Why do ethyl [2-cyano-3-(n-butylamino)acryloyl]carbamate and its analogues stay as *Z*-isomers only ?

Kuangsen Sung*, Robert Sung[‡], Michael Sung[§], and Bo-Ren Zhuang

Department of Chemistry, National Cheng Kung University, Tainan, Taiwan, ROC
E-mail: kssung@mail.ncku.edu.tw

Abstract

Density functional method and isodesmic reactions were used to explore relative stability between *Z*- and *E*-ethyl [2-cyano-3-(n-butylamino)acryloyl] carbamate (**3**). Hydrogen bonding stabilization (7.19 kcal/mol) in favor of *Z*-**3** and both steric hindrance (2.17 kcal/mol) and resonance stabilization (1.79 kcal/mol) in favor of *E*-**3** contribute the relative stability between *Z*-**3** and *E*-**3**, and that successfully explains why **3** stay as a *Z*-isomer only.

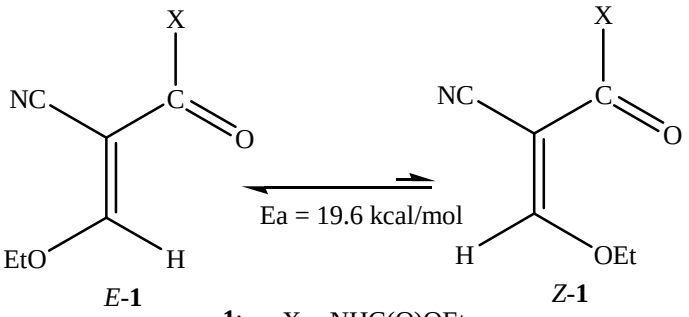
Keywords. Isodesmic reaction, *E*/*Z* isomerization, relative stability

Introduction

Isodesmic reactions are not real chemical reactions and can be set up according to the criterion that the total number of each type of bond is identical in the reactants and products.[1] They were designed to successfully predict the heat of formation,[1] substituent effects on the stability of functional groups,[2] and contribution of steric hindrance and resonance stabilization to the stability of *E*/*Z*-isomers[3a].

As shown in Scheme 1, ethyl (2-cyano-3-ethoxyacryloyl)carbamate (**1**)[3] and ethyl 2-cyano-3-ethoxyacrylate (**2**)[4] were found to stay as an *E*-isomer exclusively. *E*-**1** is much more stable than *Z*-**1** because of contribution of both resonance stabilization (1.47 kcal/mol) and steric hindrance (2.28 kcal/mol) in favor of *E*-**1**.[3a] These compounds are push-pull olefins,[5] and the barrier for the isomerization of *Z*-**1** to *E*-**1** was found as small as 19.6 kcal/mol experimentally.[3b]

[‡] Port Moody Secondary School, 300 Albert Street, Port Moody, BC V3H 2M5
[§] Pitt River Middle School, 2070 Tyner Street, Port Coquitlam, BC V3C 2Z1



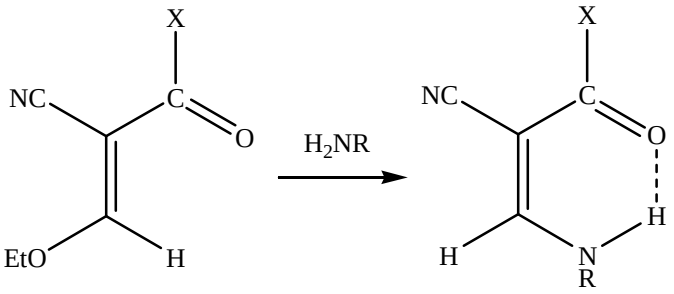
E-**1** *Z*-**1**

1: X = NHC(O)OEt

2: X = OEt

Scheme 1

When we treated *E*-**1** with *n*-$BuNH_2$, *t*-$BuNH_2$, or aniline in $CDCl_3$ and monitored the reactions with NMR spectrometry, we found that both *E*- and *Z*-isomers of **3**, **4**, or **5** were formed at the beginning but eventually all the *E*-isomers were converted to the corresponding the *Z*-isomers.[6] (Scheme 2) It is clear that **3**, **4**, or **5** are all push-pull olefins and the isomerization barriers from the *E*-isomers to the *Z*-isomers should be low, so the *E*/*Z* isomerization is feasible at room temperature. In contrast to the fact that **1** completely stays as an *E*-isomer (Scheme 1), its nitrogen analogues **3**, **4**, and **5** exist as *Z*-isomers exclusively. To explain these facts, **3** was used as a model compound. We explored relative stability between *Z*-**3** and *E*-**3** and analyzed the contribution of steric hindrance, resonance stabilization, and hydrogen bonding stabilization to the stability of *Z*-**3** and *E*-**3** by means of density functional method and isodesmic reactions.



