co-workers indicate that this conformation is also an energy minimum in oxocarbenium ions.[13] Furthermore, electrostatic attraction between the positively charged oxocarbenium oxygen and the negatively charged $TiCl_4$ alkoxide holds the alkoxide in proximity to the C–O π-bond (tight ion pair). This effectively blocks one face of the oxocarbenium ion and limits attack of the nucleophile to the exposed face. The minor diastereomer could then arise from a conformation in which the C–O π-bond is not eclipsed to the neighboring C–H, but rather is eclipsed to the neighboring C–CH_3 bond, thus exposing the opposite face of the π-system. Alternatively, it could arise from a conformation in which the ion pair is separated by solvent and is no longer effective in blocking one face of the electrophilic carbon.

This study was ostensibly performed to elucidate the mechanism of cleavage of chiral acetals (eq 1). We have seen that seemingly minor perturbations in the structure of the acetal can substantially change the outcome and mechanism of the reaction.[14] It is therefore difficult to draw any firm conclusions regarding the mechanism of other acetal reactions based on these model substrates. However, given that the equilibrating substrates which react by an oxocarbenium ion mechanism display lower selectivity than is observed in the chiral acetal substrates, it is likely that the more selective chiral acetal reactions of Johnson proceed predominantly by a direct displacement mechanism, while the less selective reactions have some amount of an oxocarbenium ion intermediate. Experiments designed to directly test this hypothesis are currently in progress.[15]

Supplementary Material Available: Experimental procedures and compound characterization data (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006. The preference for the eclipsed conformation in oxocarbenium ions is on the order of about 1–2 kcal/mol depending on the substrate according to these calculations (*O*-methylformaldehyde, 0.95 kcal/mol; *O*-isopropylformaldehyde, 1.83 kcal/mol).

(14) For an example where a minor change in the structure of an aminal leads to a reversal of stereoselectivity, see: Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858.

(15) This work was supported by the National Science Foundation (CHE-9019060), The Camille and Henry Dreyfus Foundation (New Faculty Award to T.S.), and The University of Colorado at Boulder Council on Research and Creative Works (CRCW Junior Faculty Development Award to T.S.). Dr. Greg Fu is gratefully acknowledged for stimulating discussions.

Articles

Intramolecular Diels–Alder Reactions of Pyrimidines and a Computational Study toward Their Structure and Reactivity

Werner A. W. Stolle, August E. Frissen, Antonius T. M. Marcelis, and Henk C. van der Plas*

Laboratory of Organic Chemistry, Agricultural University Wageningen, Dreyenplein 8, 6703 HB Wageningen, The Netherlands

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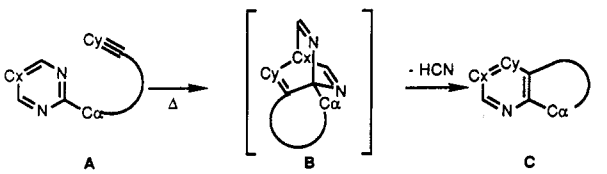
The syntheses of 2-[(prop-2-ynyloxy)carbonyl]pyrimidine (**1**), 5-[(prop-2-ynyloxy)carbonyl]pyrimidine (**2**), 5-phenyl-2-[2-(1-prop-2-ynylpyrryl)]pyrimidine (**8**), 5-phenyl-2-[2-(1-prop-2-ynylpyrrolidinyl)]pyrimidine (**9**) and 2-[2-(prop-2-ynyloxy)phenyl]-4,6-R_2-5-R_1-pyrimidine (R_1 = H, Cl, Ph; R_2 = H, Me) (**14a–d**) are described. Upon heating, the compounds **1**, **9**, and **14** undergo an intramolecular Diels–Alder reaction and a subsequent retro Diels–Alder reaction to yield the annelated pyridines **15**, **16**, and **17**, respectively. The compounds **2** and **8** did not react. The nonreactivity of the compounds **2** and **8** is ascribed to conjugation of the pyrimidine aromatic system with part of the dienophilic side chain, giving rise to conformations in which the diene and dienophile moieties cannot interact. For the compounds **1**, **9**, and **14** conjugation is absent, due to steric hindrance. To support this, semiempirical (MDNO-PM3) and molecular mechanics (MMX, CHEMX) calculations were performed. The HOMO–LUMO energy seperation of the compounds did not consequently reflect the observed reactivity. However, the probability of the compounds to be in a reactive conformation appeared to correlate with the observed rate of reaction (**9** > **14a** > **1** ≫ **2**, **8**).

Introduction

The study of intramolecular Diels–Alder reactions with inverse electron demand of cyclic aza dienes with a dienophilic side chain has received considerable attention during the last few years.[1-3] The broad scope and relatively mild conditions of these reactions make them very fruitful for synthetic as well as physico-chemical re-

Scheme I. Generalized Ring Transformation Reaction of 2-(ω-Alkynyl)pyrimidines



(1) Recent publications of our group describing intramolecular Diels–Alder reactions of pyridines and pyrazines with a dienophilic side chain. (a) de Bie, D. A.; Geurtsen, G.; van der Plas, H. C. *J. Org. Chem.* **1986**, *51*, 67. (b) de Bie, D. A.; Ostrowicz, A.; Geurtsen, G.; van der Plas, H. C. *Tetrahedron* **1988**, *44*, 2977. (c) Geurtsen, B.; de Bie, D. A.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 6519. (d) Haider, N.; van der Plas, H. C. *Tetrahedron* **1990**, *46*, 3641.

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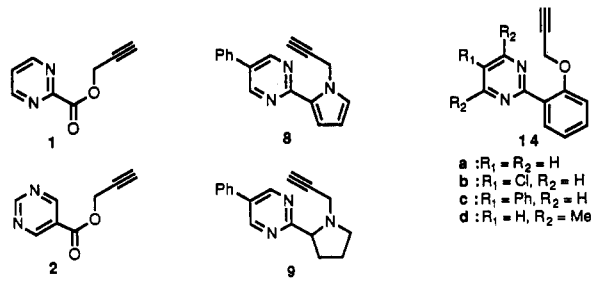
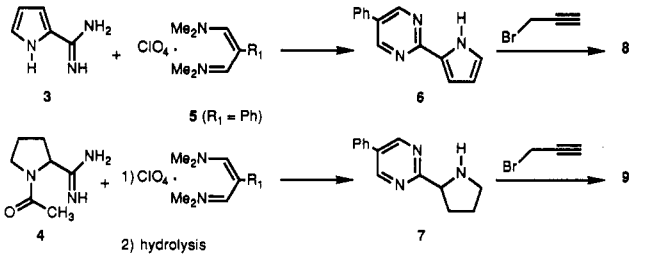


Figure 1.

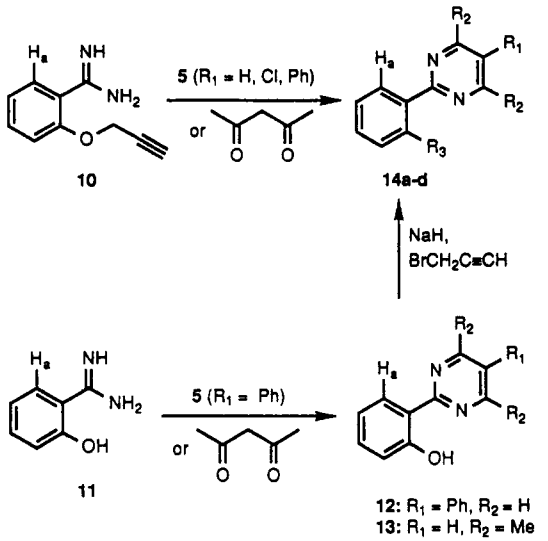
search.[4,5] The enhanced reactivity of *intra*molecular as compared to *inter*molecular Diels–Alder reactions is explained by the entropic assistance of the tether between diene and dienophile. From our previous studies on ring transformation reactions of 2-substituted pyrimidines (**A**)[2] it was found that they easily undergo a Diels–Alder reaction to form intermediates (**B**),[6] which subsequently undergo a retro Diels–Alder reaction to annelated pyridines (**C**) (see Scheme I).

