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Stable acyclic aliphatic solid enols: synthesis, characterization, X-ray structure analysis and calculations

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A synthetic approach to stable enols was introduced and series of acyclic aliphatic solid enols were obtained and characterized. Relationship between the structure and the stability of these enols was discussed. Gaussian 09 calculations had been carried out to rationalize the stability of the enols. These enol structures were confirmed by ^{1}H NMR, ^{13}C NMR, MS, IR, partly by single crystal X-ray structure analysis and the protons exchange experiments. This work showed that very stable acyclic aliphatic enols can be synthesized efficiently without any purification.

"Simple" enols are defined as compounds with substituents, such as hydrogen, alkyl, or aryl groups, bounded to their double-bond. They are known as very unstable compounds. Enols are usually short-lived as a result of their kinetically and thermodynamically unstable properties compared to their keto forms, so they are usually present as transient intermediates at very low concentrations in various organic reactions involving aldehydes and ketones[1–3]. Enol compounds have been under active investigations for over one century[4–6], not only from the viewpoints of synthesis[7–9] and their spectroscopic behavior[10] but also because of their roles in DNA damage[11–14] and biological function[15–17]. However, most of the recent investigations are focused on the spectroscopy equilibrium between keto and enol formation and the factors influencing their equilibrium[18–22]. There are still only a few reports on the synthesis of stable enol in the literature.

Early efforts to synthesize stable enols failed because of the limited synthetic means and the misunderstanding between the stability and structure of enols. Remarkable progress in the synthesis of simple enols in early years was achieved by Capon's[23,24] and Kresge's groups[25,26]. Later, scientists also made some contributions in this area[27–29]. However, in literature, with an equilibrium with its keto tautomers, enols are always obtained as mixtures with their carbonyl isomers. Furthermore, the existence of these enols are conditional, usually in specific solvent[30–32], at low temperature[33], in gas form[34,35], or in surrounding capsule cage[36]. The concentrations of the enols are usually too low that they have to be determined indirectly. Moreover, most of these enols are stabilized by aryl[27–29] or existed as cyclic structures[37–39], they rapidly tautomerized to their carbonyl isomers as a result of their kinetic instability under inappropriate conditions[23,24,40]. Synthesis of stable acyclic aliphatic enols is still a challenge for chemists.

In 1922, Diels' group reported the possibility of the existence of enol, but they were not able to confirm it[41]. They neither characterized the structure of the products of acetylacetone with DEAD nor discussed the relationship between the stability and structure of enols. After Diels' report, in 1980, Nelson reported a Nickel-catalyzed Michael addition of β-carbonyl ester with azodicarboxylate, to give 1,3-dicarbonyl compounds[42]. Later, other catalysts, such as $InCl_3$ and SiO_2, were used in similar reactions to afford 1,3-dicarbonyl compounds[43-45]. However, no stable enol compounds were reported in these reactions. Until 2010, Lawrence described the first example of a stable phenylogous enol, resulting from an extended keto-enol tautomerization across a benzene ring. The enol has been isolated, and its structure was proved by X-ray crystallography[39].

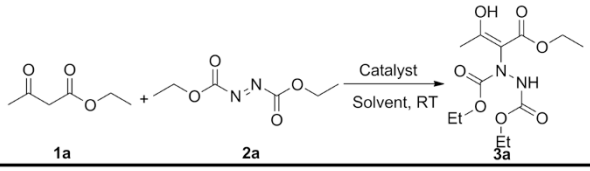
In this manuscript, an efficient way to synthesize very stable hydrazine substituted enol is provided and series of stable aliphatic solid enols, which are different from Lawrence's phenylogous enol, were obtained and studied. These enols are remarkably stable under open atmosphere, and no tautomerization to their carbonyl isomers were observed. The relationship between structure and the stability of the enol was investigated. Gaussian 09 calculations had been carried out, proving that enol forms are more superior than their keto forms in energy. These enol structures are unambiguously confirmed by ^{1}H NMR, ^{13}C NMR, MS, IR spectra partly by single crystal X-ray

structure analysis and other methods. This work showed some enol compounds can be synthesized easily without any purification. We believe this complete study on the stable enols will bring a new insight on the stability of this important species in organic synthesis.

Results

We used ethyl acetoacetate as a standard substrate to react with DEAD in the presence of quinine and expected to get product bearing one chiral centre. After the pure product was obtained, we detected it through a chiral column on HPLC. With only one signal was detected by the chiral column, we thought a product with very high *ee* value might be obtained. When we changed the chiral base quinine into an achiral base triethylamine, we thought two signals should be observed via HPLC in the same condition. To our surprise, still only one signal was observed at the same HPLC retention time. And two broad signals at 12.11 ppm and 6.80 ppm were observed in the ^{1}H NMR spectra. Then, we did rotons exchange experiments, signal at 12.11 ppm disappeared when this product was dissolved in $CDCl_3$ with a drop of D_2O, indicating the hydroxyl group is existent in the product. Besides, absorbtions at about 3280 cm^{-1} were found in IR spetrum. Based on these results, we proposed the product should be enol. This conclusion was subsequently confirmed through many ways.