E-**1** *Z*-**3**, *Z*-**4**, or *Z*-**5**

E-**1**: X = NHC(O)OEt

Z-**3**: X = NHC(O)OEt, R = *n*-Bu

Z-**4**: X = NHC(O)OEt, R = *t*-Bu

Z-**5**: X = NHC(O)OEt, R = Ph

Scheme 2

Computation

All the calculations reported here were performed with Gaussian98 program.[7] All the structures of *Z*-**3**, *Z*-**3a**, *E*-**3**, *E*-**3a**, *Z*-**4**, *E*-**4**, *Z*-**5**, *E*-**5**, *Z*-**6**, *E*-**6**, *Z*-**7**, *E*-**7**, **8**, **9**, *Z*-**10**, *E*-**10**, *Z*-**11**, *E*-**11**, and **12** were optimized at level of B3LYP/6-31+G* without any symmetry restriction except that C-F, C=C and C=O of *Z*-**11** and *E*-**11** were kept in the same plane in order to mimic *Z*-**10** and *E*-**10**. Vibration frequencies and zero-point vibration energies were calculated at the same level, and the zero-point vibration energies are scaled by 0.9804 according to the literatures.[1] Their calculated energies are shown in Table 1. Many possible conformations have been optimized for each of the structures and the one with lowest energy was chosen.

Table 1. Calculated energies E (hartrees), relative energies ΔE (kcal/mol), and dipole moment μ (debye) of *Z*-**3**, *Z*-**3a**, *E*-**3**, *E*-**3a**, *Z*-**4**, *E*-**4**, *Z*-**5**, *E*-**5**, *Z*-**6**, *E*-**6**, *Z*-**7**, *E*-**7**, **8**, **9**, *Z*-**10**, *E*-**10**, *Z*-**11**, *E*-**11**, and **12** at B3LYP/6-31+G* level

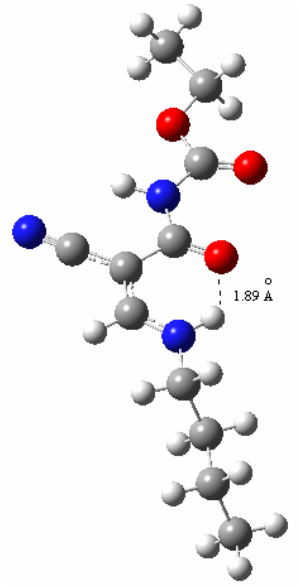
	E (ΔE) (μ)		**E (ΔE) (μ)**		**E (ΔE) (μ)**		**E (ΔE) (μ)**
Z-3	**-819.11874 (0.00) (3.97D)**	*Z*-3a	**-819.09653 (13.9)(11.4D)**	*E*-3	**-819.11338 (3.36) (4.87D)**	*E*-3a	**-819.10195 (10.5) (10.5D)**
Z-4	**-383.28824 (0.00)**	*E*-4	**-383.28560 (1.66)**	*Z*-5	**-726.86546 (0.00)**	*E*-5	**-726.85767 (4.89)**
Z-6	**-367.23231 (0.27)**	*E*-6	**-367.23274 (0.00)**	*Z*-7	**-710.79880 (2.44)**	*E*-7	**-710.80269 (0.00)**
8	**-384.47493**	9	**-728.04354**	*Z*-10	**-826.02078 (11.5)**	*E*-10	**-826.03909 (0.00)**
Z-11	**-810.03441 (11.6)**	*E*-11	**-810.05294 (0.00)**	12	**-827.24078**		

Results and Discussion

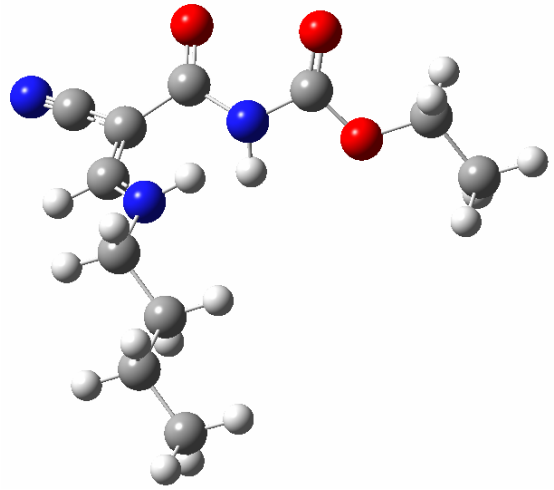
As shown in Fig. 1, major conformers, *Z*-**3** and *Z*-**3a**, were located for the *Z*-isomer of **3**, and *Z*-**3** is 13.9 kcal/mol more stable than *Z*-**3a**. All the enamine, nitrile, and C(O)NHC(O)OEt groups of *Z*-**3** stay in a plane with an intramolecular hydrogen bonding of NH--O=C whose distance is 1.89Å. However, in *Z*-**3a** the C(O)NHC(O)OEt group is twisted away from its molecular plane formed by enamine and nitrile groups in order to avoid steric hindrance with the amino group.