Furthermore, it is known that the reactivity of intramolecular Diels–Alder reactions is strongly related to the conformational properties of the side chain.[4,5,7] Rate enhancement is observed upon introduction of α-substituents on the tethering chain. The conformational changes induced by substituents on the side chain are explained by the Thorpe–Ingold[8] effect or the gem-dialkyl effect.[9] Rate reduction has been found for molecules that are able to form stable conformations in which the (aza) diene and dienophilic side chain are positioned in such a way that their interactive approach becomes more difficult. This has been observed for molecules with a heteroatom substituted directly between the pyrimidine and the tethering chain, thereby enabling the molecule to form resonance stabilized conformations.[2a,d,4a,7]

Scheme II. Reaction Schemes for the Synthesis of the Pyrimidines 8 and 9



Scheme III. Reaction Schemes for the Synthesis of the Pyrimidines 14a–d



The substituted pyrimidines **1**, **2**, **8**, **9**, and **14a–d**, as depicted in Figure 1, were synthesized and subjected to Diels–Alder reaction conditions to gain more insight into the relation between the reactivity of a compound and its conformational properties. The compounds **1**, **8**, and **14** were chosen for their ability to form, in principle, a conjugated system between the pyrimidine and part of the dienophilic side chain. The compounds **2** and **9** were chosen for comparison with **1** and **8**, respectively.

Results and Discussion

Synthesis. 2-(Prop-2-ynyloxy)carbonyl]pyrimidine (**1**) was prepared from 2-cyanopyrimidine by treatment with propargyl alcohol and dry hydrogen chloride gas. The yield of this synthesis was relatively low, but its simplicity made it the method of choice for preparing the desired compound **1**. The isomeric 5-[(prop-2-ynyloxy)carbonyl]pyrimidine (**2**) was prepared by esterification of 5-carboxypyrimidine[10] with propargyl alcohol in good yield.

The 5-phenyl-2-[2-(1-prop-2-ynylpyrryl)]pyrimidine (**8**) and the 5-phenyl-2-[2-(1-prop-2-ynylpyrrolidinyl)]pyrimidine (**9**) were prepared as depicted in Scheme II. The appropriate amidine **3** or **4** was reacted with 1-(dimethylamino)-3-(dimethyliminio)-2-phenylprop-2-ene perchlorate[11] (**5**) to give the pyrimidines **6** and the *N*-acetylpyrrolidine derivative of **7**, respectively. Hydrolysis of the *N*-acetylpyrrolidine derivative yielded **7**. Treatment

(2) Recent publications of our group describing intramolecular Diels–Alder reactions of pyrimidines with a dienophilic side chain. (a) Frissen, A. E.; Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 803. (b) Frissen, A. E.; Marcelis, A. T. M.; Buurman, D. G.; Pollmann, C. A. M.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 5611. (c) Frissen, A. E.; Marcelis, A. T. M.; Geurtsen, G.; de Bie, D. A.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 5151. (d) Stolle, W. A. W.; Marcelis, A. T. M.; van der Plas; H. C. *Tetrahedron* **1989**, *45*, 6511. (e) Frissen, A. E.; Marcelis, A. T. M.; Melger, W. C.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 6891. (f) Frissen, A. E.; Geurtsen, G.; Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron* **1990**, *46*, 595. (g) Marcelis, A. T. M.; van der Plas, H. C. *Trends Heterocyclic Chem.* **1991**, *1*, 111.

(3) (a) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (b) Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1986**, *51*, 3250. (c) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2717. (d) Trifonov, L. S.; Orahovats, A. S. *Helv. Chim. Acta* **1987**, *70*, 1732. (e) Taylor, E. C.; Macor, J. E. *J. Org. Chem.* **1987**, *52*, 4280. (f) Taylor, E. C.; Pont, J. L. *J. Org. Chem.* **1987**, *52*, 4287. (g) Taylor, E. C.; Macor, J. E. *J. Org. Chem.* **1989**, *54*, 4984. (h) Taylor, E. C.; Macor, J. E.; French, L. G. *J. Org. Chem.* **1991**, *56*, 1807. (i) Boger, D. L. *Adv. Heterocycl. Chem.* **1989**, *1*, 30.

(4) (a) Stolle, W. A. W.; Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron* **1991**, *47*, 1753. (b) Stolle, W. A. W.; Frissen, A. E.; Marcelis, A. T. M.; van der Plas, H. C.; Wang, Y.; Häming, L.; Stam, C. H. *J. Org. Chem.* **1991**, *56*, 2411.

(5) (a) Harfenist, M.; Thom, E. *J. Org. Chem.* **1972**, *37*, 841. (b) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

(6) Because we were never able to isolate or detect the tricyclic triene intermediate **B**, it is believed that the retro Diels–Alder reaction is much faster than the initial intramolecular Diels–Alder reaction. Therefore, the conversion of **A** into **B** is supposed to be the rate-determining step in the reaction sequence of **A** to **C**.

(7) (a) Boeckman, R. K., Jr.; Koo, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033. (b) Jung, M. E.; Gervay, J. *Tetrahedron Lett.* **1988**, *29*, 2429. (c) Sternbach, D. D.; Rossana, D. M.; Onan, K. D. *Tetrahedron Lett.* **1985**, *26*, 591.

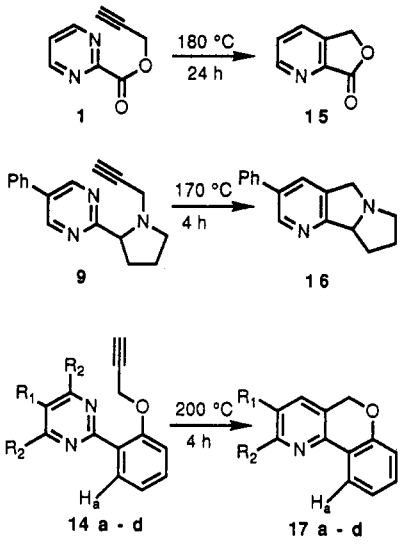
(8) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *31*, 1080. (b) Ingold, C. K. *J. Chem. Soc.* **1921**, *37*, 841.

(9) (a) Allinger, N. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701. (b) von Schleyer, P. R. *J. Am. Chem. Soc.* **1961**, *83*, 1368.

(10) (a) Gabriel, S.; Colman, J. *Ber.* **1904**, *37*, 3643. (b) Kast, H. *Ber.* **1912**, *45*, 3124.

(11) (a) Arnold, Z. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3091. (b) Holy, A.; Krupicka, J.; Arnold, Z. *Collect. Czech. Chem. Commun.* **1965**, *30*, 4127. (c) Jutz, C.; Kirchlechner, R.; Seidel, H.-J. *Chem. Ber.* **1969**, *102*, 2313.

Scheme IV. Reaction Schemes and Conditions for the Ring Transformation Reactions of the Compounds 2, 9, and 14a–d



of **6** and **7** with propargyl bromide and potassium carbonate afforded the desired compounds **8** and **9**, respectively.

