

Epimerization in Intramolecular Carbanilide Cyclization to Hydantoins: A Computational Study

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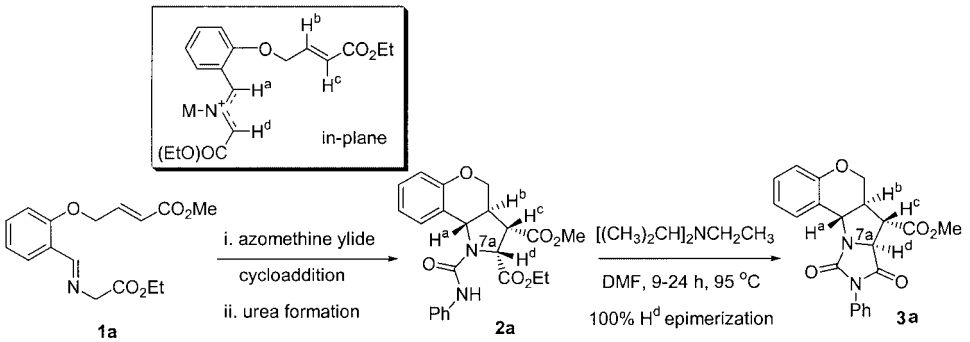
An efficient and diastereoselective route for the synthesis of 2,5,6,7-tetrasubstituted-1*H*-pyrrolo[1,2-*c*]imidazoles has been developed using intramolecular azomethine ylide cycloaddition and carbanilide cyclization. Ab initio calculations at the 6-31G (d,p) basis set reveal that the thermal stability of diastereomers determine the epimerization during the intramolecular carbanilide cyclization (→ hydantoin). These stereochemical results are consistent with an endo-like cycloaddition of a *trans*,*anti*-azomethine ylide followed by base-mediated C_{7a}-H epimerization (C_{7a}-$H_\beta \rightarrow C_{7a}$-$H_\alpha$) to deliver the thermodynamically preferred *trans*,*anti*,*trans*-(H^a-H^b, H^b-H^c, H^c-H^d)-pyrrolidine stereochemistry (**3**) which is ca. 20.1 kJ/mol more stable than the *trans*,*anti*,*cis*-pyrrolidine stereochemistry. In the case of 2-hydroxy-1-naphthaldehyde, naphthalene ring steric effects result in a different stereochemical arrangement about each pyrrolidine ring.

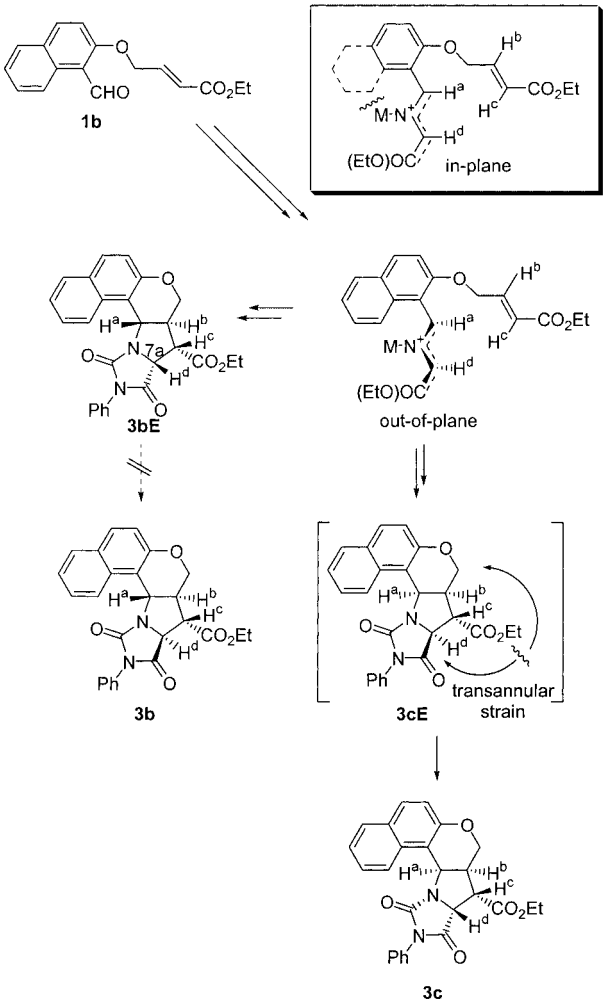
A number of hydantoins have been shown to possess a broad range of biological activities in medicinal[1] and agrochemical[2] applications (e.g. anticonvulsant, fungicide and herbicide). Given this utility, it is not surprising that a large number of hydantoins adorned with diverse substituents have been synthesized in solution[3] and on solid-phase.[4]