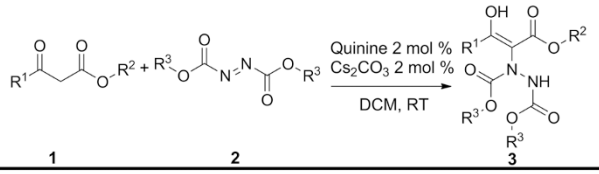
As initial optimization of the reaction conditions, ethyl acetoacetate **1a** and DEAD **2a** were chosen as the model substrates. The results are summarized in Fig. 1. Different organic bases, such as diethylamine, triethylamine, DBU, pyrrolidine, L-proline and quinine were tested in dichloromethane (DCM) at room temperature (entries 1–6). It was confirmed that all of the organic bases mentioned can be used as catalysts in this reaction. However, quinine seems to be the best one, because it can offer both the fastest rate and excellent yields with lower catalyst loading. The solvents were



Entry	Solvents	Catalysts	Time(h)	Yield(%)[b]
1	DCM	Diethylamine	8	69
2	DCM	Triethylamine	8	65
3	DCM	DBU	8	15
4	DCM	Pyrrolidine	8	63
5	DCM	L-Proline	8	51
6[c]	DCM	Quinine	4	87
7[c]	CH_3OH	Quinine	4	85
8[c]	Toluene	Quinine	4	82
9[c]	THF	Quinine	4	77
10[c]	Et_2O	Quinine	4	83
11[c]	CH_3CN	Quinine	4	70
12[d]	DCM	Quinine,KO^{t}Bu	4	92
13[e]	DCM	Quinine,K_2CO_3	4	95
14[f]	DCM	Cs_2CO_3	4	85
15[g]	DCM	Quinine,Cs_2CO_3	4	99

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.1 mmol), catalyst (2.0 mol %), solvent (2.0 mL), room temperature.
[b] Isolated yields.
[c] 2.0 mol % quinine was used.
[d] 2.0 mol % quinine and 2.0 mol % KO^{t}Bu were used.
[e] 2.0 mol % quinine and 2.0 mol % K_2CO_3 were used.
[f] 5.0 mol % Cs_2CO_3 were used.
[g] 2.0 mol % quinine and 2.0 mol % Cs_2CO_3 were used.

Figure 1 | Optimized conditions for the reaction of ethyl acetoacetate 1a with DEAD 2a[a].



Entry	R^1	R^2	R^3	Products	Yield(%)[b]	M.P.(°C)[c]
1	Me	Et	Et	**3a**	99	76-77
2	Me	^{i}Bu	Et	**3b**	95	55-57
3	Me	^{t}Bu	Et	**3c**	94	82-84
4	Me	Allyl	Et	**3d**	96	42-43
5	^{n}Pr	Et	Et	**3e**	98	60-61
6	Ph	Et	Et	**3f**	95	84-86
7	Me	Et	*i*Pr	**3g**	97	74-75
8	Me	^{t}Bu	^{i}Pr	**3h**	94	69-70
9	Me	Et	Bn	**3i**	95	60-62

[a] All reactions were carried out in DCM with 1 mmol of **1** and 1 mmol of **2** in the presence of 2 mol % of quinine and 2 mol% of Cs_2CO_3 for 4 h.
[b] Isolated yields. c Melting points are not corrected.

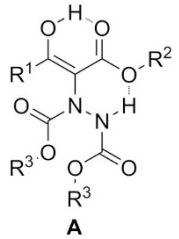
Figure 2 | Expansion of *β*-carbonyl esters 1 with azodicarboxylates 2[a].

subsequently examined, we found DCM is a suitable one among various solvents listed in Fig. 1 (entries 7–11). To our delight, the best result (99%) was achieved when quinine and Cs_2CO_3 were employed at the same time in this reaction (entries 15), compared with using KO*t*Bu, K_2CO_3 (entries 12, 13) or only use of Cs_2CO_3(entries 14).

With the optimized conditions in hand, we then investigated the scope of substitutents on this reaction. Various *β*-carbonyl esters and azodicarboxylates were examined, as summarized in Fig. 2. We found that these reactions can be carried out without limitation in the groups R^1 or R^2, because these carbonyl esters readily participated to react with DEAD. However, yields are a little bit lower when substitutents are bulky groups such as ^{t}Bu (94%) (entry 3). Even **3f** with Bn group in its structure, 95% yield was achieved (entry 6). All of the reactions performed smoothly when carbonyl esters reacted with several azodicarboxylates (entries 1, 7–9). Although **3g**, **3h**, **3i** were synthesized from substrates with bulky groups, corresponding products were obtained in excellent yields (94–97%)(entries 7–9). In all of cases, the products were obtained with excellent yields, we believe that the groups R^1, R^2, R^3 have limited impact on the yields.