The 2-[2-(prop-2-ynyloxy)phenyl]pyrimidines (**14a–d**) were prepared from *o*-(prop-2-ynyloxy)benzamidine (**10**) according to Scheme III. Reacting **10** with an appropriate trimethinium salt (**5**, R_1 = H, Cl, Ph) gave the compounds **14a–c**. 4,6-Dimethyl-2-[2-(prop-2-ynyloxy)phenyl]pyrimidine (**14d**) was obtained by reaction of **10** with 2,4-pentanedione. The yields of the compounds **14a,b** were reasonable, whereas those of compounds **14c,d** were poor. Therefore, **14c** and **14d** were also prepared by a slightly modified procedure, using *o*-hydroxybenzamidine (**11**) as a starting material. Reaction of **11** with **5** (R_1 = Ph) yielded 2-(*o*-hydroxyphenyl)-5-phenylpyrimidine (**12**) and with 2,4-pentanedione gave 4,6-dimethyl-2-(*o*-hydroxyphenyl)pyrimidine (**13**), respectively (see Scheme III). Treatment of **12** and **13** with sodium hydride and propargyl bromide in refluxing tetrahydrofuran gave the compounds **14c** and **14d**, respectively, in good yields.

Ring Transformations. The compounds **1**, **2**, **8**, **9**, and **14** were dissolved in nitrobenzene and heated at 170–210 °C to induce a ring transformation as depicted in Scheme IV. Only the compounds **1**, **9**, and **14a–d** were found to undergo a Diels–Alder addition and a subsequent retro Diels–Alder reaction to yield the annelated pyridines **15**, **16**, and **17a–d**, respectively. The compounds **2** and **8**, although exhaustively heated, did not show any reaction, except slow decomposition. The reactivities ($t_{1/2}$) of the reactive compounds were calculated after careful integration of high field signals in the ^{1}H-NMR spectra of the reaction mixtures during the reaction.

Comparison of the Reactivity of the Compounds 8 and 9. The high reactivity of **9** as compared to the nonreactivity of compound **8** under the applied Diels–Alder conditions (see Table I) is a quite interesting observation. On account of previous observations[4] we propose that the different behavior of **8** and **9** can be explained by the tendency of **8** to form conformations in which the reactive sites are too far separated to be able to undergo a cycloaddition reaction. A flat geometry around C2–C3, as in **8**, is responsible for the formation of a stabilized conjugated system, in which the diene and dienophile are not able to have any interaction. Compound **9** lacks the ability to form a conjugated system around C2–C3 and the entropic assistance by the tether between the diene and dienophile favors the cycloaddition.

Table I. Observed Reactivities (Extrapolated to 170 °C) and Calculated Energy Differences between the HOMO and LUMO of the Diene (de) and the Dienophile (dp) Moieties of the Compounds 1, 2, 8′,[12] 9′,[12] and 14a

compd	$t_{1/2}$[a]	ΔE(HOMO$_{de}$ − LUMO$_{dp}$)[b]	ΔE(HOMO$_{dp}$ − LUMO$_{de}$)[b]
1	10.0	11.857	9.826
2	c	11.536	10.110
8/8′[d]	c	9.586	10.425
9/9′[d]	0.8	12.027	9.997
14a	6.0	11.536	10.110

[a] $t_{1/2}$ in h. [b] ΔE in eV. [c] No reaction observed. [d] $t_{1/2}$ was determined for the compounds **8** and **9**, ΔE was determined for the compounds **8′** and **9′**, respectively.

The conformational properties of the molecules determine the relative rate of reaction of the intramolecular Diels–Alder reactions on condition that the heats of activation (H_{act}) of the cycloaddition reactions are *not* the rate-determining factor. For investigation of this condition, the energy differences between the HOMO and LUMO of the diene and dienophile moieties were determined for each molecule.[12] It is assumed that the energy separations between the FMOs of the molecules correlate with the heats of activation.[13]

As can be seen from Table I, the calculated energy differences[14,15] between the HOMOs and LUMOs of **8′** and **9′** are 9.586 and 9.997 eV, respectively. The relative difference in the HOMO/LUMO separation of 0.41 eV indicates that $\Delta H_{act}(8') < \Delta H_{act}(9')$. However, it is found that **9′** does react, whereas **8′** does not. Therefore, the conformational properties of the molecules are supposed to be the rate-determining factor in the Diels–Alder reaction. Furthermore, it is seen from Table I that the cycloaddition reaction of compound **8′** cannot be classified as a Diels–Alder reaction with inverse electron demand, because the ΔE(HOMO$_{diene}$ − LUMO$_{dienophile}$) is smaller than ΔE(HOMO$_{dienophile}$ − LUMO$_{diene}$).[16] The increase of the E(HOMO) of the diene moiety is due to the greater number of mixing orbitals caused by the conjugation with the pyrrole ring.

For investigation of the contribution of the conformational properties of the molecules to their reactivity, the minimum energy conformations of all compounds were calculated using the MMX program[17] and the semiempirical VAMP program[14c] (Table II). As can be seen from Table II, the nonreactive compound **8′** has indeed a

(12) In semiempirical studies on all kinds of molecules, the computation time is the limiting factor, which exponentially rises with the number of atoms in the molecules. Therefore, in this study the phenyl substituent at position 5 of the compounds **8** and **9** was replaced by a hydrogen atom, giving the compounds **8′** and **9′** (see Figure 1). Furthermore, it is assumed that the replacement of the 5-phenyl group by a hydrogen atom does not seriously influence the reactivity of the compounds. Comparison of the reactivities of the compounds **14a** and **14c** seems to justify this approximation (see also refs 2a and 4).

(13) (a) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley and Sons: London, 1972; p 113. (b) Sustmann, R.; Schubert, R. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 840.

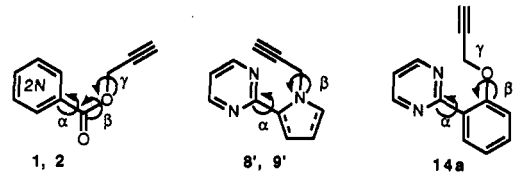
(14) The energies of the HOMO and LUMO were determined with the MNDO-PM3 Hamiltonian[14a,b] in the semiempirical VAMP program.[14c] (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209. (b) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 221. (c) VAMP 4.3 is a semiempirical orbital program derived from Dewar's AMPAC 1.0 and Stewarts MOPAC 4.0.

(15) The energy differences between the HOMOs and LUMOs have been calculated after geometry optimization, using the Fletcher–Powell–Davidon routine to optimize the geometry. (a) Fletcher, R.; Powell, M. J. D. *Computer J.* **1963**, *6*, 163. (b) Davidon, W. C. *Computer J.* **1968**, *10*, 406.

(16) (a) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57. (b) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092. (c) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.

(17) MMX is derived from MM2 (QCPE 395) with MMP1 π subroutines (QCPE 318) incorporated for delocalized π-electron systems.

Table II. Most Important Geometric Parameters, Optimized within the MMX and MNDO-PM3 Force Fields, of the Compounds 1, 2, 8′, 9′, and 14a



	α		β		γ	
compd	MMX	MNDO-PM3	MMX	MNDO-PM3	MMX	MNDO-PM3
1	96.85	93.2	0.79	0.51	−179.03	−166.72
2	−1.36	24.06	0.02	4.00	−179.33	163.91
8′	−0.49	17.33	−74.61	−86.73		
9′	96.33	94.62	22.84	58.03		
14a	94.43	78.65	25.64	48.11	79.26	60.00

