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Ionic vs Pericyclic Transition States for the Cyclization Reactions of C_α-N Anions Derived from Amides and Phosphinamides

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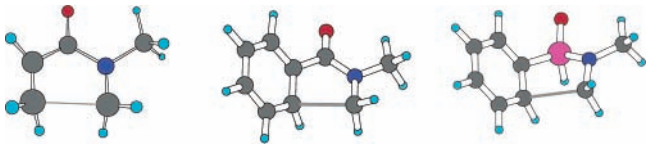
ABSTRACT



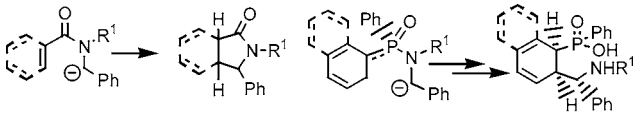
Ab initio and DFT calculations indicate that the anionic cyclization of vinyl- and phenyl-carboxamides and phosphinamides metalated at the C_α-N carbon fits better to a Michael-type ionic addition than to an electrocyclic ring closure. The lithium atom has no influence on the type of reaction mechanism.

Anionic cyclization reactions represent an efficient synthetic tool for the preparation of carbocyclic and heterocyclic systems. The sequence of reactions involves the metalation of an acyclic precursor followed by an intramolecular carbon−carbon bond formation step through addition to a suitable functional group and subsequent quench of the resulting anion with a variety of electrophiles. The process affords substituted ring systems, generally, with high regio- and stereocontrol.[1]

Clayden and co-workers reported the cyclization of lithiated *N*-benzylacrylamides **1** and *N*-benzylbenzamides **2** (Scheme 1).[2,3] On the other hand, we have recently reported a new route to conformationally restricted γ-aminophosphinic acids **7** and **8** through dearomatizing anionic cyclization of *N*-benzyldiphenyl- **5** and dinaphthylphosphinamides **6**, respectively (Scheme 1).[4]

Two different mechanisms can be envisaged to explain the anionic cyclization reaction, as illustrated with model system **9** (Figure 1): (i) a *5-endo-trig* intramolecular,[5] Michael-type nucleophilic attack of the carbanionic center to the ortho position of the electron-deficient aromatic ring or to the β-carbon atom of the double C−C bond in anions **9**, and (ii) a disrotatory electrocyclic ring-closure of the 2-azapentadienyl-like dipolar resonant structure **10**, as first proposed by Clayden and co-workers (Figure 1).[3] Considering the similarity between the carboxamide and phosphinamide linkages, we wondered if similar mechanisms would be operative in the anionic cyclization of both types of substrates.

Scheme 1



1: Acrylamides **3**: Acrylamides **5**: phenyl **7**: phenyl
2: Benzamides **4**: Benzamides **6**: 1-naphtyl **8**: 1-naphtyl

[†] Universidad de Oviedo.
[‡] Universidad de Almería.

(1) (a) For a review, see: Mealy, M. J.; Bailey, W. F. *J. Organomet. Chem.* **2002**, *646*, 59. (b) Cheng, D.; Knox, K. R.; Cohen, T. *J. Am. Chem. Soc.* **2000**, *122*, 412. (c) Sha, C. K.; Hong, A. W.; Huang, C. M. *Org. Lett.* **2001**, *3*, 2177. (d) Ashweek, N. J.; Coldham, I.; Snowden, D. J.; Vennall, G. P. *Chem. Eur. J.* **2002**, *8*, 195. (e) Christoph, G.; Hoppe, D. *Org. Lett.* **2002**, *4*, 2189. (f) Deng, K.; Bensari, A.; Cohen, T. *J. Am. Chem. Soc.* **2002**, *124*, 12106.

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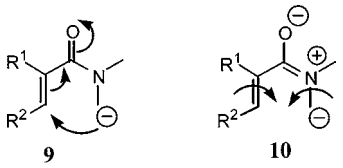


Figure 1. Michael-type cyclization of anion **9**, and six-electron, disrotatory electrocyclic ring-closure of dipolar structure **10**.