Major conformers, *E*-**3** and *E*-**3a**, were located for the *E*-isomer of **3** (Fig. 1), and *E*-**3** is 7.17 kcal/mol more stable than *E*-**3a**. All the enamine, nitrile, and C(O)NHC(O)OEt groups of *E*-**3** stay in a plane but there is no intramolecular hydrogen bonding. In contrast, in *E*-**3a** the C(O)NHC(O)OEt group is twisted away from its molecular plane formed by enamine and nitrile groups in order to avoid steric hindrance with the vinyl hydrogen. Based on the above analysis,

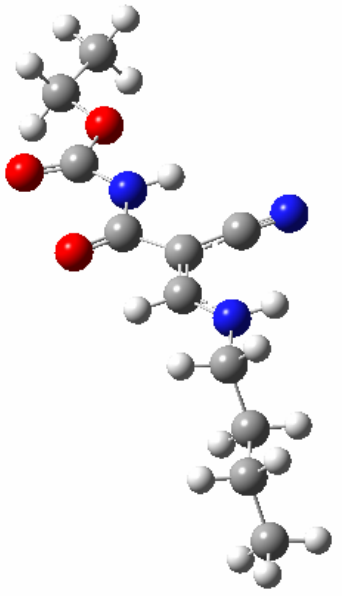
the more stable conformers for *Z*- and *E*-isomer of **3** are *Z*-**3** and *E*-**3**, respectively, which have a common structure feature: s-*cis* conformation for C=C-C=O. By this way, they can pull the C(O)NHC(O)OEt group away from vinyl hydrogen or the amino group to avoid steric hindrance.



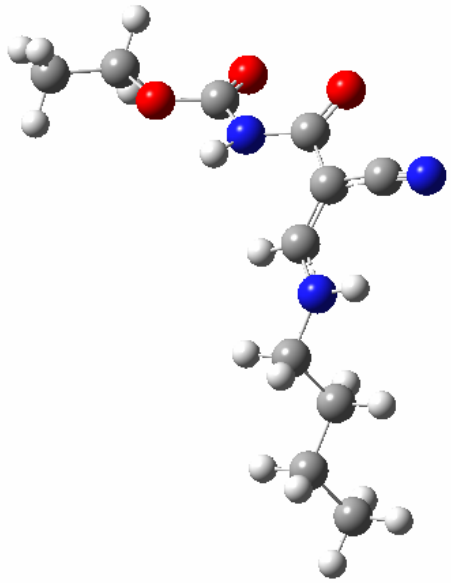
Z-**3**



Z-**3a**



E-**3**



E-**3a**

Figure 1. Optimized structures of *Z*-**3**, *Z*-**3a**, *E*-**3**, and *E*-**3a** at the B3LYP/6-31+G* level.

Table 2. Calculated thermodynamic data for the conformational and *E*/*Z* configurational isomerizations of **3** at the B3LYP/6-31+G* level

	ΔE (kcal/mol)	ΔH (kcal/mol)	ΔS(calmol^{-1}K^{-1})	ΔG (kcal/mol)
E-**3a** → *E*-**3**	-7.17	-6.98	-0.47	-6.84
Z-**3a** → *Z*-**3**	-13.9	-13.7	-5.16	-12.2
E-**3** → *Z*-**3**	-3.36	-3.31	-2.25	-2.64
E-**3a** → *Z*-**3**	-10.5	-10.3	-2.72	-9.49
E-**3** → *Z*-**3a**	10.6	10.4	2.91	9.51
E-**3a** → *Z*-**3a**	3.40	3.40	2.44	2.67

Calculated thermodynamic data for the conformational and *E*/*Z* configurational isomerizations of **3** at the B3LYP/6-31+G* level are shown in Table 2. Experimental results indicate that *E*/*Z* isomerization of **3** from the *E*-isomer to the *Z*-isomer is spontaneous at room temperature,[6] but calculated ΔG values of *E*/*Z* isomerization from *E*-**3** to *Z*-**3a** or from *E*-**3a** to *Z*-**3a** are 9.51 and 2.67 kcal/mol, respectively, indicating that these two thermodynamically unfavorable processes are not consistent with the experimental results. On the other hand, calculated ΔG values of *E*/*Z* isomerizations from *E*-**3** to *Z*-**3** or from *E*-**3a** to *Z*-**3** are -2.64 and -9.49 kcal/mol, respectively, indicating that these two processes are thermodynamically favorable. In addition, more than 99.99% of *E*-isomers of **3** stay as *E*-**3**, based on the equation of ΔG = -RT(*ln*K)[8] and its ΔG value of -6.84 kcal/mol. Therefore, *E*/*Z* isomerization of **3** from the *E*-isomer to the *Z*-isomer is supposed to involve isomerizations from *E*-**3** to *Z*-**3**. Negative entropy (ΔS) is not favorable for this process. The major factor, which dominates this isomerization, is enthalpy (ΔH), which is close to the relative stability (ΔE). At the B3LYP/6-31+G* level *Z*-**3** is 3.36 kcal/mol more stable than *E*-**3**, and that is consistent with the experimental *E*/*Z* isomerization results, indicating that the relative stability between *E*-**3** and *Z*-**3** does explain why **3** stays as a *Z*-isomer only. Then we want to analyze why *Z*-**3** is much more stable than *E*-**3** according to four independent factors: dipole moment, steric hindrance, resonance stabilization, and hydrogen bonding stabilization.