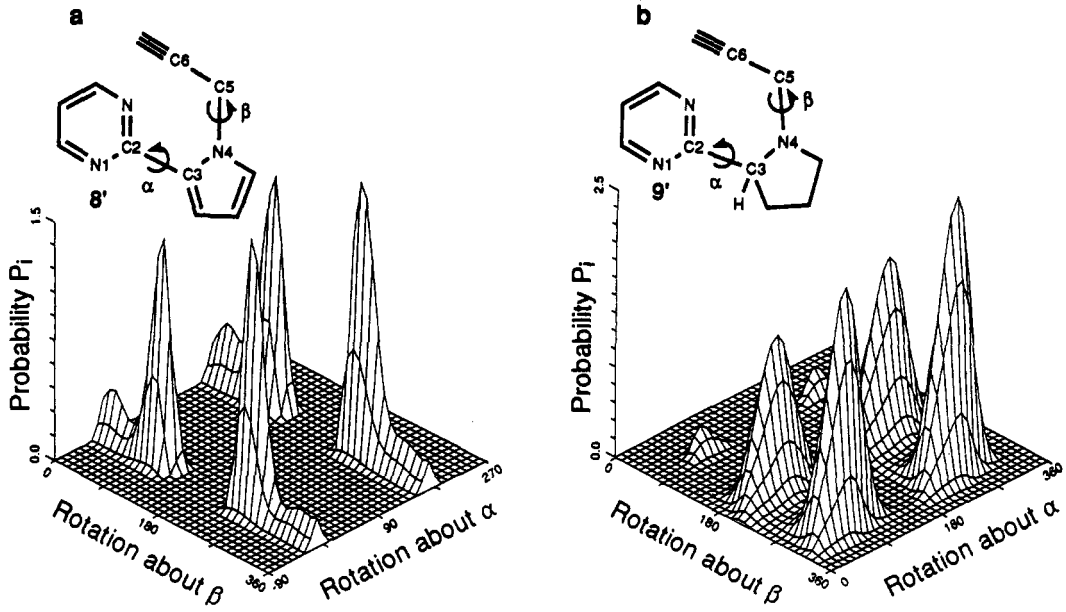


Figure 2. Probability of each conformation generated in the rotational analyses of 8′ (a) and 9′ (b) plotted versus the dihedral angles N1–C2–C3–N4 (α) and C3–N4–C5–C6 (β).

lowest energy conformation with a flat geometry around C2–C3, whereas the lowest energy conformation of 9′ possesses a twisted geometry. Remarkable is the fact that the presence of a flat geometry around C2–C3 is much more expressed in the Molecular Mechanics adapted MMX force field than in the semiempirical MNDO–PM3 force field. A rotational analysis was performed, using rigid rotor approximations,[18] to investigate the contribution of the nonminimal conformations to the reactivity. After geometry optimization (MMX values) 1225 conformations were generated[19] by dihedral angle changes of 10°,[20] rotating about the bonds C2–C3 and N4–C5 defining the rotational freedom of the compounds 8′ and 9′. For each conformation its MM energy was calculated.

Since all conformations are assumed to be thermally accessible, the *probability* (P_i) of the molecules to be in a particular conformation can be calculated, for a given temperature, using the Bolzmann distribution equation[18] (eq 1).

$$P_i = \frac{e^{-dE_i/RT}}{Q} \qquad Q = \sum_{i=1}^{n} e^{-dE_i/RT} \tag{1}$$

n = no. of conformations, $dE_i = E_i - E_{min}$ (J), R = 8.31 (J mol^{-1} K^{-1}), T = temperature (K)

For the compounds 8′ and 9′ such a rotational analysis is relatively simple, since the rotational freedom of the molecules is described by only two diheral angles: α (N1–C2–C3–N4) and β (C3–N4–C5–C6) (see Figure 2). In Figure 2, the P_i of each conformation is plotted versus the two dihedral angles α and β. From Figure 2, part a, it is seen that for compound 8′ the only conformations with a probability greater then zero are those with a flat geometry in which the reactive sites cannot interact. Apparently the formation of a stabilizing conjugated system limits the rotational freedom of the molecule. Figure 2, part b, shows that for compound 9′ the probability of being in a reactive conformation (i.e., $\alpha \sim 90°$ and $-45° < \beta < 45°$) is definitively present. Furthermore, it is seen that in compound 9′ the rotation about C2–C3 has also some restrictions, most likely caused by steric hindrance, but they act in favor of obtaining a geometry suitable for the cycloaddition reaction.

(18) (a) Smeyers, Y. G.; Hernandez-Laguna, A. *Int. J. Quantum Chem.* **1986**, *29*, 553. (b) Miller, K. E.; Rich, D. H. *J. Am. Chem. Soc.* **1989**, *111*, 8351.

(19) The conformational analyses were performed within the CHEMX program (Davies, E. K.; Murall, N. W. *Computers Chem.* **1989**, *13*, 149) with the structural parameters obtained from a geometry optimization of the molecules in the MMX force field.[20]

(20) The generation of two or three times as much conformations, using smaller increments, did not improve the outcome of the conformational analysis.

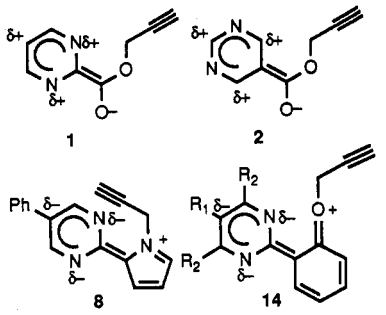


Figure 3. Important resonance structures of the compounds 1, 2, 8, and 14a.

Comparison of the Reactivity of the Compounds 1 and 2. On first sight, the compounds 1 and 2 (which is a structural isomer of 1) are not expected to differ considerably in reactivity because they are, in principle, both capable of having a resonance-stabilized flat conformation about C2–Cα (for 1) or C5–Cα (for 2), respectively. In these flat conformations, the diene and dienophile cannot interact. However, as indicated in Table I, compound 1 is found to react under the applied conditions, whereas for 2 no reaction was observed.

As possible explanation can be put forward that the steric hindrance between two lone pairs is larger than that between a lone pair and a hydrogen atom.[21] Therefore, in 1 the interaction between the lone pairs of the pyrimidine nitrogens and the lone pairs of the oxygens destabilizes a flat geometry, whereas in 2 the steric interactions of the hydrogen atoms at C4 and C6 with the lone pairs of the oxygens is not large enough to prevent the formation of a conjugated system. Furthermore, the stabilization by conjugation in compound 2 is supposed to be larger than that in 1, because the charge distribution in the resonance structures of 1 should give rise to positive charges on the nitrogen atoms (see Figure 3).

In the semiempirical study (see Table I) it is seen that the energy differences between the HOMO and LUMO of 1 and 2 are in agreement with the observed order of reactivity. However, the difference in $\Delta E(\mathrm{HOMO_{dp}} - \mathrm{LUMO_{de}})$ between 1 and 2 may not be the only factor responsible for the reactivity of 1 and the nonreactivity of 2. Therefore, a conformational study was performed for both compounds. Because 1 and 2 possess three dihedral angles describing the conformational freedom of the molecules, the probability of each conformation (eq 1), cannot be plotted versus its dihedral angles, as was done for the compounds 8′ and 9′. A universal method for parametrizing the reactivity of a conformation, independent of the number of degrees of freedom, is the determination of the distance between the reactive sites in a conformation and correlation of this to its probability.[4] For all compounds the distance Cx···Cy (see Scheme I) can be regarded as a parameter for the reactivity of a certain conformation.[22] By taking the summed probabilities[23] of

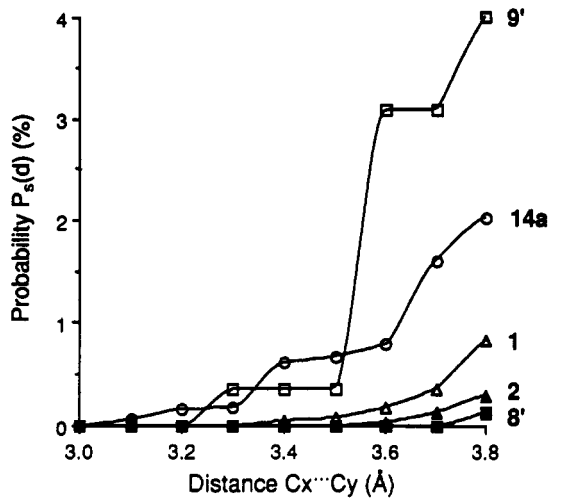


Figure 4. Probability $P_s(d)$[23] of the compounds 1, 2, 8′, 9′, and 14a versus the distance Cx···Cy.

conformations having a distance Cx···Cy shorter than a certain distance, the reactivity can be visualized (see Figure 4).