With our efforts to understand this reaction, we became interested to know why these enol form products are stable. We decided to study products **A** obtained from *β*-carbonyl esters. We found intramolecular hydrogen bonding is very important to the stability of enols. Initially, we thought **A** could be stabilized by one O–H–O intramolecular hydrogen bond and one N–H–O intramolecular hydrogen bond (Fig. 3).

We speculated that both of these two intramolecular hydrogen bonds were working together to maintain the stability of these enols and disenable the isomerization to their keto isomers. We tried to prove our hypothesis by the single crystal X-ray structure analysis



A

Figure 3 | Possible intramolecular hydrogen bonds in A.

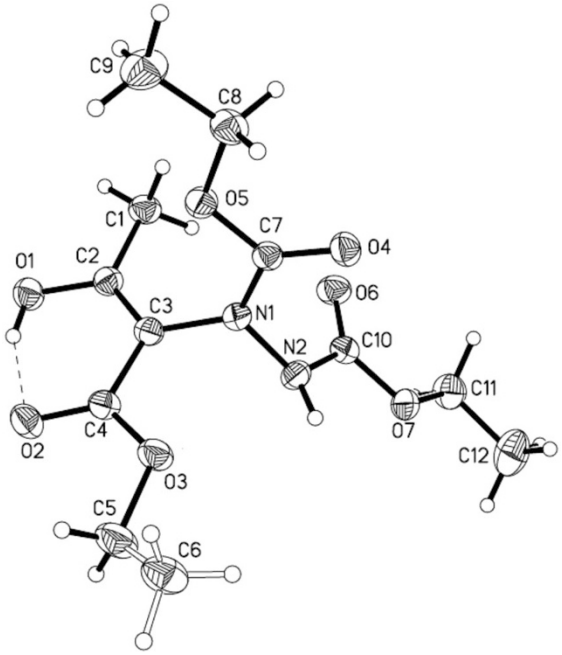


Figure 4 | The X-ray crystal structure of compound 3a. Intramolecular hydrogen bond is displayed in dashed lines.

(Fig. 4). From the data of single crystal X-ray structure analysis of compound **3a** (CCDC 816568 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif), we could see O^1H group and O^2, with a distance of 1.789 Å are close enough to form intramolecular hydrogen bonds. However, the distance of N^2H group with O^3 is beyond of the range of intramolecular hydrogen bonds. Therefore, O–H–O intramolecular hydrogen bond plays very important role to the enol and it is strong enough to maintain the enol form. This speculation was subsequently proved by performing deuterated solvent study by ^{1}H NMR. The examination of **3a** in $CDCl_3$, CD_3OD, C_6D_6, CD_3COCD_3, CD_3CN and CD_3SOCD_3 showed that enol form products can be well maintained in aprotic solvent, such as $CDCl_3$, C_6D_6 and CD_3CN. However, some protic solvents and protophilic solvents affected the intramolecular hydrogen bonds in **3a**, because second small signals in the enol proton region at 12.0 ppm were found, such as in solvents CD_3COCD_3 and CD_3SOCD_3. These additional signals should belong to enol protons which are partly released from previous intramolecular hydrogen bond as a result of the disruption of carbonyl or sulfinyl. It is worth mentioning that when CD_3COCD_3 or CD_3SOCD_3 was moved and $CDCl_3$ was added, its ^{1}H NMR data is as same as the data of **3a** which was directly collected in $CDCl_3$. Although protophilic solvent, such as CD_3COCD_3 and CD_3SOCD_3, can partly disrupt the intramolecular hydrogen bonds in these enols, enol forms remain predominant from their ^{1}H NMR data. Moreover, we are pretty confident that the products are enols since enol signal at 12.11 ppm disappeared when this product was dissolved in CD_3OD (proton exchanged).

Computationally study about enol is one topic attracted many chemists[46–50]. Energy calculated by the computer is another important factor taken into consideration by our group. Take product **3a** for example, as a result of the effect of the intramolecular hydrogen bond, the carbon-carbon double bond is formed (Fig. 5, **3a**). With oxygen atom, nitrogen atom and carbonyl bonded to the carbon-carbon double bond in **3a**, p-π conjugation and π-π conjugation are possible, which strongly dispersed the electrons. When **3a** tautomerized to **3a′**, however, p-π conjugation and π-π conjugation are not

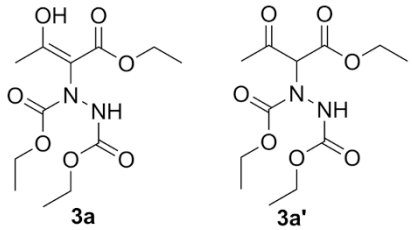


Figure 5 | The model structures of *β*-carbonyl ester 3a and its keto form 3a′.

