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Why is the reaction of ethyl (2-cyanoacetyl)carbamate with ethyl orthoformate highly stereoselective?

Kuangsen Sung,* Ming-Chi Lin, Pin-Mei Huang, Bo-Ren Zhuang, Robert Sung† and Ru-Rong Wu

Department of Chemistry, National Cheng Kung University, Tainan, Taiwan, Republic of China

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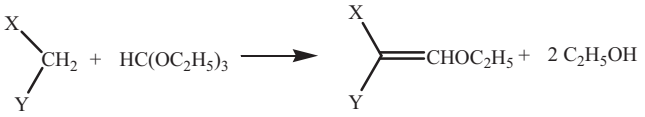
ABSTRACT: The reaction of ethyl (2-cyanoacetyl)carbamate (**1**) with ethyl orthoformate in the presence of acetic anhydride is highly stereoselective and only *E*-ethyl (2-cyano-3-ethoxyacryloyl)carbamate (*E*-**2**) is isolated. The reaction is thermodynamically controlled and the product distribution depends on the relative stability between *E*-**2** and *Z*-**2**. Both the resonance stabilization of 1.47 kcal mol^{-1} and the steric hindrance of 2.28 kcal mol^{-1} in favour of *E*-**2** contribute to the relative stability (3.75 kcal mol^{-1}) between *Z*-**2** and *E*-**2**, which is calculated from four isodesmic reactions, and this is the reason why the reaction of compound **1** with ethyl orthoformate is highly stereoselective. The electron-withdrawing ability of some substituents was evaluated. The sequence of π-accepting ability is C(O)NHC(O)OEt > C(O)NH$_2$ > CN and the sequence of σ-accepting ability is CN > C(O)NHC(O)OEt > C(O)NH$_2$.

KEYWORDS: isomerization; electron delocalization; stereoselective

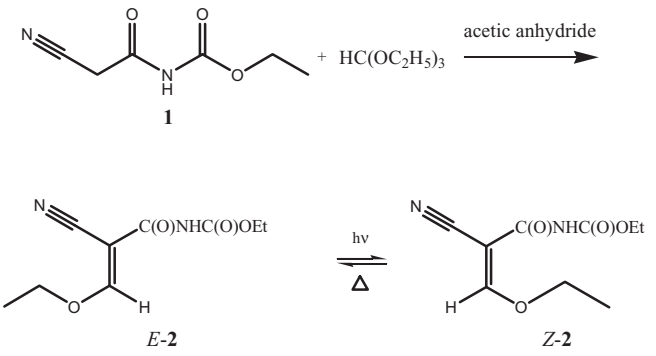
INTRODUCTION

One of the popular methods of preparing vinyl ethers is to treat active methylene compounds with ethyl orthoformate[1] [Eqn (1)]. Some of the reactions of this type are highly stereoselective but it was not until 1973 that Ceder and Stenhede figured out the configuration of the highly stereoselective product by NMR studies using a chemical-shift reagent Eu(fod)$_3$-d$_{27}$.[2] However, none of the literature reports on why this type of reaction is highly stereoselective.



(1)

To prepare an intermediate to uracil derivatives, ethyl (2-cyanoacetyl)carbamate (**1**) was treated with ethyl orthoformate in the presence of acetic anhydride in our laboratory and only *E*-ethyl (2-cyano-3-ethoxyacryloyl)-carbamate (*E*-**2**) was found [Eqn (2)]. This reaction is a good model to study why this type of reaction is highly stereoselective.



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COMPUTATION

All the calculations reported here were performed with the Gaussian 98 program.[3] Geometry optimizations of compounds *Z*-**2**, *Z*-**2a**, *E*-**2**, *E*-**2a**, *Z*-**3**, *E*-**3**, *Z*-**4**, *E*-**4,** *Z*-**5**, *E*-**5**, *Z*-**6**, *E*-**6**, *E*-**7**, **8**, **9** and **10** at the B3LYP/6-31+G* level and geometry optimizations of compounds **11a–11d** and **12a–12d** at the HF/6-31+G* level were carried out without any symmetry restriction. Optimized structures of compounds *Z*-**2**, *Z*-**2a**, *E*-**2**, *E*-**2a**, *Z*-**3**, *E*-**3**, *Z*-**4**, *E*-**4,** *Z*-**5**, *E*-**5**, *Z*-**6**, *E*-**6**, *E*-**7**, **8**, **9** and **10** at the B3LYP/6-31+G* level are shown in Figs 1 and 2. After all the geometry optimizations had been performed, analytical