In Figure 4, the summed probabilities for each compound to have a distance Cx···Cy shorter than 2 times the van der Waals distance of carbon (1.9 Å) is depicted for all compounds. For compound 1 the probability of being in a reactive conformation is significantly higher than that for 2. This result combined with the energy difference between the FMOs of 1 and 2 explains why the reactivity of 2 is much lower than that of 1.

Comparison of the lowest energy conformations of 1 and 2 also supports the flat geometry of compound 2 as the most favored one, whereas the optimized geometry of 1 reveals a geometry around C2–Cα that is suitably orientated for a cycloaddition (see Table II). Again it is remarkable that the MMX program calculates a much smaller dihedral angle α than the VAMP program, whereas the dihedral angles β and γ agree much better.

Comparison of the Reactivity of the Compounds 14a–d. Although the molecules 14a–d are, in principle, able to form a conjugated system around C2–Cα, they are found to undergo the intramolecular Diels–Alder reactions rather easily. Apparently, steric interactions between the pyrimidine and the 2-(prop-2-ynyloxy) group of the phenyl part forces the molecules out of the planar conformations. Rotation about C2–Cα creates a reactive conformation for the Diels–Alder reaction.

A support for the statement that steric hindrance prevents the formation of a stabilizing conjugated system in the compounds 14 is given by comparison of the UV spectra of 12, 14a, and 17a. A λ_{max} value of 334 and 333 nm for the compounds 12 and 17a, respectively, indicates a flat geometry. For compound 14a the lack of a λ_{max} above 300 nm indicates a twisted geometry. Upon comparing the ^{1}H-NMR spectra of these compounds one observes a clear anisotropic effect for the proton Ha (see Scheme IV). In the flat geometries of the compounds 12 and 17a, Ha has a chemical shift of 8.50 and 8.25 ppm, respectively, whereas the chemical shift of the same proton in the twisted compound 14a is 7.81 ppm.

In the computational study of compound 14a, it is seen that the lowest energy conformation (see Table II) shows

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(22) For a molecule the probability of being in a conformation with a certain distance Cx···Cy ($P_d(d(Cx\cdots Cy))$ is given by adding the probabilities P_i (see eq 1) of the conformations having a distance within a sorting interval of 0.1 Å.

$$P_d(d(Cx\cdots Cy)) = \sum_{d=d-0.1}^{d} P_i(d)$$

(23) The probabilities ($P_s(d)$) of a molecule to have a distance Cx···Cy smaller than a certain distance d is given by

$$P_s(d) + \sum_{d=0}^{d} P_d(d(Cx\cdots Cy))$$

a twisted geometry about C2–Cα. This agrees with the UV and ^{1}H-NMR measurements of **14a**. Determination of the probability distribution, using the method applied for the compounds **1** and **2**, showed that for **14a** the probability of being in a reactive conformation is certainly present (see Figure 4). Although the entropic assistance for the formation of 5-membered rings in intramolecular reactions is usually larger than that for the formation of 6-membered rings, the favorable orientation of the diene and dienophile in **14**, due to the limited conformational freedom of the tether, compensates for this disadvantage. Calculation of the HOMO and LUMO energies of **14a** revealed that they are of the same magnitude as the other compounds under study (see Table I). Combination of these results clearly indicates that both the conformational and electronical properties of the compounds **14** are favorable toward cycloaddition.

Comparison of the Reactivity of the Compounds 1, 2, 8′, 9, and 14a. From Table I it can be seen that the energy differences between the HOMOs and LUMOs of the compounds under study are all of the same order of magnitude, which is normal for Diels–Alder reactions of these kinds of compounds. From Figure 4 it is seen that the probabilities ($P_s(d)$) of the compounds to have a distance C*x*···C*y* < 3.8 Å agree with the observed rate of reactivity (**9′** ≫ **14a** > **1** ≫ **2**, **8′**). As was already suggested, the reason for the increase in reactivity when going from **8′** to **9′** is correlated with the probability of the molecules to be in a geometry which is favorable for undergoing a Diels–Alder reaction. The very small probability of **8′** to be in reactive conformations is mainly due to its geometrical inability to form conformations with a short distance C*x*···C*y*.

In conclusion, the differences in reactivity of the studied compounds cannot always be ascribed to an unfavorable energy difference between the HOMO and LUMO of the diene and dienophile moieties of the molecules. It appears that the conformational properties of the molecules in question are an important factor in the reactivity of the compounds. Furthermore, the described method for comparing the relative reactivities by calculating the probability partition related to the distance of the reactive sites appears to be very fruitful in our systems.

Experimental Section

Synthesis and Ring Transformations. Melting points are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker AC200 spectrometer. Chemical shifts are determined in ppm downfield from tetramethylsilane. Mass spectral data were obtained on a AEI MS 902 spectrometer equipped with a VG ZAB console and a Hewlett Packard 5970B MSD. Column chromatography was performed on Merck silica gel 60 (70–230-mesh ASTM).

2-[(Prop-2-ynyloxy)carbonyl]pyrimidine (1). 2-Cyanopyrimidine (1.0 g) was dissolved in a mixture of 10 mL of dry ether and 3 mL of propargyl alcohol. This mixture was saturated with dry HCl gas. After 2 h the mixture was concentrated, water (15 mL) was added, and the mixture was extracted with dichloromethane. Column chromatography with ethyl acetate gave **1**. Yield: 4.5%. White needles, mp: 120–121 °C (hexane/toluene). ^{1}H NMR ($CDCl_3$) δ: 8.98 (d, *J* = 5.0 Hz, 2 H), 7.56 (t, *J* = 5.0 Hz, 1 H), 5.07 (d, *J* = 2.4 Hz, 2 H), 2.59 (t, *J* = 2.5 Hz, 1 H).

Anal. Calcd for $C_8H_6N_2O_2$ (162.15): C, 59.25; H, 3.73; N, 17.27. Found: C, 59.38; H, 3.78; N, 17.30.

5-[(Prop-2-ynyloxy)carbonyl]pyrimidine (2). A mixture of 4.0 g of 5-carboxypyrimidine,[10] 1.8 g of propargyl alcohol, 6.5 g of dicyclohexylcarbodiimide (DCC), 3.9 g of 4-(dimethylamino)pyridine, and 100 mL of dichloromethane was stirred for 24 h at room temperature. After filtration, the product was obtained by column chromatography using ether/ethyl acetate (1:1) as eluent. Yield: 77%. Light yellow crystals, mp: 75–76 °C. ^{1}H NMR ($CDCl_3$) δ: 9.41 (s, 1 H), 9.31 (s, 1 H), 4.99 (d, *J* = 2.5 Hz, 2 H), 2.56 (t, *J* = 2.5 Hz, 1 H). HRMS calcd for $C_8H_6N_2O_2$: 162.0429. Found: 162.0429.

Anal. Calcd for $C_8N_2H_6O_2$ (162.15): C, 59.25; H, 3.73; N, 17.27. Found: C, 59.03; H, 3.69; N, 17.18.