As shown in Table 1, dipole moments of *Z*-**3** and *E*-**3** are 3.97 and 4.87 debye, respectively, at B3LYP/6-31+G* level. Chloroform is a nonpolar aprotic solvent with dielectric constant of 4.81 while acetonitrile is a dipolar aprotic solvent with dielectric constant of 36.6.[9a] Based on a useful rule of thumb -"like dissolves like",[9b] acetonitrile may stabilize *E*-**3** better than *Z*-**3**, while chloroform may stabilize *Z*-**3** better than *E*-**3**. However, the only stable isomer of **3** in both chloroform and acetonitrile is *Z*-**3**, indicating that dipole moment is not a major factor to make *Z*-**3** much more stable than *E*-**3**.

The isomers, *E*-**3** and *Z*-**3**, can be divided into two systems: *Z*-**4**/*E*-**5** and *E*-**4**/*Z*-**5**, respectively. Isodesmic reactions of Eq.1~4 were designed to explore contribution of steric hindrance, resonance stabilization, and hydrogen bonding stabilization to the stability of *Z*-**4**, *E*-**5**, *E*-**4**, and *Z*-**5**, respectively. Optimized structures of *Z*-**4**, *E*-**4**, *Z*-**5**, *E*-**5**, **8**, **9** at the B3LYP/6-

31+G* level are shown in Fig. 2. Therefore, the sum of ΔE_1 and ΔE_2 of Eq.1~2 is the estimate for the contribution of steric hindrance and resonance stabilization to the stability of *E*-**3**, and the contribution of steric hindrance, resonance stabilization, and hydrogen bonding stabilization to the stability of *Z*-**3** is estimated by the sum of ΔE_3 and ΔE_4 of Eq.3~4. Based on the isodesmic reactions of Eq.1~4, the relative stability between *Z*-**3** and *E*-**3** should equal to $(\Delta E_3 + \Delta E_4) - (\Delta E_1 + \Delta E_2) = 3.23$ kcal/mol, which is close to their relative energy difference of 3.36 kcal/mol at the B3LYP/6-31+G* level.

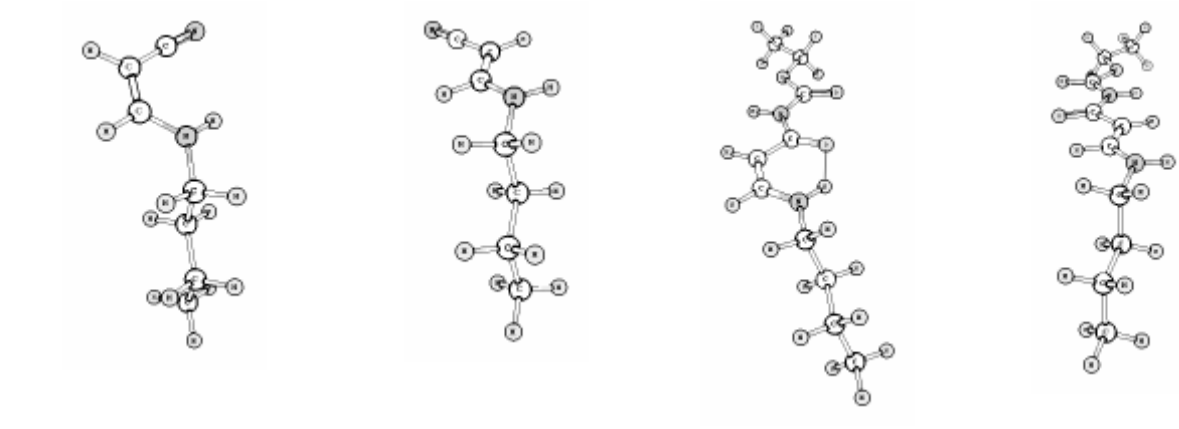
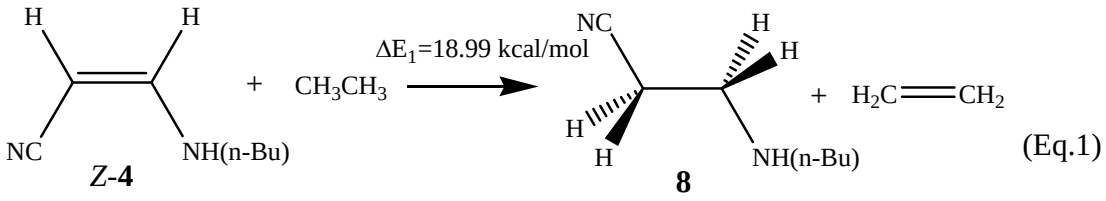
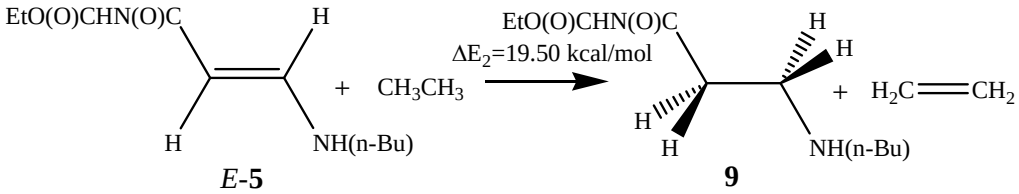


Figure 2. Optimized structures of *Z*-**4**, *E*-**4**, *Z*-**5**, *E*-**5**, **8**, and **9** at the B3LYP/6-31+G* level.