**Correspondence to:* K. Sung, Department of Chemistry, National Cheng Kung University, Tainan, Taiwan, Republic of China
E-mail: kssung@mail.ncku.edu.tw
†Current address: Riverside Secondary School, 2215 Reeve Street, Port Coquitlan, B.C., Canada V3C6K8.
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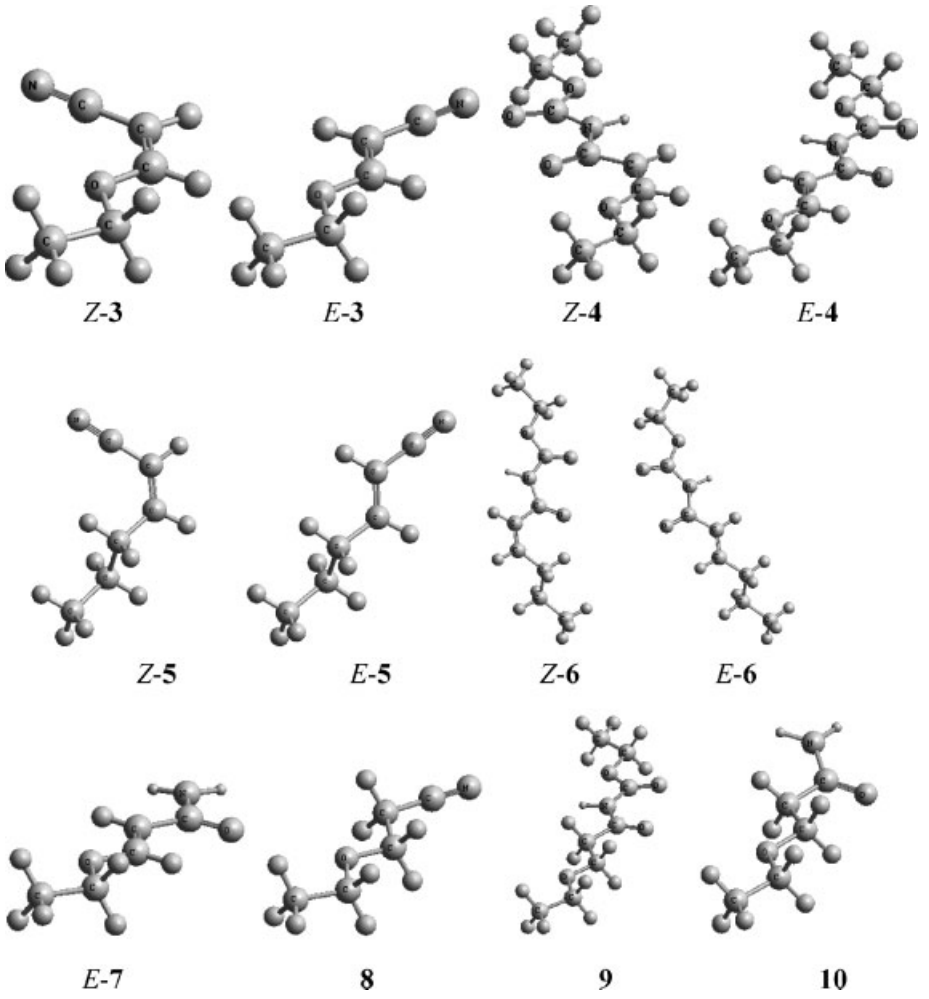


Figure. 1. Optimized structures of compounds *Z*-**3**, *E*-**3**, *Z*-**4**, *E*-**4,** *Z*-**5**, *E*-**5**, *Z*-**6**, *E*-**6**, *E*-**7**, **8**, **9** and **10** at the B3LYP/6-31+G* level

vibration frequencies were calculated at the same level to determine the nature of the located stationary points. Thus, all the stationary points found were characterized properly by evaluation of the harmonic frequencies. The single-point energies of the optimized structures of *Z*-**2** and *E*-**2** were calculated at the B3LYP/6-31+G*, HF/6-311++G(3df,3pd) or B3LYP/6-311++G(3df,3pd) level with scale zero-point vibration energies included. The single-point energies of the optimized structures of **11a–11d** and **12a–12d** were calculated at the MP2/6-31+G* level with scale zero-point vibration energies included. The scale factor of 0.9804 for zero-point vibration energies is used according to the literature.[4] Calculated energies of all the above structures are shown in Table 1.