In previous studies, we developed a novel route to hexahydro-1*H*-pyrrolo[1,2-*c*]imidazole derivatives by sequential azomethine ylide cycloaddition (→ proline) and carbanilide cyclization (→ hydantoin) reactions.[5] This strategy delivered polycylic hydantoin targets with stereoselective control of the four contiguous pyrrolidine stereogenic centers. This carbanilide formation step, outlined in Scheme 1, delivered (*trans*,*anti*,*cis*)-hexadydro-1*H*-pyrrolo[1, 2-*c*]imidazole **2a** as a single isomer, implying that the key 1,3-dipolar cycloaddition step proceeded via an endo-like transition state and that C_{7a} epimerization occurred during the carbanilide cyclization step (**2** → **3**).[6] We had already demonstrated that the kinetically favorable product **3aE** (*trans*,*anti*,*cis*-stereochemistry) was epimerized to the thermodynamically more stable product **3a** (*trans*,*anti*,*trans*-stereochemistry; Scheme 1).[6c] In contrast, use of 2-hydroxy-1-naphthaldehyde results in a different stereochemical arrangement at the pyrrolidine ring.[6] With this substrate, the major product (**3bE**) is obtained with *trans*, *anti*, *cis*-stereochemistry (**3a** has *trans*,*anti*,*trans*-stereochemistry) and a minor product (**3c**) is obtained with *cis*,*anti*,*cis*-stereochemistry (Scheme 2). Moreover, epimerization of the kinetic product **3bE** did not provide **3b** under the same reaction conditions shown in Scheme 1.

The rarity of this phenomenon and the different epimerization behaviors of these hydantoin ring systems prompted us to investigate the epimerization in a computational study. In this



Scheme 1.



Scheme 2.

paper, we discuss the epimerization results of two diastereomers based on ab initio calculations.

Computational Methods

All calculations were carried out using Gaussian 94[7] and Sybyl programs (v. 6.4) on an Origin server (R10000) and O_2 (R5000) workstation. Initial geometries of all compounds for semi-empirical calculations were obtained from random search, selecting all rotational torsion angles (the option: 3,000 iterations, 3 kcal/mol energy cutoff, chirality check). The lowest energy conformers from random search were optimized by the semi-empirical calculation with PM3 charge[8] at the restricted Hartree Fock (RHF) level. We then carried out ab initio calculations for all PM3-optimized structures, starting from STO-3G up to the 6-31G (d, p) basis set.[9] When we calculated the energy difference between **2a** & **3aE**, **2b** & **3bE**, and **2c** & **3cE**, the energy of ethanol, which was calculated by the same basis set, was added. For the calculation of energy difference between **2a** and its reaction intermediate, the energy difference was corrected by adding the hydrogen atomic energy, E_H (-0.4712 a.u.), and the average C–H bond dissociation energy, E_{CH} (378 kJ/mol).[10]