5-Phenyl-2-(2-pyrryl)pyrimidine (6). To a mixture of 10 mmol of 2-pyrrolecarboxamidine **2** (prepared from 2-cyanopyrrole by the method of Pinner[24]) and 10 mmol of 1-(dimethylamino)-3-(dimethyliminio)-2-phenylprop-1-ene perchlorate (**5**, R_1 = Ph) in 20 mL of ethanol was added dropwise in 0.5 h a solution of 25 mmol of sodium ethanolate in 15 mL of ethanol. The mixture was refluxed for 2 h. After concentration and addition of 25 mL of water the mixture was neutralized with 2 N H_2SO_4 and extracted with dichloromethane. After drying ($MgSO_4$) the organic layer was concentrated and the residue was recrystallized from toluene/hexane to give **6**. Yield: 45%. Yellow-brown crystals, mp: 172 °C dec. ^{1}H NMR ($CDCl_3$) δ: 9.5 (br, NH), 8.84 (s, 2 H), 7.7–7.4 (mc, 5 H), 7.18 (m, 1 H), 6.98 (m, 1 H), 6.35 (m, 1 H).

Anal. Calcd for $C_{14}H_{11}N_3$ (221.25): C, 75.99; H, 5.01; N, 18.99. Found: C, 76.12; H, 5.06; N, 19.31.

5-Phenyl-2-[2-(1-prop-2-ynylpyrryl)]pyrimidine (8). To a vigorously stirred mixture of 10 mL of a 50% aqueous solution of sodium hydroxide and 2.5 mL of DMSO was added 1 mmol of **6**. After 0.1 h 1.5 mmol of bromopropyne was added dropwise under stirring and the mixture was heated at 40 °C for 2 h. The mixture was diluted with water (15 mL) and extracted with dichloromethane. The organic layer was concentrated to a small volume. Column chromatography of the resulting mixture with dichloromethane gave **8**. Yield: 28%. Brown crystals, mp: 109–111 °C (hexane). ^{1}H NMR ($CDCl_3$) δ: 9.03 (s, 2 H), 7.8–7.5 (mc, 5 H), 7.42 (m, 1 H), 7.27 (m, 1 H), 6.43 (m, 1 H), 5.63 (d, *J* = 2.5 Hz, 2 H), 2.48 (t, *J* = 2.5 Hz, 1 H).

Anal. Calcd for $C_{17}H_{13}N_3$ (259.30): C, 78.73; H, 5.05; N, 16.20. Found: C, 78.98; H, 5.35; N, 15.90.

5-Phenyl-2-(pyrrolidin-2-yl)pyrimidine (7). To a suspension of 40 mmol (6.28 g) of *N*-acetylprolinamide[25] in 120 mL of dichloromethane was added 40 mmol (7.6 g) of triethyloxonium tetrafluoroborate. The mixture is stirred for 24 h at room temperature. After an initial dissolution a solid material deposits. The solvent was decanted, the residue was stirred with 300 mL of dry ether, and the solvent was decanted again. Then 25 mL of methanol saturated with ammonia was added at 0 °C and the mixture was stirred for 1 day. The solution was filtered and concentrated to give crude *N*-acetylprolinamidine (**4**) as judged by its ^{1}H-NMR spectrum.

The crude amidine was dissolved in 80 mL of ethanol and 8.0 g of 1-(dimethylamino)-3-(dimethyliminio)-2-phenylprop-1-ene perchlorate (**5**, R_1 = Ph) was added. To this stirred mixture was added dropwise a solution of sodium ethanolate, prepared from 600 mg of sodium in 40 mL of absolute ethanol, during 0.5 h. Then the mixture was refluxed for 3 h. After concentration of the reaction mixture 100 mL of water was added and the mixture was extracted with dichloromethane (4 × 70 mL). The combined organic layers were dried on $MgSO_4$ and concentrated. The residue, which contains 5-phenyl-2-(1-acetylpyrrolidin-2-yl)pyrimidine (^{1}H NMR) was hydrolyzed by refluxing for 2 h in 50 mL of 6 N HCl. After cooling, 50 mL of water was added and solid sodium hydrogen carbonate was added until pH 8. Continuous extraction with ether gave **7**. ^{1}H NMR ($CDCl_3$) δ: 8.87 (s, 2 H), 7.7–7.3 (mc, 5 H), 4.5 (m, 1 H), 3.5–2.9 (3 H), 2.6–1.7 (4 H). HRMS calcd for $C_{14}H_{15}N_3$: 225.1266. Found: 225.1262.

5-Phenyl-2-(1-prop-2-ynylpyrrolidin-2-yl)pyrimidine (9). A mixture of 2 g of the crude amine **7**, 3 g of bromopropyne, and 2 g of potassium carbonate in 50 mL of ethanol was stirred vigorously at room temperature for 3 h. The solid material was filtered and washed with ethanol and the filtrate was concentrated. Column chromatography of the residue with dichloromethane/ether 1:1 gave pure **9**. Yield: 0.75 g (7.5%, overall yield starting from *N*-acetylprolinamide). Mp: 73–74 °C (hexane). ^{1}H NMR ($CDCl_3$) δ: 8.90 (s, 2 H), 7.7–7.4 (mc, 5 H), 4.05 (t, *J* = 7.5 Hz, 1 H), 3.50 (2 x dd, J_1 = 17.4 Hz, J_2 = 2.4 Hz, 2 H), 3.20 (m, 1 H), 2.85 (m, 1 H), 2.33 (m, 1 H), 2.18 (t, *J* = 2.4 Hz, 1 H), 2.15–1.8

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(25) Buschauer, A.; Wegner, K.; Schunack, W. *Arch. Pharm.* **1984**, *317*, 9.

(3 H). HRMS calcd for $C_{17}H_{17}N_3$: 263.1422. Found: 263.1419.

Anal. Calcd for $C_{17}H_{17}N_3$ (263.33): C, 77.53; H, 6.50; N, 15.95. Found: C, 77.25; H, 6.54; N, 15.68.

Synthesis of the 2-[2-(Prop-2-ynyloxy)phenyl]pyrimidines 14a–c. A solution of 1.14 g (6.0 mmol) of triethyloxonium tetrafluoroborate in 5 mL of dry dichloromethane was added to a suspension of 1.05 g (6.0 mmol) of *o*-(prop-2-ynyloxy)benzamide[26] in 20 mL of dry dichloromethane. After stirring the mixture overnight, the resulting clear solution was evaporated to about 10 mL and treated with 50 mL of dry ether upon which a brownish slurry was deposited. The organic solvent was decanted and the residue was additionally twice treated with 25 mL of dry ether and the solvent decanted. The residue was then evaporated to dryness. To this residue was added 5 mL of absolute ethanol saturated with ammonia. The resulting mixture was stirred for 3 days at room temperature in a tightly stoppered flask. Then the mixture was evaporated to dryness to yield crude *o*-(prop-2-ynyloxy)benzamidine (**10**). To a stirred solution of this crude amidine and 5 mmol of the appropriate trimethinium perchlorate **5** in 15 mL of ethanol was added dropwise a solution of 7.5 mmol of sodium ethanolate. After 0.5 h at room temperature the mixture was refluxed for 2 h. After concentration of the mixture, 20 mL of water was added and the mixture was extracted three times with dichloromethane. The combined organic extracts were dried with $MgSO_4$, concentrated, and purified by column chromatography on silica gel using dichloromethane/ether 4:1 as eluent.

2-[2-(Prop-2-ynyloxy)phenyl]pyrimidine (14a) was prepared from 1-(dimethylamino)-3-(dimethyliminio)prop-1-ene perchlorate (**5**, R_1 = H), according to the general procedure described above. Yield: 40%. Mp: 67–71 °C (hexane). ^{1}H NMR ($CDCl_3$) δ: 8.78 (d, J = 5.0 Hz, 2 H), 7.73 (dd, J_1 = 7.0 Hz, J_2 = 1.8 Hz, 1 H), 7.5–7.0 (4 H), 4.70 (d, J = 2.4 Hz, 2 H), 2.45 (t, J = 2.4 Hz, 1 H).