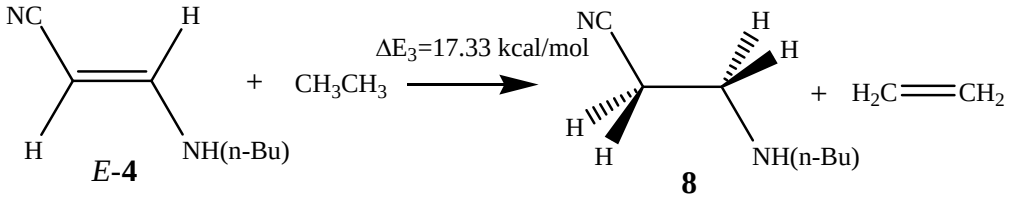
(Eq.1)

Z-**4**: steric hindrance [Es(*Z*-**4**)] = 0.27 kcal/mol; resonance stabilization [E_R(*Z*-**4**)] = 19.26 kcal/mol



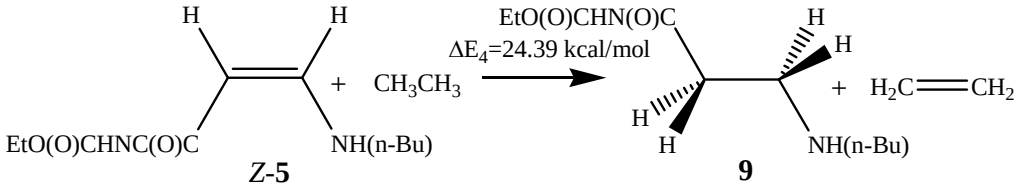
E-**5** **9** (Eq.2)

E-**5**: steric hindrance [Es(*E*-**5**)] = 0.0 kcal/mol; resonance stabilization [E_R(*E*-**5**)] = 19.50 kcal/mol



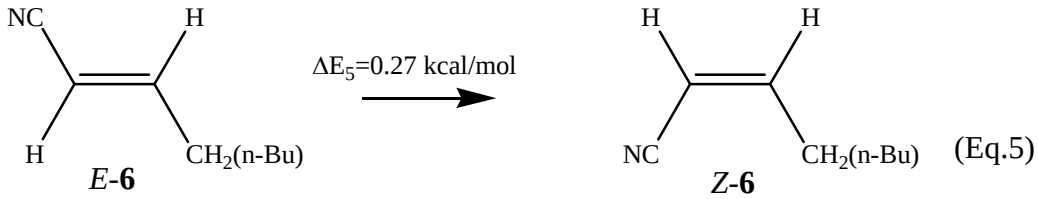
E-**4** **8** (Eq.3)

E-**4**: steric hindrance [Es(*E*-**4**)] = 0.0 kcal/mol; resonance stabilization [E_R(*E*-**4**)] = 17.33 kcal/mol



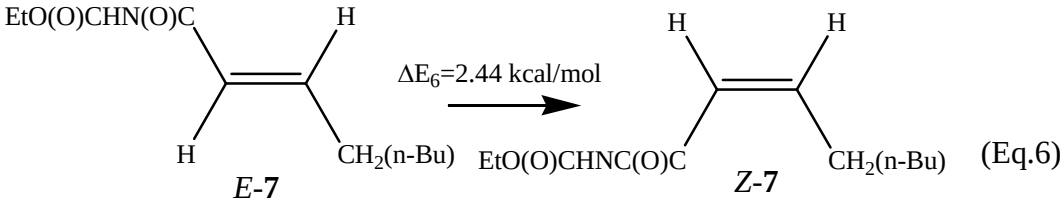
Z-**5** **9** (Eq.4)

Z-**5**: steric hindrance [Es(*Z*-**5**)] = 2.44 kcal/mol; resonance stabilization [E_R(*Z*-**5**)] = 19.64 kcal/mol; H-bonding stabilization [E_H(*Z*-**5**)] = 7.19 kcal/mol



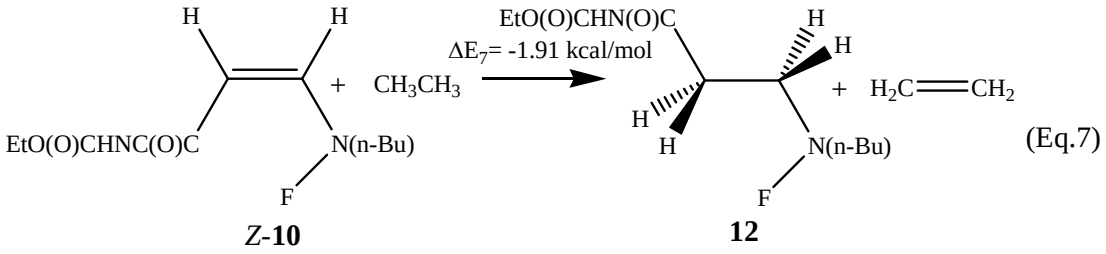
E-**6** *Z*-**6** (Eq.5)