RESULTS AND DISCUSSION

Reaction of compound **1** with ethyl orthoformate in the presence of acetic anhydride in chloroform was carried out under reflux for 2 h and only *E*-**2** was isolated in 75% yield. No trace of *Z*-**2** has been found. In *E*-**2**, the ^{3}J coupling constant between the vinyl proton and the nitrile carbon is 11 Hz whereas that between the vinyl proton and amide carbon is 2 Hz, indicating that the vinyl proton is *trans* to the nitrile group.[5] The configuration assignment for *E*-**2** is consistent with that made by Ceder and Stenhede.[2]

After 2 h of ultraviolet irradiation at $\lambda = 254$ nm, 40% of *E*-**2** was isomerized to *Z*-**2**. Two days after stopping the irradiation, most of the *Z*-**2** was isomerized back to *E*-**2** at room temperature. The *E*-**2** cannot be isomerized to *Z*-**2** thermally but it can photochemically whereas *Z*-**2** can be isomerized back to *E*-**2** thermally. This implies that the reaction of compound **1** with ethyl orthoformate in the presence of acetic anhydride is very likely to be under thermodynamic control.

Whether the β-ketoester part of *E*-**2** stays as the keto or enol form is important for the configuration assignment. On applying NMR of ^{1}H–^{15}N HSQC an off-diagonal cross-peak shows a correlation between hydrogen at δ 9.20 and urethane nitrogen at δ 138.6 by means of their spin–spin coupling, indicating that *E*-**2** stays as the keto

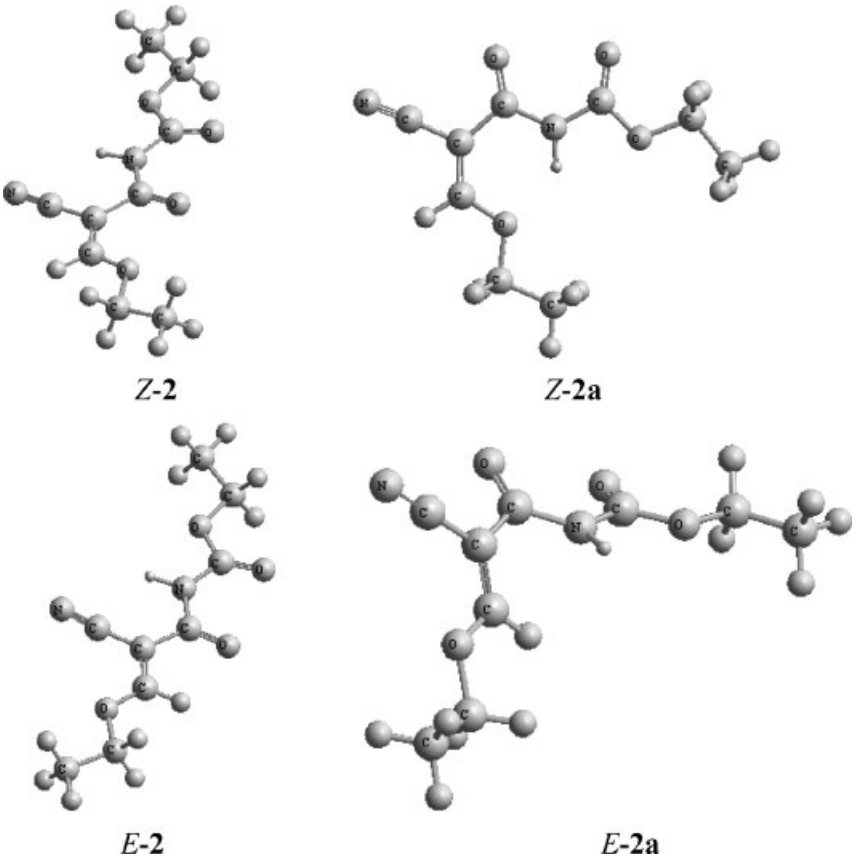


Figure 2. Optimized structures of compounds *Z*-**2**, *Z*-**2a**, *E*-**2** and *E*-**2a** at the B3LYP/6-31+G* level