Anal. Calcd for $C_{13}H_{10}N_2O$ (210.23): C, 74.26; H, 4.79; N, 13.32. Found: C, 74.10; H, 4.82; N, 13.47.

5-Chloro-2-[2-(prop-2-ynyloxy)phenyl]pyrimidine (14b) was prepared from 2-chloro-1-(dimethylamino)-3-(dimethyliminio)prop-1-ene perchlorate (**5**, R_1 = Cl), according to the general procedure described above. Yield: 46%. Mp: 79–80 °C (hexane). ^{1}H NMR ($CDCl_3$) δ: 8.74 (s, 2 H), 7.73 (dd, J_1 = 7.2 Hz, J_2 = 1.8 Hz, 1 H), 7.5–7.0 (3 H), 4.70 (d, J = 2.4 Hz, 2 H), 2.47 (t, J = 2.4 Hz, 1 H).

Anal. Calcd for $C_{13}H_9ClN_2O$ (244.68): C, 63.80; H, 3.70; N, 11.45. Found: C, 63.67; H, 3.68; N, 11.36.

5-Phenyl-2-[2-(prop-2-ynyloxy)phenyl]pyrimidine (14c) was prepared from 1-(dimethylamino)-3-(dimethyliminio)-2-phenylprop-1-ene perchlorate (**5**, R_1 = Ph), according to the general procedure described above. Yield: 49%. Mp: 133–134 °C (toluene/hexane). ^{1}H NMR ($CDCl_3$) δ: 9.03 (s, 2 H), 7.81 (dd, J_1 = 7.2 Hz, J_2 = 1.8 Hz, 1 H), 7.7–7.0 (8 H), 4.79 (d, J = 2.4 Hz, 2 H), 2.45 (t, J = 2.4 Hz, 1 H).

Anal. Calcd for $C_{19}H_{14}N_2O$ (286.32): C, 79.69; H, 4.92; N, 9.78. Found: C, 80.00; H, 5.04; N, 9.79.

Synthesis of 4,6-Dimethyl-2-[2-(prop-2-ynyloxy)phenyl]-pyrimidine (14d). A mixture of 1.5 g of crude 2-(prop-2-ynyloxy)benzamidine (**10**), obtained as described above, and 5 mmol of pentanedione in a saturated solution of potassium carbonate in 10 mL of water and 3 mL of ethanol was stirred for 3 days at room temperature. After addition of 20 mL of water the mixture was extracted with dichloromethane. The organic layer was dried on $MgSO_4$ and concentrated to give **14d**. Yield: 5%. Oil. ^{1}H NMR ($CDCl_3$) δ: 7.63 (dd, J_1 = 7.2 Hz, J_2 = 1.8 Hz, 1 H), 7.5–7.0 (3 H), 6.96 (s, 1 H), 4.72 (d, J = 2.4 Hz, 2 H), 2.50 (s, 6 H), 2.43 (t, J = 2.4 Hz, 1 H). HRMS calcd for $C_{15}H_{14}N_2O$: 238.1106. Found: 238.1101.

2-(2-Hydroxyphenyl)-5-phenylpyrimidine (12). To a stirred suspension of 2-hydroxybenzamidinium sulfate (7.5 mmol) and 1-(dimethylamino)-3-(dimethyliminio)-2-phenylprop-1-ene perchlorate **5** (R_1 = Ph) (5.0 mmol) in ethanol (25 mL) was added at room temperature a solution of 12.5 mmol of sodium ethanolate in 25 mL of ethanol. After 0.5 h another 5.0 mmol of sodium ethanolate solution was added and the reaction mixture refluxed for 2 h. After concentration of the mixture, 50 mL of water was added and the water layer acidified with 4 N H_2SO_4. The water layer was then extracted with dichloromethane (2 × 75 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give **12**. Yield: 78%. Mp: 157–158 °C (toluene). ^{1}H NMR ($CDCl_3$) δ: 8.96 (s, 2 H), 8.50 (dd, J_1 = 7.5 Hz, J_2 = 1.8 Hz, 1 H), 7.6–6.8 (mc, 8 H).

Anal. Calcd for $C_{16}H_{12}N_2O$ (248.27): C, 77.39; H, 4.87; N, 11.28. Found: C, 77.34; H, 4.84; N, 11.20.

5-Phenyl-2-[2-(prop-1-ynyloxy)phenyl]pyrimidine (14c) from 12. To a stirred suspension of sodium hydride (0.18 g; 80% oil dispersion) in 20 mL of tetrahydrofuran was added 2-(2-hydroxyphenyl)-5-phenylpyrimidine (**12**) (1.0 g; 4.0 mmol). After the initial effervescence had subsided 4.80 g of propargyl bromide (80% solution in toluene) was added and the reaction mixture refluxed for 25 h. The tetrahydrofuran was removed under reduced pressure and water (50 mL) was added. The water layer was extracted with dichloromethane (2 × 75 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Column chromatography of the residue (eluting with dichloromethane) gave **14c**. Yield: 50% (based on **12** consumed). Mp and ^{1}H NMR ($CDCl_3$) are identical with those of the same compound obtained in a different way (see above).

4,6-Dimethyl-2-(2-hydroxyphenyl)pyrimidine (13). To a mixture of *o*-hydroxybenzamidinium sulfate (5.0 mmol), pentanedione (5.0 mmol), and potassium carbonate (40 mmol) was added water until dissolution. The resulting solution was then stirred for 3 days, neutralized with 2 N H_2SO_4, and extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated and the residue was subjected to column chromatography (eluting with dichloromethane) to obtain **13**. Yield 12%. Mp: 81 °C (hexane). ^{1}H NMR ($CDCl_3$) δ: 8.48 (dd, J_1 = 7.2 Hz, J_2 = 1.8 Hz, 1 H), 7.3 (m, 1 H), 7.1–6.8 (2 H), 6.86 (s, 1 H).

Anal. Calcd for $C_{12}H_{12}N_2O$ (200.23): C, 71.97; H, 6.04; N, 13.99. Found: C, 72.03; H, 6.15; N, 13.99.

4,6-Dimethyl-2-[2-(prop-2-ynyloxy)phenyl]pyrimidine (14d) from 13. To a solution of 5.0 g of sodium hydroxide in 5 mL water and 2.5 mL dimethyl sulfoxide was added 150 mg of **12**. The resulting mixture was stirred vigorously for 5 min. Then propargyl bromide (1.5 equiv) was added dropwise and the resulting mixture heated at 35–40 °C for 2 h. The mixture was then poured into water (100 mL) and extracted with ether. The ethereal layer was dried ($MgSO_4$), concentrated, and subjected to column chromatography (eluting first with dichloromethane, then ether) to give **13d**. Yield 80%. Oil. ^{1}H NMR ($CDCl_3$) spectrum is identical with that of the same compound obtained in a different way (see above).