Z-**6**: steric hindrance [Es(*Z*-**6**)] = 0.27 kcal/mol



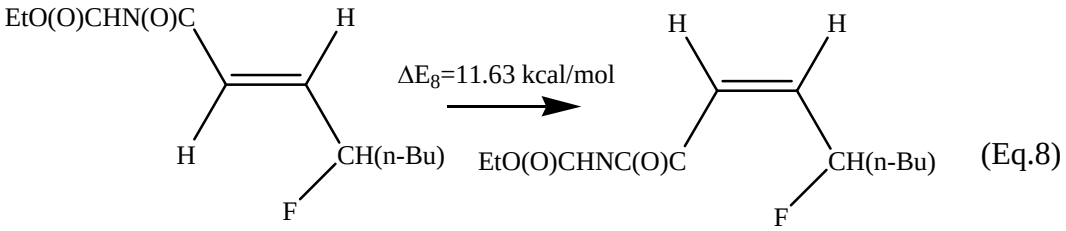
E-**7** *Z*-**7** (Eq.6)

Z-**7**: steric hindrance [Es(*Z*-**7**)] = 2.44 kcal/mol



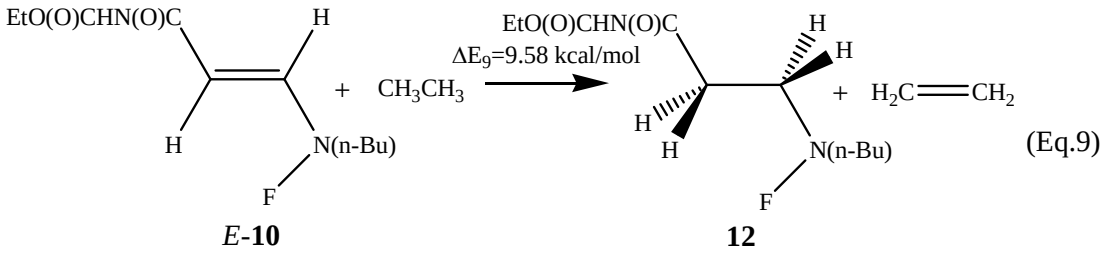
Z-**10** **12** (Eq.7)

Z-**10**: steric hindrance [Es(*Z*-**10**)] = 11.63 kcal/mol; resonance stabilization [E_R(*Z*-**10**)] = 9.72 kcal/mol.



E-**11** *Z*-**11** (Eq.8)

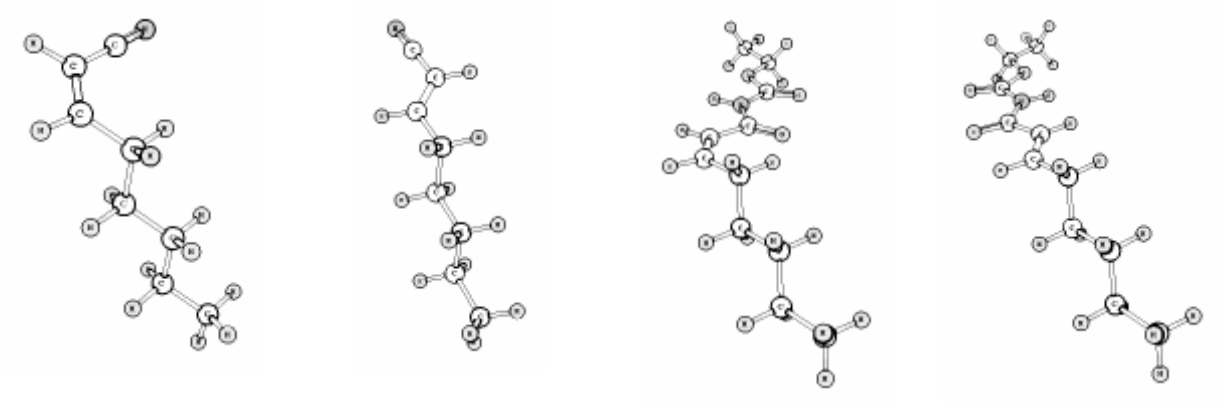
Z-**11**: steric hindrance [Es(*Z*-**11**)] = 11.63 kcal/mol



E-**10** **12** (Eq.9)

E-**10**: steric hindrance [Es(*E*-**10**)] = 0.0 kcal/mol; resonance stabilization [E_R(*E*-**10**)] = 9.58 kcal/mol.