possible because of the barrier of the tertiary carbon. As a result of this, we supposed **3a** should have lower energy in theory, which benefits the enol form and stabilizes the enol forms. This hypothesis was proved by the Gaussian 09 calculations in this paper (See supporting information). We chose **3a** and its keto form isomer **3a′** as the model structure to perform the Gaussian 09 calculations (Fig. 5). The optimized structure is quite in accord with the single crystal X-ray structure (Fig. 6). The results showed that energies of **3a** are lower than **3a′**($H_{3a} - H_{3a'} = -9.6$ Kcal/mol, $G_{3a} - G_{3a'} = -8.8$ Kcal/mol in gas form, $H_{3a} - H_{3a'} = -6.9$ Kcal/mol, $G_{3a} - G_{3a'} = -6.2$ Kcal/mol in the solvent model of CH_2Cl_2) (See supporting information), supporting that the superiority of the enol form of **3a** is obvious when it is compared with its keto form isomer **3a′**.

To confirm that the intramolecular hydrogen bond is strong enough to maintain the enol form, we expanded the substrate from *β*-carbonyl esters to *β*-carbonyl ketone compounds, some enol form products were obtained (Fig. 7). It was pleasant that all the reactions performed very well by carrying out the foregoing condition and all substrates provided high yield products (entries 1–5). Such as, products **5a** and **5b** were obtained with 99% and 97% yields (entries 1, 2). However, substrates with bulky groups, such as, ^{t}Bu, Ph slightly lowered the yields (entries 3–5). It should be mentioned that the size of the central substituent has slightl effect on the formation of the intramolecular hydrogen bonds because additional signals in the enol proton region at 16.0 ppm were found in the spectra of **5b** and **5c** and the second signal in ^{1}H NMR spectra of **5c** with groups ^{t}Bu is stronger than the second signal in ^{1}H NMR spectra of **5b** with groups ^{i}Pr. Steric hindrance should lead to a distortion and disrupted intramolecular hydrogen bonds so that the enol proton can partly release from intramolecular hydrogen bond to give an additional signal. For the same reason, additional signals could be found in the ^{13}C NMR spectrum of **5b** and **5c.** However, all the products were detected through the chiral column on HPLC, each of them gave one signal, which means the enol form was obtained with overwhelming superiority by the mobile phase of *n*-Hexane and 2-propanol.

Thus, product **5a** was easily obtained as the only product in enol form. Because only one signal was determined through the chiral

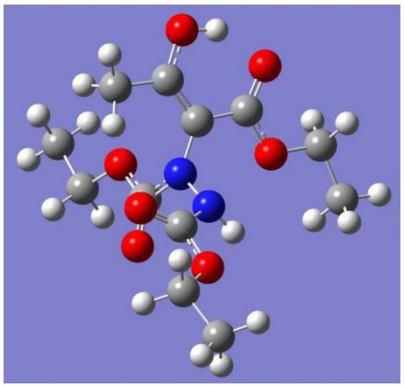
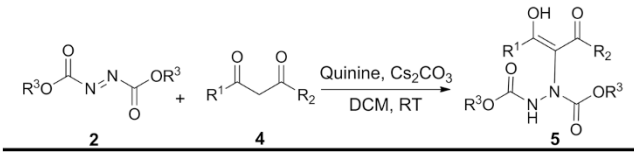


Figure 6 | The optimized structure of 3a.



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Entry	R^1	R^2	R^3	Products	Yield(%)[b]	M.P.(°C)[c]
1	Me	Me	Et	**5a**	99	126-128
2	Me	Me	^{i}Pr	**5b**	97	114-116
3	Me	Me	^{t}Bu	**5c**	93	138-139
4	Me	Me	Bn	**5d**	94	123-125
5	Ph	Ph	Et	**5e**	93	132-134

[a] All reactions were carried out in DCM with 1 mmol of **4** and 1 mmol of **2** in the presence of 2 mol % of quinine and 2 mol% of Cs_2CO_3 for 4 h.
b Isolated yields.
[c] Melting points are not corrected.

Figure 7 | Expansion of *β*-carbonyls 4 with azodicarboxylates 2[a].

column on HPLC and signal at 16.02 ppm disappeared while deuterated with D_2O in $CDCl_3$, it indicates that the product **5a** is also an enol form with overwhelming superiority.

Similarly, **5a** also have lower energy which benefits the enol form and stabilizes its enol structure. Luckily, this was also proved by the Gaussian 09 calculations when we chose **5a** and its keto form isomer **5a′** as the model structure to perform the calculations. The optimized structure is quite similar with the single crystal X-ray structure (See supporting information). The results showed that the energy of **5a** is lower than **5a′** ($H_{5a} - H_{5a'} = -9.4$ Kcal/mol, $G_{3a} - G_{3a'} = -9.5$ Kcal/mol in gas form, $H_{5a} - H_{5a'} = -6.5$ Kcal/mol, $G_{5a} - G_{5a'} = -6.7$ Kcal/mol in the solvent model of CH_2Cl_2), indicating enol forms are more superior than their keto forms in energy. Enol form structure of product **5a** was unambiguously confirmed by the single crystal X-ray structure analysis at last (Fig. 8). (CCDC 849478 contains the supplementary crystallographic data for this compound.

