reactions, and the greater velocities of the ketonizations over the vinyl ether hydrolyses, and their consequent earlier and more reactant-like transition states, can be invoked to rationalize the somewhat smaller size of the effects in ketonization than in vinyl ether hydrolysis.



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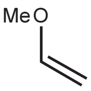

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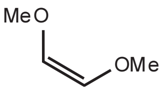

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Keto–enol equilibrium

Keto–enol equilibrium constants have traditionally been determined by the halogen titration method invented nearly a century ago (16). This method, unfortunately, fails when enol contents are as low as is commonly the case for simple aldehydes and ketones (17), and in that situation it is useful to employ a kinetic method where the keto–enol equilibrium constant is determined as the ratio of enolization to ketonization rate constants: $K_E = k_E/k_K$.

The presently determined ketonization rate constants, of course, refer only to the *Z* enol isomer, but the enolization rate constants are global values referring to the production of both *Z* and *E* enols, as shown in eq. [9]. Simply taking the ratio of the enolization to ketonization rate constants determined here will therefore not produce a proper keto–enol equilibrium constant: the global rate constants should be separated into values for production of the individual isomers, but that cannot be done because the method of analysis used, bromination, does not distinguish between the isomers. A simple ratio of presently determined rate constants does, however, provide an upper limit to K_E for the *Z* isomer, and that is enough to produce an interesting result.

The keto–enol equilibrium involving the *Z* isomer promoted by hydroxide ion may be represented as shown in eq. [10], and the equilibrium constant for this representation is given by eq. [11].

$$[11] \qquad K_E = \frac{f k_E^{\,gl}}{k'_o} \; \frac{Q_w}{Q_a^{\,E}}$$

In the latter expression, *f* is the (unknown) fraction of the global enolization rate constant, k_E^{gl}, that refers to production of the *Z* isomer only, Q_w is the autoprotolysis constant of water, and the remaining symbols are as defined by eq. [6]. Insertion of numerical values into this expression then leads to $K_E = (f)\ (4.22 \times 10^{-6})$. Since *f* is a fraction less than one, K_E must be less than 4.22×10^{-6} with $pK_E > 5.38$ as a lower limit.

Comparison of this result with $pK_E = 7.96$ for acetophenone (18) shows that β-phenyl and β-methoxy substituents introduced together increase enol content, and since $pK_E = 5.38$ is a lower limit, the combined effect of these groups can be no greater than 7.96 – 5.38 = 2.58 p*K* units. The effect of a β-phenyl substituent introduced alone may be estimated as $\delta\Delta pK_E = 3.16$, by comparing $pK_E = 3.07$ for the *trans*-enol of phenylacetaldehyde, (10), **6**, with $pK_E = 6.23$ for acetaldehyde (11), **7**. This difference is greater than the upper limit of 2.58 p*K* units estimated above for the combined effect of β-phenyl and β-methoxy substituents, which means that the effect of β-methoxy alone must be in the opposite direction, i.e., the effect of this group must be to lower rather than to raise enol content, and its magnitude must be greater than 3.16 – 2.58 = 0.58 p*K* units.

This is a surprising result. It implies that β-methoxy substituents destabilize enols thermodynamically,[5] in contrast to the kinetic stabilization shown by their marked retarding effect on rates of enol ketonization (vide supra). It is possible, however, that the various comparisons made leading to this result are not entirely valid, inasmuch as they were made using models containing only single phenyl substituents in which steric crowding interfered little, if at all, with substituent-functional group interaction. The enol investigated, 2-methoxy-1,2-diphenylvinyl alcohol, on the other hand, is a sterically congested molecule, as shown by the fact that its phenyl groups are twisted out of the vinyl plane by some 47° (1).

Acknowledgement

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[5] It is likely that β-substituents influence the position of keto–enol equilibria largely by altering the energy of the enol rather than that of the keto isomer, because in the enol the substituent is placed directly on the functional group, whereas in the keto isomer it is insulated from the functional group by a saturated carbon atom.