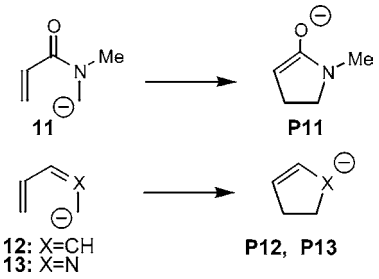
According to the predictions of the Baldwin rules,[5] the intramolecular nucleophilic addition could, in principle, be ruled out, at least in the case of the anions derived from acrylamide derivatives, but recent experiments reported by Clayden and co-workers,[2] and our own results on the case of phosphinamides, throw some doubts over the mechanism of these reactions.

In this communication, theoretical evidences obtained with high level ab initio and density functional theory electronic structure methods, about the nature of the transition states of the cyclization reactions of anions derived from carboxamides and phosphinamides, are reported.[6] The geometry of each stationary point located was fully optimized at the Becke3LYP/6-31+G* level of theory, and the nature of the stationary points was verified by frequency calculations. In some cases, MP2/6-31+G* optimizations were also carried out. All calculations were performed with the Gaussian 98 program.[7]

The potential energy surface for the cyclization of the anion **11** (Scheme 2), as a model of the reaction of acrylamide derivatives, was explored at the MP2/6-31+G* and Becke3LYP/6-31+G* levels of theory.

Also, the prototypical six-electron disrotatory ring closure reactions of anions **12** and **13** were studied, thus allowing the comparison between the transition structure for the cyclization of **11** and those corresponding to true electrocyclic transition structures.

Scheme 2



The transition structures located at the MP2/6-31+G* and Becke3LYP/6-31+G* levels of theory are shown in Figure 2.

TS11 shows a forming C−C bond of 2.419 Å, with the hydrogens at bonding termini rotated in a disrotatory mode. The geometrical features of **TS11** are quite close to those found for the transition structures **TS12** and **TS13**, corresponding to the electrocyclic closure of pentadienyl and 2-azapentadienyl anions, respectively; in these transition structures, the forming C−C bond is shortened as compared with the case of **TS11**. Also, the terminal methylene groups show the expected disrotatory rotation. The imaginary vibrational normal mode of transition structures **TS11**−**TS13** corresponds to the simultaneous C−C bond formation and disrotatory movement of the terminal methylene groups.[8]

It is interesting to note that the calculated reaction barriers for the nitrogen-containing transition structures are significantly reduced when compared with the parent pentadienyl system. In addition, it should be noted that the description of the reaction mechanism is quite similar with the two theoretical methods employed.

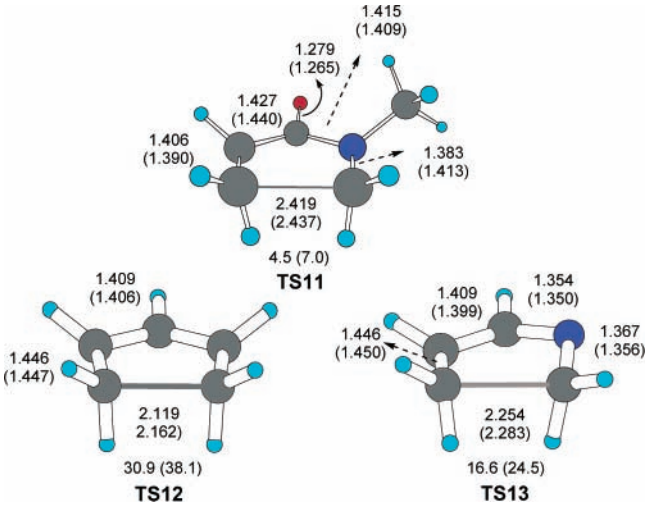


Figure 2. MP2 and Becke3LYP/6-31+G* transition structures for the cyclization of **11**, **12**, **13**. Relevant bond lengths (Å) and relative energies (kcal mol^{-1}). Becke3LYP/6-31+G* values in parentheses.

(2) Clayden, J.; Watson, D. W.; Helliwell, M.; Chambers, M. *Chem. Commun.* **2003**, 2582.

(3) Clayden, J.; Purewal, S.; Helliwell, M.; Mantell, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1049.