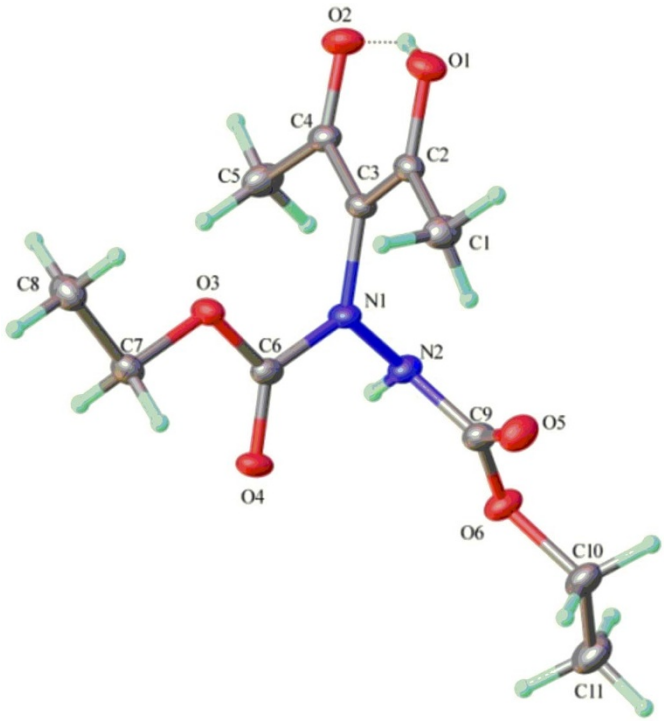


Figure 8 | The X-ray crystal structure of compound 5a. Intramolecular hydrogen bond is displayed in dashed lines.

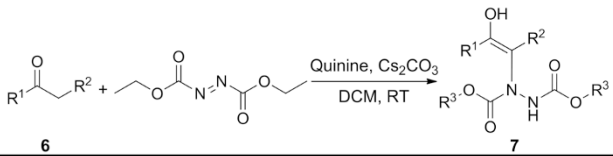
These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif). From the data of single crystal X-ray of **5a**, we can find proton H1 is between O1 and O2, the distance of H1 with O1 and the distance of H1 with O2 are close enough to form intramolecular hydrogen bonds. However, the acetoacetate fragment is not completely symmetrical because the distance of H1- O1 and the distance of H1-O2 are not equivalent. And the distance of O1-C2 and O2-C4 are not equivalent either. With a 72.4 deg. angle between C4-C3 and N1-N2, it seems that the hydrazine moiety is not orthogonal with the acetoacetate fragment. But hydrazine with bulky groups should have impact on the structure because it can lead to a deformation. Indeed, large hydrazine substituents could also likely favor the formation of the enol relative to the keto isomer.

In conclusion, three main reasons should be responsible for the stability of enol form. 1) the intramolecular hydrogen bond of O–H–O, 2) the p-π conjugation and π-π conjugation in these compounds. 3) appropriate group is another factor to the enol.

With our efforts to understand the relation between the structure and the stability of enols, we expanded substrates with groups at the beta position to more common groups, such $–NO_2$,–CN, Me and CF_3 to react with DEAD (Fig. 9). Substrates with electron withdrawing group, such as, CN and NO_2 readily performed with DEAD in the present of quinine, giving **7a** and **7b** with good yields (entries 1 and 2). Each one of **7a** and **7b** showed one signal through the chiral column on HPLC, which means two enol form compounds were yielded. However, when we used propiophenone as a substrate to react with DEAD in the presence of quinine and Cs_2CO_3, only trace amount of product was determined after 24 h (entry 3). This is probably because the reaction can't be carried out with this condition[51]. For the same reason entry 4 can't work either.

Discussion

As a conclusion, an efficient method to prepare stable enols was introduced and series of acyclic aliphatic solid enols were synthesized. The relationship between structure and the stability of enols was discussed. We found that groups beta to the carbonyl in substrates are important to formation of enols, because these groups could either balance the electron by the p-π conjugation and π-π conjugation or could form intramolecular hydrogen bond with OH. With our method, stable acyclic aliphatic solid enols were easily obtained as only products. Notably, all of the enols synthesized can be stably maintained in normal condition. Gaussian 09 calculations had been carried out by using enols mentioned in this paper and their keto isomers as models structures, proving that enol forms are more predominant than their keto forms in energy. These enol structures are confirmed by ^{1}H NMR, ^{13}C NMR, MS, partly by single crystal



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Entry	R^1	R^2	Products	Yield(%)[b]
1	^{t}Bu	CN	**7a**	89
2	Ph	NO_2	**7b**	98
3	Ph	Me	-	trace
4	Me	CF_3	-	trace

[a] All reactions were carried out in DCM with 1 mmol of **6** and 1 mmol of DEAD in the presence of 2 mol % of quinine and 2 mol% of Cs_2CO_3 for 4 h.
[b] Isolated yields.