form. The results have been found with solvents such as acetone-d_6, acetonitrile-d_3 and $CDCl_3$. Based on the NMR results, *Z*/*E*-isomers of **2** were optimized at the B3LYP/6-31+G* level and at least two interesting conformers were located for each of the geometric isomers (Fig. 2). Conformers *Z*-**2** and *Z*-**2a** were located for the *Z*-isomer of **2**, and *Z*-**2** is 0.60 kcal mol^{-1} (1 kcal = 4.184 kJ) more stable than *Z*-**2a**. Conformers *E*-**2** and *E*-**2a** were located for the *E*-isomer of **2**, and *E*-**2** is 7.36 kcal mol^{-1} more stable than *E*-**2a**. The backbones of *Z*-**2**, *Z*-**2a** and *E*-**2** stay in the same plane whereas the C(O)NHC(O)OEt group is twisted away from the plane of the rest of the structure in *E*-**2a**. The major structure difference of the conformers is the dihedral angle of C═C—C═O. The more stable conformers (*Z*-**2** and *E*-**2**) have the s-*cis* conformation of C═C—C═O, so they can pull the bulky C(O)NHC(O)OEt group away from the vinyl hydrogen or ethoxy group to avoid steric hindrance.

Table 1. Calculated energies *E* (hartrees) of compounds *Z*-**2**, *Z*-**2a**, *E*-**2**, *E*-**2a**, *Z*-**3**, *E*-**3**, *Z*-**4**, *E*-**4,** *Z*-**5**, *E*-**5**, *Z*-**6**, *E*-**6**, *E*-**7**, **8**, **9**, **10**, **11a**–**11d** and **12a**–**12d**

Compound	*E*	Compound	*E*	Compound	*E*	Compound	*E*
Z-**2**	−760.39510[a] (μ = 3.61 D)[a] −756.20947[b] (μ = 4.05 D)[b] −760.64792[c] (μ = 3.52 D)[c]	*Z*-**2a**	−760.39415[a] (μ = 11.46 D)[a]	*E*-**2**	−760.40220[a] (μ = 3.11 D)[a] −756.21758[b] (μ = 3.50 D)[b] −760.65472[c] (μ = 3.12 D)[c]	*E*-**2a**	760.39047[a] (μ = 10.32 D)[a]
Z-**3**	−324.58158[a]	*E*-**3**	−324.58279[a]	*Z*-**4**	−668.14732[a]	*E*−**4**	−668.15450[a]
Z-**5**	−288.65880[a]	*E*-**5**	−288.65914[a]	*Z*-**6**	−632.22523[a]	*E*-**6**	−632.22920[a]
E-**7**	−401.02284[a]	**8**	−325.78183[a]	**9**	−669.35125[a]	**10**	−402.22028[a]
11a	−327.96330[d]	**11b**	−419.98200[d]	**11c**	−496.19390[d]	**11d**	−762.54350[d]
12a	−328.32998[d]	**12b**	−420.32998[d]	**12c**	−496.55515[d]	**12d**	−762.90122[d]

[a] B3LYP/6-31+G*//B3LYP/6-31+G*. At this level, $E(Z\text{-}\mathbf{2}) - E(E\text{-}\mathbf{2}) = 4.5$ kcal mol^{-1} (1 kcal = 4.184 KJ).
[b] HF/6-311++G(3df,3pd)//B3LYP/6-31+G*. At this level, $E(Z\text{-}\mathbf{2}) - E(E\text{-}\mathbf{2}) = 5.1$ kcal mol^{-1}.
[c] B3LYP/6-311++G(3df,3pd)//B3LYP/6-31+G*. At this level, $E(Z\text{-}\mathbf{2}) - E(E\text{-}\mathbf{2}) = 4.3$ kcal mol^{-1}.
[d] MP2/6-31+G*//HF/6-31+G*.

The less stable conformers (*Z*-**2a** and *E*-**2a**) have the s-*trans* conformation of C═C—C═O, causing significant steric hindrance between the bulky C(O)NHC(O)OEt group and the vinyl hydrogen or ethoxy group. To reduce the steric hindrance, *E*-**2a** twists C(O)NHC(O)OEt away from the C═C plane (dihedral angle of C═C—C═O = 145.4°) but loses resonance stabilization along the ethoxy, C═C and C(O)NHC(O)OEt groups, which makes it 2.31, 2.91 and 7.36 kcal mol^{-} less stable than *Z*-**2a**, *Z*-**2** and *E*-**2**, respectively, implying that there is intramolecular hydrogen bonding between the N—H group and the oxygen of the ethoxy group in *Z*-**2a**. In *Z*-**2a**, the C(O)NHC(O)OEt group stays in the same plane as the moiety of ethyl vinyl ether in spite of steric hindrance between the C(O)NHC(O)OEt and ethoxy groups, and the distance between the hydrogen of the N—H group and the oxygen of the ethoxy group is 1.97 Å, indicating that it has intramolecular hydrogen bonding, which means that *Z*-**2a** is only 0.6 kcal mol^{-1} less stable than *Z*-**2**.