(4) (a) Fernández, I.; López-Ortiz, F.; Tejerina, B.; García-Granda, S. *Org. Lett.* **2001**, *3*, 1339. (b) Fernández, I.; López-Ortiz, F.; Menéndez-Velázquez, A.; García-Granda, S. *J. Org. Chem.* **2002**, *67*, 3852. (c) Ruiz-Gómez, G. López-Ortiz, F. *Synlett* **2002**, 781.

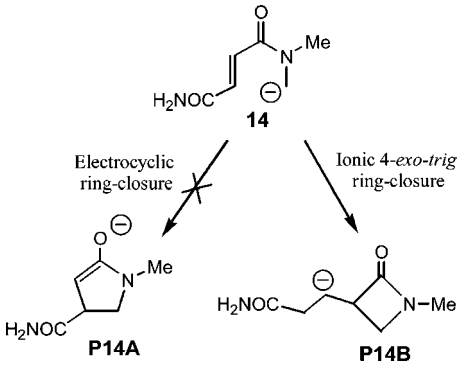
(5) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.

(6) For a description of the theoretical methodology, see: Jensen, F. *Introduction to Computational Chemistry*; Wiley: New York, 1999.

(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.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.3; Gaussian, Inc.: Pittsburgh, PA, 1998.

(8) For a detailed theoretical description of transition structures for several types of pericyclic reactions, including the one corresponding to the electrocyclic closure of pentadienyl anion, see: Houk, K. N.; Li, T.; Evanseck, J. D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 682.

Scheme 3



From these data, it can be concluded that the transition structure for the cyclization of the acrylamide anions shows some pericyclic character, as proposed by Clayden.[3] However, it should be noted that, according to the experimental results,[2] the presence of an electron-withdrawing group in the double bond of the acrylamide system changes the cyclization pathway, leading to the formation of a four-membered ring. Thus, the cyclization of the anion of dicarboxamides derived from fumaric or maleic acids leads to a β-lactam derivative, which can be formed not in an electrocyclic reaction but in an ionic 4-*exo-trig* cyclization, favored by the Baldwin rules.[5] This reaction offers a nice opportunity for testing the energetic difference between the electrocyclic and ionic cyclization modes, shown in Scheme 3.

We explored the potential energy surface corresponding to the cyclization reaction of the model dicarboxamide **14** (Scheme 3), at the Becke3LYP/6-31+G* level of theory.

Two reaction pathways, leading to the five- and four-membered rings, **P14A** and **P14B**, respectively, were found. The transition structure **TS14A** (Figure 3), corresponding to the cyclization leading to the five-membered ring, is quite similar to **TS11** and shows the characteristics of a disrotatory ring closure. However, **TS14B** corresponds to the formation of the β-lactam ring, in an ionic 4-*exo-trig* cyclization reaction.

In good agreement with the experimental results shown in Scheme 3, the 4-*exo-trig* ionic cyclization pathway is strongly favored over the pericyclic-type one, with **TS14B** being 11.3 kcal mol^{-1} more stable than **TS14A**. For this case, the precedent results indicate that, while electrocyclic transition structures are present on the potential energy surface for the anionic cyclizations of acrylamide anions, the ionic Michael-type reaction pathway, favored by the Baldwin rules, is clearly preferred.

The participation of aromatic rings has been observed in the anionic cyclization reactions of anions such as **2**, **5**, and **6** (Scheme 1).[3,4] We have studied the cyclization reactions of anions **15** and **16** (Figure 4), derived from *N*,*N*-dimethylbenzamide and *N*,*N*-dimethyl phosphinamide, respectively, at the Becke3LYP/6-31+G* level of theory.

(9) Anionic cyclization reactions of nonactivated hydrocarbon derivatives such as **19** have been reported: Schaap, L.; Pines, H. *J. Am. Chem. Soc.* **1957**, *79*, 4967.