Figure 9 | Expansion of carbonyls 6 with DEAD[a].

X-ray structure analysis and the protons exchange experiments. We believe this is a complete study on an important species in organic synthesis. Further studies about other types of stable enols are currently under investigation and will be presented in a due time.

Methods

All calculations were carried out with the Gaussian 09 programs. The geometrical optimizations of all the complexes were performed using M05-2X with the 6–31G** basis set for all atoms. Frequency calculations at the same level were performed to confirm each stationary point to be a minimum. The free energies of solvation in this study were calculated based on the gas phase optimized structures with the polarizable continuum model (PCM) using UA0 radii. The dielectric constant in the PCM calculations was set to 8.93 to simulate dichloromethane (CH_2Cl_2), the solvent medium in the experiments. The single point energies were also computed using the M05-2X method with the 6–311++G** basis set for all atoms. The report free energies and enthalpies include zero-point energies and thermal corrections calculated at 298.15K and 1 atm.

Unless otherwise noted, materials were used as commercial suppliers. All solvents were purified by standard method. Flash column chromatography was performed using 200–300 mesh silica gel.

Reaction progress was followed by TLC analysis at 254 nm. NMR spectroscopy was performed on 400 MHz spectrometer operating at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR). TMS was used as an internal standard and $CDCl_3$ was used as the solvent ^{1}H NMR data were reported as follows: chemical shifts in ppm downfield from tetramethylsilane, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad), J = coupling constant. IR spectra were recorded by using KBr optics. All the reagents are used directly from commercial and without further purification.

General procedure for the synthesis of all enols. To a solution of carbonyl compounds (1.0 mmol) in CH_2Cl_2, azodicarboxylates (1.0 mmol) was added. And followed by the addition of quinine (0.02 mmol) and Cs_2CO_3 (0.02 mmol). The mixture was stirred for 4–8 h at room temperature. The reaction was monitored by TLC (ethyl acetate : petroleum ether = 1:5 V/V). After evaporation of the solvents, the residue was purified by silica gel column chromatography (ethyl acetate : petroleum ether = 1:5 V/V). Full experimental details and the characterization data for all the compounds are given in the Supplementary Information.