Results and Discussion

Upon heating (90 °C) DMF solutions of **2a** in the presence of *N*,*N*-diisopropylethylamine, we obtained hexahydro-1*H*-pyrrolo[1,2-*c*]imidazole **3a** (95% yield) as a single isomer. Through X-ray crystallographic studies, we could suggest that 1,3-dipolar cycloaddition proceeded via an endo-like transition state, followed by an epimerization at C_{7a} during the carbanilide cyclization step.[6] We believe that the thermodynamic stability of the *trans*,*anti*,*trans*-pyrrolidine stereochemistry found in **3a** during base-mediated C_{7a}-H epimerization (C_{7a}-$H_\beta \rightarrow C_{7a}$-$H_\alpha$) determines the stereoselectivity of the product in both solution and solid-phase. To confirm this, we determined structural energies for all diastereomers using PM3 and ab initio calculations (Table 1). The basis set was extended from STO-3G to 6-31G** and we found the energy values to be dependent on their basis sets. PM3 and ab initio methods gave some differences in the relative thermodynamic stability of compounds **2a** vs **2aE** as well as **3bE** vs **3b**; ab initio methods correlated better with the experimental results. Although the energy difference in the 3-21G basis set was a little higher than those of other basis sets, it showed the same thermal stability results. Indeed, the overall conformations of the most stable structures from the PM3, HF/STO-3G, HF/3-21G, and HF/6-

Table 1. Calculated Relative Energies (kJ/mol) Depending on the Basis Set at HF Levels

Molecule	PM3	STO-3G	3-21G	6-31G**
2a	0	0	0	0
2aE	−9.58	12.09	36.44	20.96
3aE	7.99	7.32	13.01	20.38
3a	0	0	0	0
2b	55.19	55.27	60.17	58.07
2c	0	0	0	0
3bE	46.78	42.09	70.25	55.06
3b	44.10 (−2.68)[a)]	50.84 (8.74)[a)]	70.08 (−0.17)[a)]	51.13 (−3.93)[a)]
3cE	7.49	19.12	43.39	7.05
3c	0	0	0	0

a) The value in parenthesis is relative to the energy of **3bE**.

31G** methods were quite similar. In addition, compared to the crystal structures of **3bE** and **3c**, their low energy conformations from ab initio calculations showed an overall similarity. Only the ethyl ester group showed different conformations between the two structures, due to its flexibility.

The low energy conformer of **2a** is stabilized by intramolecular hydrogen bonding between the amide hydrogen and the ester oxygen (2.14 Å). Indeed, **2a** is more stable than **2aE** due to intramolecular hydrogen bonding differences (**2a**, 2.14 Å vs **2aE**, 2.34 Å) and the ring strain of **2aE**. The epimerized product, **3a**, is thermodynamically favored by ca. 20.4 kJ/mol over **3aE** according to 6-31G** calculations.

We can suggest two postulates for the epimerization process. In process **A**, the hydantoin cyclization reaction to **3aE** is followed by H^d-epimerization (**3a**). In process **B**, H^d-epimerization to **2aE** occurs first and then the hydantoin cyclization reaction to **3a** occurs (Fig. 1). When we calculate the reaction intermediates for cyclization (**2a** to **3aE**) and epimerization (**2a** to **2aE**), the reaction intermediate energy of **2a** to **3aE** is lower by ca. 40.4 kJ/mol than that of **2a** to **2aE**. Therefore, it seems that epimerization of **2a** to **2aE** is thermodynamically less favorable compared to cyclization of **2a** to **3aE** at the beginning of the reaction. Thus, the epimerization reaction should take place not through the urea intermediate **2aE**, but through the hydantoin intermediate **3aE**. Indeed, these calculated results are well correlated with the experimental results[6b] where we obtained only compound **3aE**, not **2aE**.