Steric hindrance between vicinal substituents across C=C bond in *E*-**4** and *E*-**5** is around 0.0 kcal/mol. Because Van der Waals radii of NH is close to that of CH_2,[8] in order to consider steric hindrance in *Z*-**4** and *Z*-**5**, the pentyl group replaced *n*-butylamino substituent and *Z*-**6**, *E*-**6**, *Z*-**7**, and *E*-**7** were designed for a significant reduction of resonance effect along two substituents across C=C. Optimized structures of *Z*-**6**, *E*-**6**, *Z*-**7**, and *E*-**7** at the B3LYP/6-31+G* level are shown in Fig. 3. Therefore, steric hindrance [Es(*Z*-**4**)] in *Z*-**4** is close to that [Es(*Z*-**6**)] in *Z*-**6**, which is estimated to be 0.27 kcal/mol by the isodesmic reaction of Eq.5. Similarly, steric hindrance [Es(*Z*-**5**)] in *Z*-**5** is about the same as that [Es(*Z*-**7**)] in *Z*-**7**, which is approximately 2.44 kcal/mol based on the isodesmic reaction of Eq.6.



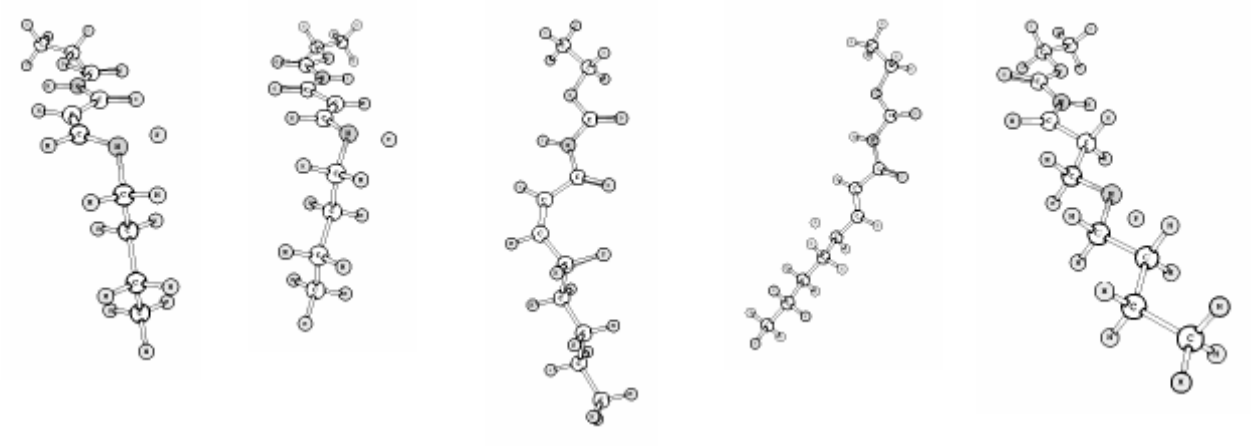
Z-**6** *E*-**6** *Z*-**7** *E*-**7**

Figure 3. Optimized structures of *Z*-**6**, *E*-**6**, *Z*-**7**, and *E*-**7** at the B3LYP/6-31+G* level.

The ΔE_1, ΔE_2, and ΔE_3 of Eq.1~3 include the contribution of repulsive steric hindrance and resonance stabilization to the stability of *Z*-**4**, *E*-**5**, and *E*-**4**, and their repulsive steric hindrance is just estimated, so the contribution of resonance stabilization to the stability of *Z*-**4**, *E*-**5**, and *E*-**4** is approximately 19.26, 19.50, and 17.33 kcal/mol, respectively. On the other hand, ΔE_4 of Eq.4 includes the contribution of repulsive steric hindrance, resonance stabilization, and hydrogen bonding stabilization to the stability of *Z*-**5**, and its steric hindrance [Es(*Z*-**5**)] is 2.44 kcal/mol, so the contribution from both resonance stabilization and hydrogen bonding stabilization to the stability of *Z*-**5** is approximately 26.83 kcal/mol.

To explore what the hydrogen bonding stabilization in *Z*-**5** is, *Z*-**10** was designed with N-F bond replacing N-H bond and its optimized structure at the B3LYP/6-31+G* level is shown in Fig. 4. The isodesmic reaction of Eq. 7 can estimate the contribution of steric hindrance and resonance stabilization to the stability of *Z*-**10**. To find out what the steric hindrance in *Z*-**10** is, the 1-fluoropentyl group replaced *N*-fluoro-*n*-butylamino substituent and *Z*-**11** and *E*-**11** were designed for a significant reduction of resonance effect along two substituents across C=C. The optimized structures of *Z*-**11** and *E*-**11** at the B3LYP/6-31+G* level are shown in Fig. 4. Therefore, the steric hindrance [Es(*Z*-**10**)] in *Z*-**10** is close to that [Es(*Z*-**11**)] in *Z*-**11**, which is estimated to be around 11.63 kcal/mol according to the isodesmic reaction of Eq. 8. Then, based on ΔE_7 of the isodesmic reaction of Eq.7 and Es(*Z*-**10**), the contribution of resonance stabilization [E_R(*Z*-**10**)] to the stability of *Z*-**10** is approximately 9.72 kcal/mol, which is small compared with the resonance stabilization in *Z*-**4**, *E*-**5**, and *E*-**4**. It is clear that the N-F substituent may change resonance stabilization when *Z*-**5** is replaced by *Z*-**10**. To find out the change extent of this resonance stabilization, *E*-**10** and the isodesmic reaction of Eq.9 were designed and the resonance stabilization difference between *Z*-**5** and *Z*-**10** is approximately equal to that between *E*-**5** and *E*-**10**, which is 9.92 kcal/mol (= E_R(*E*-**5**) - E_R(*E*-**10**)). Based on this calculated resonance stabilization difference and E_R(*Z*-**10**), the contribution of resonance stabilization [E_R(*Z*-**5**)] to the stability of *Z*-**5** is calculated to be 19.64 kcal/mol, which is reasonable compared with the