1. Rappoport, Z. & Biali, S. E. Sterically crowded stable simple enols. *Acc. Chem. Res.* **21**, 442–449 (1988).
2. Kresge, A. J. Carboxylic acid enols and other unstable species. *Chem. Soc. Rev.* **25**, 275–280 (1996).
3. Hart, H. Simple enols. *Chem. Rev.* **79**, 515–528 (1979).
4. Erlenmeyer, E. Verhalten der Glycerinsäure und der weinsäure gegen wasserentziehende substanzen. *Chem. Ber.* **14**, 320–323 (1881).
5. Fuson, R. C., Corse, J. & McKeever, C. H. A stable vinyl alcohol, 1, 2-dimesityl-1-propen-1-ol. *J. Am. Chem. Soc.* **62**, 3250–3251 (1940).
6. Fuson, R. C., Armstrong, L. J., Chadwick, D. H., Kneisley, J. W., Rowland, S. P., Shenk Jr.,W. J., Soper, Q. F. & Vinyl alcohols, X. V. trisubstituted vinyl alcohols. *J. Am. Chem. Soc.* **67**, 386–393 (1945).
7. Piers, E. & Friesen, R. W. Annulations leading to diene systems. Total synthesis of the diterpenoid (±)–(14*S*)-dolasta -1(15),7,9-trien-14-ol. *J. Org. Chem.* **51**, 3405–3406 (1986).
8. Carling, R. W. & Holmes, A. B. A new synthetic method for the preparation of 2, 8 - disubstituted oxocane derivatives: synthesis of lauthisan and laurenan. *J. Chem. Soc. Chem. Commun.* 565–567 (1986).
9. Paquette, L. A. & Belmont, D. T. Synthetic studies aimed at the dolastanes. An attempted A + C. fwdarw. ABC approach. *J. Org. Chem.* **50**, 4102–4107 (1985).
10. Kol′tsov, A. & Kheifets, G. M. Investigation of keto-enol tautomerism by nuclear magnetic resonance spectroscopy. *Russ. Chem. Rev. (End. Transl.)* **40**, 773–788 (1971).
11. Knapp, W. & Tullius, T. D. Oxidative strand scission of nucleic acids: routes initiated by hydrogen abstraction from the sugar moiety. *Chem. Rev.* **98**, 1089–1108 (1998).
12. Burrows, C. J. & Muller, J. G. Oxidative nucleobase modifications leading tostrand scission. *Chem. Rev.* **98**, 1109–1152 (1998).
13. Newcomb, M., Miranda, N., Huang, X. & Crich, D. Laser flash photolysis kinetic studies of α-methoxy-β-phosphatoxyalkyl radical heterolysis reactions: a method for alkoxyalkyl radical cation detection. *J. Am. Chem. Soc.* **122**, 6128–6129 (2000).
14. Müller, S. N. *et al.* Chemistry of C-2 glyceryl radicals: indications for a new mechanism of lipid damage. *J. Am. Chem. Soc.* **119**, 2795–2803 (1997).
15. Stubbe, J. & Van der Donk, W. A. Protein radicals in enzyme catalysis. *Chem. Rev.* **98**, 705–762 (1998).
16. Smith, D. M., Golding, B. T. & Radom, L. Understanding the mechanism of B_{12}-dependent diol dehydratase: a synergistic retro-push-pull proposal. *J. Am. Chem. Soc.* **123**, 1664–1675 (2001).
17. Smith, D. M., Golding, B. T. & Radom, L. Toward a consistent mechanism for diol dehydratase catalyzed reactions: an application of the partial-ptroton-transfer concept. *J. Am. Chem. Soc.* **121**, 5700–5704 (1999).
18. Cook, G. & Feltman, P. M. Determination of solvent effects on keto-enol equilibria of 1,3-dicarbonyl compounds using NMR. Revisiting a classic physical chemistry experiment. *J. Chem. Edu.* **84**, 1827–1829 (2007).
19. Moon, S. & Kwon, Y. Theoretical studies of the equilibria between two enolic forms of asymmetric β–diketones. *Magn. Reson. Chem.* **39**, 89–93 (2001).
20. Lee, D., Kim, C. K., Lee, B.-S. & Lee, I. A theoretical study on keto-enol tautomerization involving simple carbonyl derivatives. *J. Comput. Chem*, **18**, 56–69 (1997).
21. Gorodetsky, M., Luz, Z. & Mazur, Y. Oxygen-17 nuclear magnetic resonance studies of the equilibria between the enol forms of β-diketones. *J. Am. Chem. Soc.* **89**, 1183–1189 (1967).
22. Iglesias, E. & Ojea-Cao, V. Effects of *β*-cyclodextrin on the keto-enol equilibrium of benzoylacetone and on enol reactivity. *J. Org. Chem.* **64**, 3954–3963 (1999).
23. Capon, B., Rycroft, D. S. & Watson, T. W. Generation of vinyl alcohol in solution and its slow conversion into acetaldehyde. *J. Chem. Soc. Chem. Commun.* 724–725 (1979).
24. Capon, B., Rycroft, D. S., Watson, T. W. & Zucco, C. Simple enols. 1. The generation of vinyl alcohol in solution and its detection and characterization by NMR spectroscopy. *J. Am. Chem. Soc.* **103**, 1761–1765 (1981).
25. Chiang, Y., Kresge, A. J. & Walsh, P. A. Ketonization of enols. Enol content and acid dissociation constants of simple carbonyl compounds. *J. Am. Chem. Soc.* **104**, 6122–6123 (1982).
26. Chiang, Y., Kresge, A. J., Tang, Y. S. & Wirz, J. The pKa and keto-enol equilibrium constant of acetone in aqueous solution. *J. Am. Chem. Soc.* **106**, 460–462 (1984).
27. Iglesias, E. Determination of keto-enol equilibrium constants and the kinetic study of the nitrosation reaction of *β*-dicarbonyl compounds. *J. Chem. Soc. Perkin Trans. 2* **0**, 431–440 (1997).