Calculated thermodynamic data of the conformational isomerization for *Z*/*E* isomers of compound **2** are shown in Table 2. According to the relationship $\Delta G = -RT(\ln K)$,[6] a $\Delta G(298\,\mathrm{K})$ value of -1.77 kcal mol^{-1} indicates that around 95% of the *Z*-isomer of **2** stays as *Z*-**2**, and around 99.99% of the *E*-isomer of **2** stays as *E*-**2** due to a $\Delta G(298\,\mathrm{K})$ value of -6.67 kcal mol^{-1}. According to experimental results, isomerization of **2** from the *Z*-isomer to the *E*-isomer is spontaneous at room temperature but calculated free energies of *Z*/*E* isomerization from *Z*-**2** to *E*-**2a** or from *Z*-**2a** to *E*-**2a** are 3.24 and 1.47 kcal mol^{-1}, respectively, indicating that these two processes are not thermodynamically favourable and *E*-**2a** is much less stable than *Z*-**2** and *Z*-**2a**. On the other hand, calculated free energies of *Z*/*E* isomerization from *Z*-**2** to *E*-**2** or from *Z*-**2a** to *E*-**2** are -3.43 and -5.19 kcal mol^{-1}, respectively, which are consistent with experimental results and much more negative than -0.62 kcal mol^{-1} for *Z*/*E* isomerization of 2-butene.[7] Because around 95% of the *Z*-isomer of **2** stays as *Z*-**2**, the process from *Z*-**2** to *E*-**2** is considered. Negative entropy is not favourable for this isomerization from *Z*-**2** to *E*-**2** but favourable enthalpy dominates this isomerization. Therefore, to answer the question of why the reaction of **1** with ethyl orthoformate is highly stereoselective, one needs to look further into the relative stability between *Z*-**2** and *E*-**2**.

Table 2. Calculated energies ΔE (kcal mol^{-1}), enthalpies (kcal mol^{-1}), entropies (cal mol^{-1} K^{-1}) and free energies (kcal mol^{-1}) of *Z*/*E* and conformational isomerization of compound **2** at the B3LYP/6-31+G*//HF/6-31+G* level

	ΔE	$\Delta H(298\,\mathrm{K})$	$\Delta S(298\,\mathrm{K})$	$\Delta G(298\,\mathrm{K})$
Z-**2** → *E*-**2**	−4.46	−4.29	−2.87	−3.43
Z-**2** → *E*-**2a**	+2.91	+2.88	−1.22	+3.24
Z-**2a** → *E*-**2**	−5.05	−5.05	0.49	−5.19
Z-**2a** → *E*-**2a**	+2.31	+2.11	+2.14	+1.47
Z-**2a** ⇌ *Z*-**2**	−0.60	−0.77	+3.36	−1.77
E-**2a** ⇌ *E*-**2**	−7.36	−7.16	−1.65	−6.67

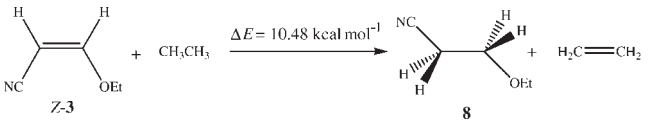
Single point energies of B3LYP/6-31+G*-optimized structures of *Z*-**2** and *E*-**2** at three different levels are shown in Table 1. Why is *E*-**2** 4.3–5.1 kcal mol^{-1} more stable than *Z*-**2**?. The relative stability of geometric isomers may be controlled by several factors such as intramolecular hydrogen bonding, dipole moment, steric hindrance, and electron delocalization, which will be discussed in order to explain the relative stability between *Z*-**2** and *E*-**2**.

Based on the optimized structure of *Z*-**2**, it is unlikely that *Z*-**2** has intramolecular hydrogen bonding. On the other hand, *Z*-**2a** does form intramolecular hydrogen bonding, but this stabilization effect is offset by steric hindrance between C(O)NHC(O)OEt and ethoxy groups, making *Z*-**2a** 0.6 kcal mol^{-1} less stable than *Z*-**2**. In *E*-**2**, the distance between the vinyl hydrogen and the oxygen of the amide moiety is 2.40 Å and the electronegativity of the vinyl carbon is not strong enough, so it is unlikely that *E*-**2** has intramolecular hydrogen bonding. Thus intramolecular hydrogen bonding is not important in explaining why *E*-**2** is much more stable than *Z*-**2**.