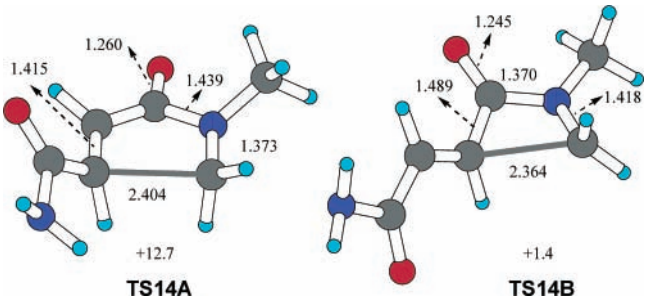


Figure 3. Becke3LYP/6-31+G*-optimized transition structures for the cyclization of dicarboxamide anion **14**. Relevant bond lengths (Å) and relative energies (kcal mol^{-1}).

The results obtained for the cyclization reaction of the aromatic systems **15** and **16** significantly differ from the case of the analogue **11**. The main difference is that in **TS15** and **TS16** the hydrogens at bonding termini do not rotate in a disrotatory mode. In addition, the normal mode corresponding to the imaginary frequency shows only the stretching movement of the two carbon atoms involved on the bond formation, while in the pericyclic transition structures **TS11**, **TS12**, and **TS13**, in addition to the stretching normal mode, the movement corresponding to the disrotatory rotation is observed. On the basis of the geometrical characteristics of **TS15** and **TS16**, the reaction can be considered to have a mechanism that clearly resembles a Michael-type ionic reaction.

To obtain additional evidence regarding the characteristics of the transition structures for intramolecular nucleophilic additions, we studied the cyclization reaction of anions **17**−**19** (Figure 5), which lack any pericyclic character.[9]

As can be seen, the geometrical features of the transition structures for the ionic cyclization of anions **17**−**19** are quite similar to those found in the case of benzamide and phosphinamide anions. The bond-forming lengths and py-

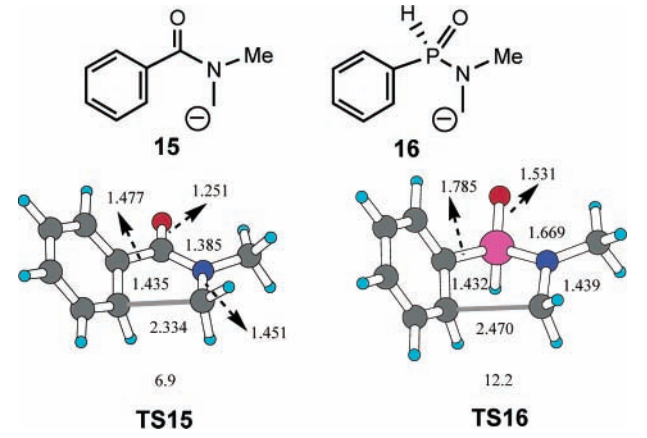


Figure 4. Becke3LYP/6-31+G*-optimized transition structures for the cyclization of benzamide and phosphinamide anions **15** and **16**. Relevant bond lengths (Å) and relative energies (kcal mol^{-1}).

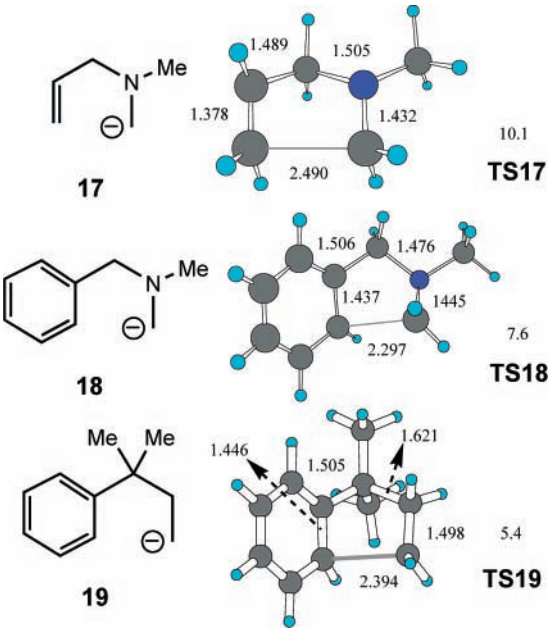


Figure 5. Becke3LYP/6-31+G*-optimized transition structures for the ionic cyclization of anions **17**−**19**. Relevant bond lengths (Å) and relative energies (kcal mol^{-1}).

ramidalization of the carbon atoms involved in the formation of the new bond are very close to the values reported before for the transition structures found in the cyclization reactions of **15** and **16**.