However, in the case of 2-hydroxy-1-naphthaldehyde, a different stereochemical arrangement around the pyrrolidine ring was obtained. The major product (**3bE**) is generated with *trans*,*anti*,*cis*-stereochemistry and a minor product (**3c**) is generated with *cis*,*anti*,*cis*-stereochemistry. We suggest that two separate issues drive this stereoselectivity. First, salicylaldehyde-derived azomethine ylides can adapt an "in-plane" (conjugated) conformation which leads to the observed *trans*,*anti*,*cis*-intermediate by *endo* addition. In contrast, the 2-hydroxy-1-naphthaldehyde derived azomethine ylide is forced "out-of-plane" where favored *endo* addition again delivers a *trans*,*anti*,*cis*-intermediate; competing *exo* addition leads to a *cis*,*anti*,*trans*-intermediate. Second, *N*-acylation and carbanilide cyclization delivers **3bE** as the major product without H^d epimerization and **3c** as the minor product after H^d epimerization of hypothetical intermediate **3cE** (Scheme 2). Calculations show that the naphthalene ring prevents **3bE** H^d epimerization because this structural change would bring O(2) of the hydantoin ring into close proximity with H(8) of the naphthalene ring (Fig. 2). In structure **3bE**, the hydantoin ring is located below the plane of the naphthalene ring. But in order to form **3b** where the hydantoin ring is placed above the naphthalene plane, the hydantoin ring in the reaction intermediate is in close contact with the naphtalene ring. Epimerization **3cE** → **3c** relieves trans annular strain without placing O(2) of the hydantoin ring into close proximity with H(8) of the naphthalene ring. In the case of **2b**, it does not epimerize to **3b** — even though **3b** is thermodynamically favored over **3bE** by ca. 3.97kJ/mol — because the angle between the naphthalene and hydantoin rings causes increased steric hindrance. In the case of **2c**, which has *cis*,*anti*,*trans*-stereochemistry about the pyrrolidine ring, it easily accommodates H^d epimerization to give **3c** (*cis*,*anti*,*cis*) through the geometry of reaction intermediate **3cE** (*cis*,*anti*,*trans*). Figure 3 shows that the naphthalene ring of **3c** encounters less steric hindrance than in **3cE**. Another piece of evidence which supports this result is that **3c** is thermodynamically favored by ca. 29.5 kJ/mol over **3cE** (Table 1). Upon epimerization, the reaction intermediate for **3bE** to **3b** is higher in energy by ca. 27.1 kJ/mol than that for **3cE** to **3c**.

Thus, endo-like cycloaddition of a *trans*,*anti*-azomethine ylide followed by base-mediated C_{7a}-H epimerization (C_{7a}-H_β → C_{7a}-H_α) delivers the thermodynamically preferred *trans*,*anti*,*trans* (H^a-H^b, H^b-H^c, H^c-H^d)-pyrrolidine stereochemistry (**3**) which is ca. 2.01 kJ/mol more stable than its *trans*,*anti*,*cis*-pyrrolidine stereochemistry. However, 2-hydroxy-1-naphthaldehyde accomodates a different stereochemical arrangement about the pyrrolidine ring due to the steric effects of the naph-

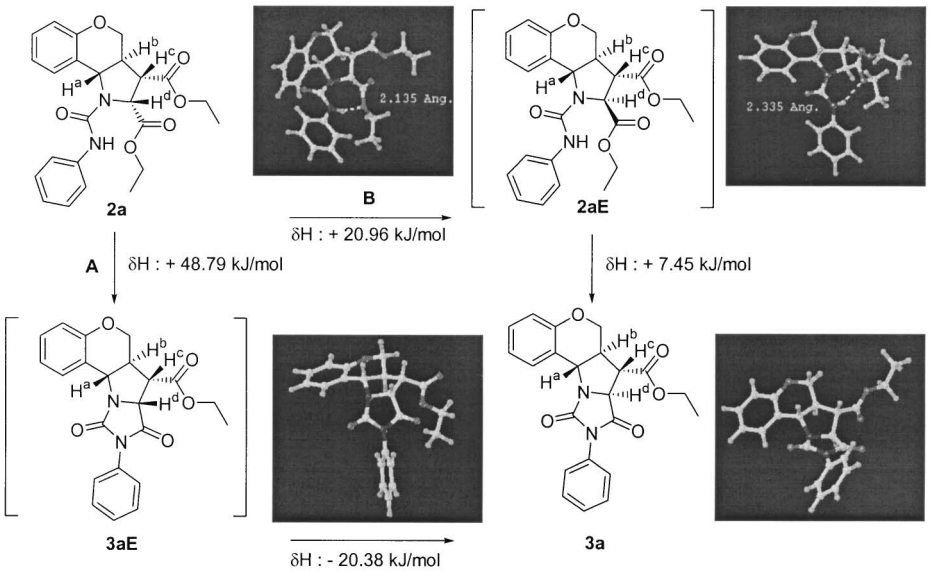


Fig. 1. The calculated structures and enthalpies of **2a**, **2aE**, **3aE**, and **3a** by HF/6-31G (d, p) method.