Furo[3,4-*b*]pyridin-7(5*H*)-one (15). **1** (1 mmol) in 1 mL of nitrobenzene was heated at 180 °C for 24 h. Column chromatography first with dichloromethane and second with ether/ethyl acetate 1:1 as eluent gave **15**. Yield: 80%. Mp: 161–162 °C. ^{1}H NMR ($CDCl_3$) δ: 8.85 (d, J = 6 Hz, 1 H), 7.92 (d, J = 8 Hz, 1 H), 7.55 (m, 1 H), 5.37 (s, 2 H). ^{13}C NMR ($CDCl_3$) δ: 168.23, 152.29, 144.08, 140.16, 130.85, 126.97, 67.49. The ^{13}C NMR spectrum and melting point are identical to those mentioned in the literature.[27]

5,5a,6,7,8,8a-Hexahydro-3-phenylpyrido[3,2-*c*]pyrrolizine (16). **9** (1 mmol) in 2 mL of nitrobenzene was heated under nitrogen at 170 °C for 4 h. Column chromatography with ethyl acetate/methanol/triethylamine 15:4:1 as eluents gave **16**. Yield: 30%. Oil. ^{1}H NMR ($CDCl_3$) δ: 8.65 (d, J = 2 Hz, H-2, 1 H), 7.67 (d, J = 2 Hz, H-4, 1 H), 7.6–7.3 (5 H), 4.6 (m, H-8a, 1 H), 4.44 (d, J = 15 Hz, 1 H), 3.92 (d, J = 15 Hz, 1 H), 3.23 (m, 1 H), 2.7–1.7 (5 H). HRMS calcd for $C_{16}H_{16}N_2$: 236.1313. Found: 236.1313.

Intramolecular Diels–Alder Reactions of the 2-[2-(Prop-2-ynyloxy)phenyl]pyrimidines 14. A solution of 1 mmol of the appropriate pyrimidine **14** in 2 mL of nitrobenzene was heated under a nitrogen atmosphere at 200 °C for 4 h. Column chromatography of the reaction mixture on silica gel with dichloromethane as eluent gave the corresponding light yellow colored 5*H*-[1]benzopyrano[4,3-*b*]pyridines **17a–d**.

5*H*-[1]Benzopyrano[4,3-*b*]pyridine (17a) was prepared from **14a**, according to the general procedure described above. Yield: 87%. Oil. ^{1}H NMR ($CDCl_3$) δ: 8.52 (dd, J_1 = 4.8 Hz, J_2 = 1.5

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Hz, H-2, 1 H), 8.20 (dd, J_1 = 7.5 Hz, J_2 = 1.9 Hz, H-10, 1 H), 7.4–6.8 (5 H), 5.12 (s, 2 H). HRMS calcd for $C_{12}H_9NO$: 183.0684. Found: 183.0670.

3-Chloro-5*H*-[1]benzopyrano[4,3-*b*]pyridine (17b) was prepared from **14b**, according to the general procedure described above. Yield: 83%. Light yellow crystals, mp: 99–100 °C (hexane). ^{1}H NMR ($CDCl_3$) δ: 8.44 (d, J = 2.4 Hz, H-2, 1 H), 8.12 (dd, J_1 = 7.5 Hz, J_2 = 1.8 Hz, H-10, 1 H), 7.4–6.8 (4 H), 5.09 (s, 2 H).

Anal. Calcd for $C_{12}H_8ClNO$ (217.65): C, 66.21; H, 3.70; N, 6.43. Found: C, 65.92; H, 3.61; N, 6.34.

3-Phenyl-5*H*-[1]benzopyrano[4,3-*b*]pyridine (17c) was prepared from **14c**, according to the general procedure described above. Yield: 66%. Light yellow crystals, mp: 93–95 °C (toluene/hexane). ^{1}H NMR ($CDCl_3$) δ: 8.82 (d, J = 2.4 Hz, H-2, 1 H), 8.25 (dd, J_1 = 7.5 Hz, J_2 = 1.8 Hz, H-10, 1 H), 7.7–6.9 (9 H), 5.28 (s, 2 H).

Anal. Calcd for $C_{18}H_{13}NO$ (259.29): C, 83.37; H, 5.05; N, 5.40. Found: C, 83.43; H, 5.05; N, 5.37.

3-Methyl-5*H*-[1]benzopyrano[4,3-*b*]pyridine (17d) was prepared from **14d**, according to the general procedure described above. Yield: 80%. Oil. ^{1}H NMR ($CDCl_3$) δ: 8.23 (dd, J_1 = 7.5 Hz, J_2 = 1.8 Hz, H-10, 1 H), 7.4–6.8 (5 H), 5.12 (s, 2 H), 2.57 (s, 3 H). HRMS calcd for $C_{13}H_{11}NO$: 197.0841. Found: 197.0837.

Computations. All Molecular Mechanics calculations were performed on the VAX cluster of the CAOS/CAMM Centre, University of Nijmegen, The Netherlands. The semiempirical VAMP program was used on the CONVEX C120 computer of the CAOS/CAMM Centre. For the determination of P_i (eq 1), $P_d(d(Cx\cdots Cy))$,[22] and $P_s(d)$[23] of the compounds **1**, **2**, and **14a**, 42875 conformations were generated[19] by dihedral angle changes of 10°,[20] rotating about the bonds defining their rotational freedom. For each conformation its MM energy was calculated.

The methods used for the calculations have been described in earlier publications of our group.[4]

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Registry No. **1**, 139584-77-3; **2**, 139584-78-4; **3**, 105533-75-3; **4**, 139584-79-5; **5** (R_1 = H), 1611-78-5; **5** (R_1 = Cl), 2009-80-5; **5** (R_1 = Ph), 7089-34-1; **6**, 139584-80-8; **7**, 139584-81-9; **7** acetyl, 139584-87-5; **8**, 139584-82-0; **9**, 139584-83-1; **10**, 57075-98-6; **11**, 37597-80-1; **12**, 139584-84-2; **13**, 139584-85-3; **14a**, 139584-88-6; **14b**, 139584-89-7; **14c**, 139584-90-0; **14d**, 139584-91-1; **15**, 4733-69-1; **16**, 139584-86-4; **17a**, 29767-29-1; **17b**, 139584-92-2; **17c**, 139584-93-3; **17d**, 139584-94-4; $CH_3COCH_2COCH_3$, 123-54-6; $BrCH_3C{\equiv}CH$, 106-96-7; 2-cyanopyrimidine, 14080-23-0; propargyl alcohol, 107-19-7; 5-carboxypyrimidine, 4595-61-3; *N*-acetylprolinamide, 16395-58-7; *o*-(prop-2-ynyloxy)benzamide, 66362-34-3.

Synthesis and Properties of the Eight Isostatine Stereoisomers[1]

Kenneth L. Rinehart,* Ryuichi Sakai, Vimal Kishore, David W. Sullins, and Kai-ming Li

Roger Adams Laboratory, University of Illinois, Urbana, Illinois 61801

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The eight possible stereoisomers of isostatine, (3*S*,4*R*,5*S*)-4-amino-3-hydroxy-5-methylheptanoic acid, have been synthesized from the four isomeric D- and L-isoleucinals and D- and L-*allo*-isoleucinals and ethyl lithioacetate. The eight isomers have been compared for the GC retention times of their bis(trifluoroacetyl) methyl ester derivatives and the ^{1}H NMR properties of the γ-lactams derived from them. The natural isomer was shown to be the 3*S*,4*R*,5*S* isomer.

Didemnin B (**2**) is currently in phase II clinical trials as an anticancer agent.[2] A structure study of didemnins A–E (**1–5**),[3-6] antitumor, antiviral, and immunosuppressive cyclic depsipeptides from the marine tunicate (sea squirt, subphylum Urochordata) *Trididemnum solidum*,[2] was completed by our recent identification and assignment of the stereochemistry of (3*S*,4*R*,5*S*)-isostatine (**6**, Ist), the C_8 amino acid of the didemnins,[1,7] and by our total synthesis of didemnin A [**1**, as well as B and C (**2**, **3**)], involving the incorporation of **6** into the didemnins.[7] We describe here the syntheses and properties of all eight stereoisomers of isostatine (**6–13**) (Chart I).

The novel C_8 γ-amino-β-hydroxy acid isostatine (**6**) has thus far been found only in the didemnins.[8] It is, however, related to statine (**14**, Sta, which has an isobutyl instead of a *sec*-butyl terminus), found previously in the proteinase

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