As shown in Table 1, the dipole moments of *Z*-**2** and *E*-**2** are 3.52 and 3.12 D, respectively, at the B3LYP/6-311++G(3df,3pd)//B3LYP/6-31+G* level. Dipole moments of chloroform and acetonitrile are 1.04 and 3.92 D,[8] and their dielectric constants are 4.81 and 36.6, respectively.[8] Chloroform is a non-polar aprotic solvent whereas acetonitrile is a dipolar aprotic solvent. Based on the useful rule of thumb of 'like dissolves like',[9] chloroform may stabilize *E*-**2** better than *Z*-**2** whereas acetonitrile may stabilize *Z*-**2** better than *E*-**2**. However, the reaction of **1** with ethyl orthoformate is highly stereoselective in both chloroform and acetonitrile, indicating that the dipole moment is not a major factor in making *E*-**2** much more stable than *Z*-**2**.

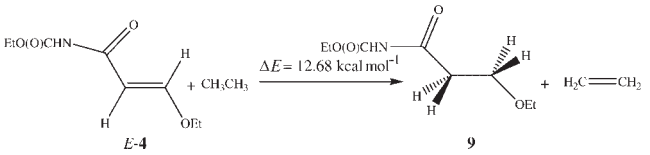
To investigate the contribution of resonance effects and steric hindrance to the stability of both *E*-**2** and *Z*-**2,** *E*-**2** is divided into two systems (*Z*-**3** and *E*-**4**) and *Z*-**2** is divided into another two systems (*E*-**3** and *Z*-**4**). The isodesmic reactions of Eqns (3)–(6) were designed to predict resonance stabilization in *Z*-**3**, *E*-**4**, *E*-**3** and *Z*-**4**, respectively. The isodesmic reaction in which the total number of each type of bond is identical in the reactants and products[4b] successfully predicts the heat of formation[4b] and substituent effects on the stability of functional groups.[10] To consider steric hindrance in *Z*-**2**, *E*-**2**, *Z*-**3** and *Z*-**4**, the *n*-propyl group replaces the ethoxy substituent and *Z*-**5**, *E*-**5**, *Z*-**6** and *E*-**6** were designed for a significant reduction in the resonance effect along two substituents across C═C. Thus, the steric hindrance in *Z*-**3** is close to that in *Z*-**5**, which is 0.21 kcal mol^{-1} according to Eqn (7), and the resonance stabilization in *Z*-**3** is $\sim$10.69 kcal mol^{-1} (= 10.48 + 0.21) based on Eqn (3). Similarly, the steric hindrance in *Z*-**4** is close to that in *Z*-**6**, which is equal to

2.49 kcal mol^{-1} based on Eqn (8), and the resonance stabilization in *Z*-**4** is ~10.66 kcal mol^{-1} (= 2.49 + 8.17) according to Eqn (6).



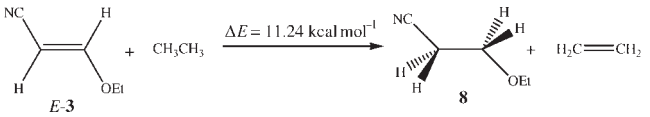
(3)

Z-**3**: steric hindrance ~0.21 kcal mol^{-1}; resonance stabilization ~10.69 kcal mol^{-1}



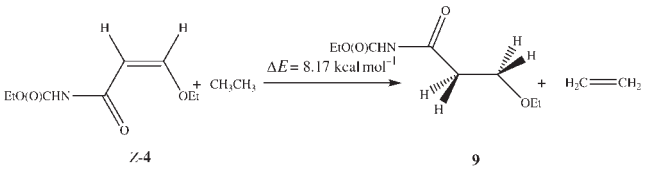
(4)

E-**4**: steric hindrance ~0.0 kcal mol^{-1}; resonance stabilization ~12.68 kcal mol^{-1}



(5)

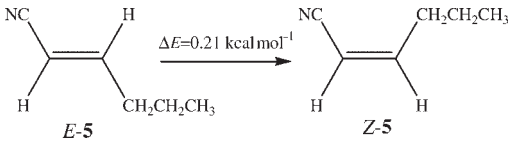
E-**3**: steric hindrance ~0.0 kcal mol^{-1}; resonance stabilization ~11.24 kcal mol^{-1}



(6)

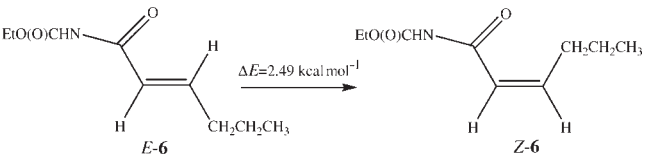
Z-**4**: steric hindrance ~2.49 kcal mol^{-1}; resonance stabilization ~10.66 kcal mol^{-1}