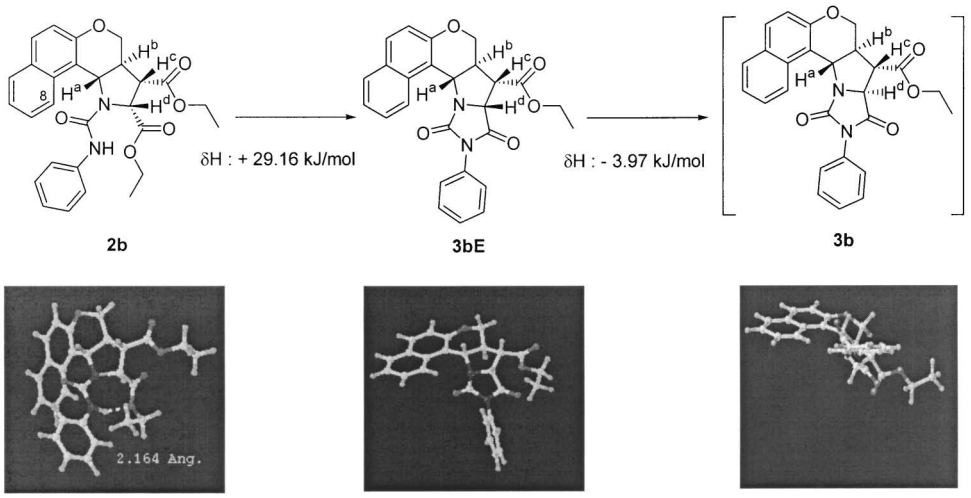


Fig. 2. The calculated structures and enthalpies of **2b**, **3bE** and **3b** by HF/6-31G(d, p) method.

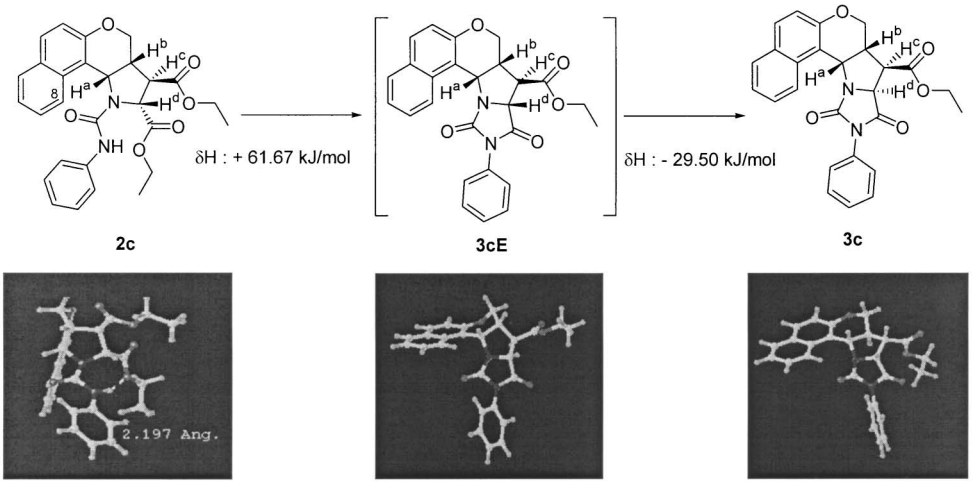


Fig. 3. The calculated structures and enthalpies of **2c**, **3cE** and **3c** by HF/6-31G(d, p) method.

thalene ring. Ab initio calculations at the 6-31G** basis set reveal that the thermal stability of diastereomers determine the stereoselectivity of these 1,3-dipolar cycloadditions.

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