As an additional criterion for assessing the pericyclic nature of the reactions considered, we computed the magnetic properties for the cyclization of anions **11**, **12**, **13**, **15**, and **17** (see Supporting Information).[10,11] According to these results, no pericyclic character can be ascribed to the cyclization reactions of anions derived from the amide or phosphinamide derivatives considered in this work.

It is interesting to note that several of the anionic cyclizations studied present very low activation barriers and are very exothermic reactions (see Figure 6 and Table S2 of Supporting Information). The formation of the cyclization products is strongly favored both kinetically and thermodynamically. The thermodynamic stability of the products may be attributed to the greater charge delocalization as compared with the starting anions.

Though anionic cyclization reactions are usually carried out in strongly coordinating solvents, and it can be argued

(10) (a) Jiao, H.; Schleyer, P. v. R. *J. Phys. Org. Chem.* **1998**, *11*, 655. (b) Jiao, H.; Schleyer, P. v. R. *J. Chem. Soc., Perkin Trans. 2* **1994**, 407. (c) Herges, R.; Hiao, H.; Schleyer, P. v. R *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1376.

(11) For a definition of χ, see: Gomes, J. A. N. F.; Mallion, R. B. *Chem. Rev.* **2001**, *101*, 1349.

(12) (a) Reich, J. H.; Borst, J. P.; Dykstra, R. R. *Tetrahedron* **1994**, *50*, 5869. (b) Sikorski, W. H.; Reich, H. J. *J. Am. Chem. Soc.* **2001**, *123*, 6527.

(13) HMPA, hexamethylphosphoramide; DMPU, 1,3-dimethyl-3,4,5,6-tetrhydro-2(1*H*)-pyrimidinone.

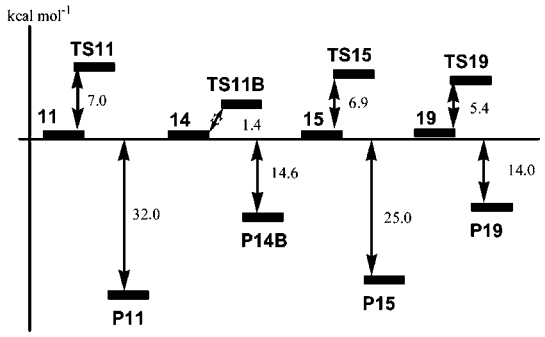


Figure 6. Energy diagram for the cyclization reactions of anions **11**, **14**, **15**, and **19**, at the Becke3LYP/6-31+G* level of theory.

that the species participating have the structure of *separated ion pairs* proposed by Reich and co-workers, it cannot be excluded that the presence of the metal could play some role in the reaction mechanism.[12]

To test the possible influence of the metal atom in both the geometry and/or energy of the transition structures, we carried out calculations at the Becke3LYP/6-31+G* level of theory, on the potential energy surface of several organolithium derivatives **20** and **21** (Figures S1 and S2, Supporting Information). It can be seen that the reaction mechanism does not change, but the activation barriers increase significantly. The sharp increase of the activation barriers caused by the presence of the lithium counter ion can be explained assuming that the metal stabilizes the starting anions more than the transition structures. When the reactions are carried out in the presence of solvents that strongly coordinate the lithium (such as HMPA or DMPU),[13] the species participating can be considered to have an almost purely anionic character.

In summary, on the basis of density functional and ab initio calculations, we propose that the anionic cyclization of anions derived from acrylamides, benzamides, and phosphinamides takes place through a Michael-type nucleophilic addition of the carbanionic center to the electron-deactivated carbon−carbon double bond and not through an electrocyclic mechanism. The presence of the lithium counterion appears to strongly influence the relative energies of the stationary points located but does not change the reaction pathway.

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Supporting Information Available: Cartesian coordinates and energies of the stationary points located. This material is available free of charge via the Internet at http://pubs.acs.org.

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