The contribution of resonance stabilization and steric hindrance in *E*-**2** can be estimated to be the sum of stabilization energies in Eqns (3) and (4), which is 23.16 kcal mol^{-1}. Similarly, the contribution of resonance stabilization and steric hindrance in *Z*-**2** presumably equals the sum of stabilization energies in Eqns (5) and (6), which is 19.41 kcal mol^{-1}. Thus, the energy difference between *E*-**2** and *Z*-**2**, which is calculated from these four isodesmic reactions, is 3.75 kcal mol^{-1} which is close to the energy difference (4.5 kcal mol^{-1}) of these two molecules calculated at the B3LYP/6-31+G* level.



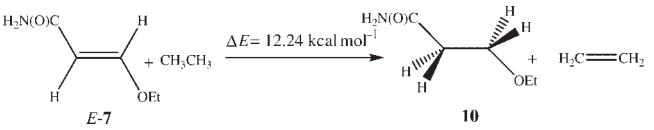
(7)

Z-**5**: steric hindrance ~0.21 kcal mol^{-1}



(8)

Z-**6**: steric hindrance ~2.49 kcal mol^{-1};



(9)

E-**7**: steric hindrance ~0.0 kcal mol^{-1}; resonance stabilization ~12.24 kcal mol^{-1}

To investigate the contribution of resonance effects and steric hindrance to the stability of *E*-**2** and *Z*-**2**, the isodesmic reactions of Eqns (3)–(8) are considered. Equations (7) and (8) show a small steric interaction (0.21 kcal mol^{-1}) with the cyano group *cis* to an *n*-propyl group, whereas there is a significant steric interaction of 2.49 kcal mol^{-1} with the C(O)NHC(O)OEt group *cis* to an *n*-propyl group. The difference (2.28 kcal mol^{-1}) is taken as the steric contribution to the energy difference between *E*-**2** and *Z*-**2**. The total energy difference between *E*-**2** and *Z*-**2** may be estimated as the stabilization energy difference of Eqn (3) + Eqn (4) − Eqn (5) − Eqn (6) = 3.75 kcal mol^{-1}, so the resonance stabilization for *E*-**2** relative to *Z*-**2** is estimated as 3.75−2.28 = 1.47 kcal mol^{-1}.

The *trans* delocalization energy from the ethoxy to the C(O)NHC(O)OEt group in *E*-**4** is 12.68 kcal mol^{-1} based on Eqn (4), whereas the *trans* delocalization energy from the ethoxy to the nitrile group in *E*-**3** is 11.24 kcal mol^{-1} according to Eqn (5), indicating that the C(O)NHC(O)OEt group is a better π-acceptor than the nitrile group by 1.44 kcal mol^{-1}. Based on Eqn (9) the *trans* delocalization energy from the ethoxy to the C(O)NH_2 group in *E*-**7** is 12.24 kcal mol^{-1}, indicating that the C(O)NH_2 group is a better π-acceptor than the nitrile group by 1.00 kcal mol^{-1} but a worse π-acceptor than the C(O)NHC(O)OEt group by 0.44 kcal mol^{-1}. However, reported resonance substituent constants *R* (or σ_R) of nitrile and C(O)NH_2 are 0.15 and 0.10 by Hansch *et al.*[11a] and 0.08 and 0.08 by Charton,[11b] indicating that the resonance substituent constants vary with different models or solvents.

π-accepting ability: C(O)NHC(O)OEt > C(O)NH_2 > CN

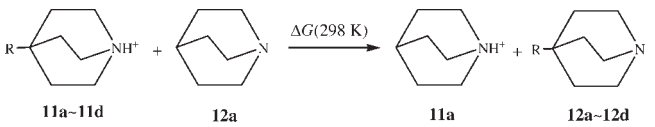
σ-accepting (inductive) ability: CN > C(O)NHC(O)OEt > C(O)NH_2

We successfully obtained field substituent constants from relative deprotonation Gibbs free energies of 4-substituted quinuclidinium ions **11** [Eqn (10)] by *ab initio* calculations at the CBS-4M level.[11] The relative deprotonation Gibbs free energies were rescaled by a factor of

Table 3. Relative deprotonation Gibbs free energies [ΔG(298 K), kcal mol^{-1})] of 4-substituted quinuclidinium ions **11a**–**11d** [Eqn (10)], the calculated field substituent constants (σ_F^G) at the MP2/6-31+G*//HF/6-31+G* and CBS-4M levels in the gas phase and Charton's inductive substituent constant (σ_I)[11b]