28. Langer, P. & Bose, G. [3+3] Cyclizations of 1, 3 - bis(silyl enol ether)s with 1,1-diacetylcyclopentane and 1,1-diacetylcyclopropane. *Angew. Chem. Int. Ed.* **42**, 4033–4036 (2003).
29. Lane, C. A. & Green, T. K. Usnic acid and the intramolecular hydrogen bond. a computational experiment for the organic laboratory. *J. Chem. Edu.* **83**, 1046–1048 (2006).
30. Bogdan, E. *et al.* Solvent effects on the second-order nonlinear optical responses in the keto-enol equilibrium of a 2-Hydroxy-1-naphthaldehyde derivative. *J. Phys. Chem. C* **114**, 12760–12768 (2010).
31. Iglesias, E. Tautomerization of 2-acetylcyclohexanone. 1. Characterization of keto-enol/enolate equilibria and reaction rates in water. *J. Org. Chem.* **68**, 2680–2688 (2003).
32. Perrin, C. L. & Kim, Y.-J. Symmetry of the hydrogen bond in malonaldehyde enol in solution. *J. Am. Chem. Soc.* **120**, 12641–12645 (1998).
33. Burdett, J. L. & Rogers, M. T. Keto-enol tautomerism in *β*-dicarbonyls studied by nuclear magnetic resonance spectroscopy. III. studies of proton chemical Shifts and equilibrium constants at different temperatures. *J. Phys. Chem.* **70**, 939–941 (1966).
34. Yamabe, S., Tsuchida, N. & Miyajima, K. Reaction paths of keto-enol tautomerization of *β*-diketones. *J. Phys. Chem. A* **108**, 2750–2757 (2004).
35. Fokendt, M. M., Weiss-Lopez, B. E., Cbauvel, Jr., J. P. & True, N. S. Gas-phase ^{1}H NMR studies of keto-enol tautomerism of acetylacetone, methyl acetoacetate, and ethyl acetoacetate. *J. Phys. Chem.* **89**, 3347–3352 (1985).
36. Watanabe, S., Goto, K., Kawashima, T. & Okazaki, R. An endohedral simple enol: the first isolation of α,β-unsubstituted simple enol utilizing a lantern-shaped molecular framework. *J. Am. Chem. Soc.* **119**, 3195–3196 (1997).
37. Pratt, D. V. & Hopkins, P. B. Isolation and characterization of a stable simple enol. *J. Am. Chem. Soc.* **109**, 5553–5554 (1987).
38. Dahn, H. & Rotzler, G. Unstable 1,1,2-enetriols as (probable) entermediates in the decarboxylation of *α,β*-diketo acids. *J. Org. Chem.* **56**, 3080–3082 (1991).
39. Lawrence, A. J., Hutchings, M. G., Kennedy, A. R. & McDouall, J. J. W. Benzodifurantrione: a stable phenylogous enol. *J. Org. Chem.* **75**, 690–701 (2001).
40. Hart, H. & Sasaoka, M. Simple enol:how rare are they. *J. Chem. Educ.* **57**, 685–688 (1980).
41. Diels, O. Über die azo-ester-reaktion der amine und enole. *Ber.* **55B**, 1524 (1922).
42. Nelson, J. H., Howells, P. N., DeLullo, G. C. & Landen, G. L. Nickel-catalyzed michael additions of *β*-dicarbonyls. *J. Org. Chem.* **45**, 1246–1249 (1980).
43. Meseguer, M., Moreno-Mañas, M. & Vallribera, A. Conjugate addition to diethyl azodicarboxylate under organic-perfluorinated biphasic homogeneous catalysis by nickel (II) species. *Tetrahedron Lett.* **41**, 4093–4095 (2000).
44. Yadav, J. S., Subba Reddy, B. V., Venugopal, C. & Padmavani, B. $InCl_3/SiO_2$-catalyzed *a*-amination of 1,3-dicarbonyl compounds under microwave irradiation. *Tetrahedron Lett.* **45**, 7507–7509 (2004).
45. Wilson, R. M., Hengge, A. C. Ataei, A. & Chantarasiri, N. Addition of 4-phenyltriazolinedione to carbonyl compounds: the formation of a-urazolylcarbonyl compounds. *J. Org. Chem.* **55**, 193–197 (1990).
46. Sanna, D., Varnágy, K., Timári, S., Micera, G. & Garribba, E. VO^{2+} Complexation by Bioligands Showing Keto_Enol Tautomerism: A Potentiometric, Spectroscopic, and Computational Study. *Inorg. Chem.* **50**, 10328–10341 (2011).
47. Acton, A. W., Allen, A. D., Antunes, L. M., Fedorov, A. V., Najafian, K., Tidwell, T. T. & Wagner, B. D. Amination of Pyridylketenes: Experimental and Computational Studies of Strong Amide Enol Stabilization by the 2-Pyridyl Group. *J. Am. Chem. Soc.* **124**, 13790–13794 (2002).
48. Chin, W., Mons, M., Piuzzi, F., Tardivel, B., Dimicoli, I., Gorb, L. & Leszczynski, J. Gas Phase Rotamers of the Nucleobase 9-Methylguanine Enol and Its

Monohydrate: Optical Spectroscopy and Quantum Mechanical Calculations. *J. Phys. Chem. A* **108**, 8237–8243 (2004).
49. Pérez, P. & Toro-Labbé, A. Characterization of Keto-Enol Tautomerism of Acetyl Derivatives from the Analysis of Energy, Chemical Potential, and Hardness. *J. Phys. Chem. A* **104**, 1557–1562 (2000).
50. Solans-Monfort, X., Bertran, J., Branchadell, V. & Sodupe, Mariona. Keto-Enol Isomerization of Acetaldehyde in HZSM5. A Theoretical Study Using the ONIOM2 Method. *J. Phys. Chem. B* **106**, 10220–10226 (2002).
51. Licandro, E. & Perdicchia, D. *N*-acylhydrazines: future perspectives offered by new syntheses and chemistry. *Eur. J. Org. Chem.* 665–675 (2004).

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