resonance stabilization in *Z*-**4**, *E*-**5**, and *E*-**4**. According to the calculated E_R(*Z*-**5**), Es(*Z*-**5**), and ΔE_4 of Eq.4, the contribution of hydrogen bonding stabilization [E_H(*Z*-**5**)] to the stability of *Z*-**5** is estimated to be 7.19 kcal/mol, which is reasonable compared with known hydrogen bonding.[8]



Z-**10** *E*-**10** *Z*-**11** *E*-**11** **12**

Figure 4. Optimized structures of *Z*-**10**, *E*-**10**, *Z*-**11**, *E*-**11**, and **12** at the B3LYP/6-31+G* level.

Conclusions

At the B3LYP/6-31+G* level *Z*-**3** is 3.36 kcal/mol more stable than *E*-**3**, and that explains why **3** stays as a *Z*-isomer only. The relative stability between *Z*-**3** and *E*-**3** is contributed from 7.19 kcal/mol of hydrogen bonding stabilization in favor of *Z*-**3** and both 2.17 kcal/mol of steric hindrance and 1.79 kcal/mol of resonance stabilization in favor of *E*-**3**. Intramolecular hydrogen bonding in *Z*-**3** plays an important role in the relative stability between *E*-**3** and *Z*-**3**.

Acknowledgments

This work is supported by NSC of Taiwan, ROC. (NSC 94-2113-M-006-009)

Reference

1. Foresman, J. B.; Frisch, A. *Exploring Chemistry with Electronic Structure Methods*, 2nd Ed. Gaussian Inc.: Pittsburgh, 1996.
2. (a) Gong, L.; McAllister, M. A.; Tidwell, T. T. *J. Am. Chem. Soc.* **1991**, *113*, 6021. (b) Sung, K. *J. Org. Chem.* **1999**, *64*, 8984. (b) Sung, K. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1169. (c) Sung, K. *J. Chem. Soc., Perkin Trans. 2* **2000**, 847.

3. (a) Sung, K.; Lin, M. C.; Huang, P. M.; Zhuang, B. R.; Sung, R.; Wu, R. R. *J. Phys. Org. Chem.* **2005**, *18*, 1183. (b) Sung, K.; Lin, M. C.; Huang, P. M.; Zhuang, B. R.; Sung, R.; Wu, R. R. *Archivoc* **2005**,(*xiii)*, 131.
4. Ceder, O; Stenhede, U. *Tetrahedron* **1973**, *29*, 1585.
5. (a) Kleinpeter, E.; Klod, S.; Rudorf, W. D. *J. Org. Chem.* **2004**, *69*, 4317. (b) Fischer, G.; Rudorf, W. D.; Kleinpeter, E. *Magn. Reson. Chem.* **1991**, *29*, 212. (c) Sandström, J. In *Topics in Stereochemistry*; Allinger, N. L.; Eliel, E. L.; Wilen, S. H.; Eds. John Wiley and Sons: New York, 1983, Vol. 14. (d) Markovic, R.; Baranac, M.; Jovanovic, V.; Dzambaski, Z. *J. Chem. Edu.* **2004**, *81*, 1026. (e) Sin, H. S.; Holler, M.; Burger, A.; Biellmann, J. F. *Tetrahedron Lett.* **1997**, *38*, 3585. (f) Zhu, S. Z.; Qin, C. Y.; Xu, G. L.; Chu, Q. L. *Tetrahedron Lett.* **1998**, *39*, 5265. (g) Abbotto, A.; Bradamante, S.; Capri, N.; Rzepa, H.; Williams, D. J.; White, A. *J. Org. Chem.* **1996**, *61*, 1770-1778. (h) Forni, A.; Destro, R. *Chem. Eur. J.* **2003**, *9*, 5528.
6. Zhuang, B. R.; Hsu, G. J.; Sung, K. *Bioorg. & Med. Chem.* **2006**, *14*, 3399.
7. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; AlLaham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzales, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian98. Revision A9*, Gaussian, Inc., Pittsburgh, PA, 1998.
8. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A: Structure and Mechanism*, 2nd Edn. Plenum Press: New York, 1984.
9. (a) Lide DR. *Handbook of Chemistry and Physics*, 85th Edn. CRC Press: New York, 2004. (b) Morrison, R. T.; Boyd, R. N. *Organic Chemistry*, 6th Edn. Prentice Hall International Limited: London, 1992.