R	$-\Delta G$(298 K)	σ_F^G	σ_I
H	0.00 (0.00)	0.00 (0.00)	0.00
CN	11.61 (11.65)	0.66 (0.66)	0.57
$C(O)NH_2$	4.72 (4.21)	0.27 (0.24)	0.28
C(O)NHC(O)OEt	6.16	0.35	

$-1/17.53$ to become σ_F^G,[12] which is well correlated with Taft's σ_F and Charton's σ_I.[11] Now we obtain the field substituent constants of CN, $C(O)NH_2$, and C(O)NHC(O)OEt in the same way at the MP2/6-31+G*//HF/6-31+G* level. As shown in Table 3, both the CBS-4M and MP2/6-31+G*//HF/6-31+G* calculation levels give similar and coherent results. The σ_F^G of CN, $C(O)NH_2$ and C(O)NHC(O)OEt is 0.66, 0.27, and 0.35, respectively, indicating that the sequence of the inductive effect is CN > C(O)NHC(O)OEt > $C(O)NH_2$. It was reported that acetonitrile is three orders of magnitude more acidic than *N*,*N*-dimethylacetamide,[6] indicating that more of the acidity of acetonitrile is dominated by the inductive effect because the amide group is a better π-acceptor than the nitrile group.



(10)

11a,**12a**: R = H; **11b**,**12b**:R = CN; **11c**,**12c**: R = $C(O)NH_2$; **11d**,**12d**: R = C(O)NHC(O)OEt

CONCLUSION

The highly stereoselective reaction of **1** with ethyl orthoformate in the presence of acetic anhydride produces *E*-**2** only. The *E*-**2** cannot be isomerized to *Z*-**2** thermally but it can photochemically, whereas *Z*-**2** can be isomerized back to *E*-**2** thermally, indicating that the reaction of **1** with ethyl orthoformate is thermodynamically controlled. The calculated free energy of *Z*/*E* isomerization from *Z*-**2** to *E*-**2** is -3.43 kcal mol^{-1}, which is thermodynamically favourable and consistent with the experimental results. Negative entropy is not favourable for this isomerization, but favourable enthalpy dominates. Both the resonance stabilization of 1.47 kcal mol^{-1} and the steric hindrance of 2.28 kcal mol^{-1} in favor of *E*-**2** contribute to the energy difference (3.75 kcal mol^{-1}) between *Z*-**2** and *E*-**2** calculated from the four isodesmic reactions of Eqns (3)–(6), which causes the reaction of **1** with ethyl orthoformate to be highly stereoselective. The nitrile group is a better σ-acceptor than the C(O)NHC(O)OEt group, whereas the C(O)NHC(O)OEt group is a better π-acceptor than the nitrile group.

EXPERIMENTAL

General. Unless stated otherwise reagents were obtained from commercial suppliers and used as received. Ethyl (2-cyanoacetyl)carbamate (**1**), was prepared according to the literature method.[13]

E-*Ethyl (2-cyano-3-ethoxyacryloyl)carbamate* (*E*-**2**). To a solution of **1** (0.156 g, 1 mmol) and acetic anhydride (1 ml) in 2ml of chloroform, ethyl orthoformate (0.296 g, 2 mmol) was added. The mixture was refluxed at 80 °C under a nitrogen atmosphere for 2 h. After the reaction was complete, the reaction mixture was cooled down and concentrated by rotary evaporator. Ether was poured into the reaction mixture and the mixture stayed in the fridge for 12 h. After filtration of the mixture, a white powder was collected and recrystallized in chloroform–ether. Yield: 75%; ^{1}H NMR (CD_3CN), δ 1.23 (3H, t, CH_3), 1.34 (3H, t, CH_3), 4.12 (2H, q, CH_2), 4.39 (2H, q, CH_2), 8.17 (1H, s, CH), 9.12 (1H, s, NH); ^{13}C NMR ($CDCl_3$), δ 14.80, 15.87, 63.13, 75.69, 89.30, 114.69, 152.22, 162.01, 175.13; IR (thin film), 2227 (CN), 1774, 1689 (C═O) cm^{-1}; MS (EI) *m*/*z* 212 (4, M$^+$), 118 (100), 88 (32), 74 (24), 57 (28); HRMS (EI), *m*/*z* calc. for $C_9H_{12}N_2O_4$ 212.0797, found 212.0801.

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