JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2003; **16:** 348–354
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.639

Computational study of maleamic acid cyclodehydration

Daniela Ivanov[1]* and Mircea Constantinescu[2]

[1]'P. Poni' Institute of Macromolecular Chemistry, 41A Gr. Ghica Voda Alley, RO-6600 Iasi, Romania
[2]Department of Physical Chemistry and Theoretical, 'Al. I. Cuza' University, Faculty of Chemistry, 71 Mangeron Blvd, RO-6600 Iasi, Romania

Received 27 December 2002; revised 7 March 2003; accepted 11 March 2003

ABSTRACT: The mechanism of cyclodehydration of alkyl (Bu) and aryl (Ph) substituted maleamic acids to the corresponding maleimides and isomaleimides using *N*,*N*′-dicyclohexylcarbodiimide as dehydration agent in CH_2Cl_2 as the solvent was investigated by PM3/AMSOL semiempirical calculations. An addition intermediate between the dehydrating agent and the maleamic acid carboxyl group was considered to be formed at the very beginning of the reaction. Two mechanisms reported in the literature were considered, one involving initial formation of a cyclic anion intermediate and the other proposing an acyclic amide anion. Our computational results supported the latter mechanism and a new reaction step was proposed that could also explain the ratio between the maleimide and isomaleimide formation depending on the amide substituent (alkyl or aryl type). The computational data are in good agreement with reported experimental results. Copyright © 2003 John Wiley & Sons, Ltd.

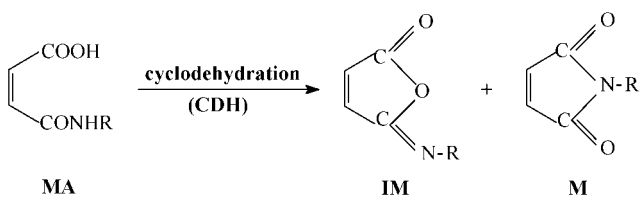
KEYWORDS: cyclodehydration; reaction mechanism; PM3/AMSOL; isomaleimide; maleimide

INTRODUCTION

Maleamic acids are maleic anhydride derivatives that lead, by cyclodehydration reactions, to maleimides and isomaleimides, of high interest owing to their special properties. *N*-Substituted isomaleimides can be used as fungicides, defoliants,[1–4] coupling compounds of clinical or biological interest,[5,6] etc. They can be also used as reaction intermediates which, by rearrangement, provide the corresponding *N*-substituted maleimides,[7,8] used as monomers in copolymer synthesis.[9,10] Maleimides[11,12] are widely employed used as insecticides, components of curable adhesives, etc. *N*,*N*′-Disubstituted maleimides and isomaleimides can undergo addition reactions to olefin bonds, a reaction of interest in polymer synthesis. Thus bisisomaleimides react with diamines to give polymaleamides[13,14] that are used as adhesives, sealants, binders for abrasives, potting compounds, cross-linking agents (to form insoluble, infusible products), molding compounds (such as lamp bases, television cabinets, toys, etc.), cast materials (wrapping films for food articles, etc.), fibers for clothes,[15] etc. Bismaleimides[16] can lead to polyimides, polymer networks,[17] advanced composites having special properties with applications in aircraft, automotive or electronic-related products, etc.

Despite the large and important practical applications of maleimides and isomaleimides, the theoretical background of the reaction mechanism of their synthesis has not yet been completely elucidated; the literature reports mainly synthetic aspects, and just a few papers refer to possible mechanisms. When maleamic acids (MA) are heated, their pyrolytic dehydration gives mainly maleimides.[18] Mixtures of maleimides (M) and isomaleimides (IM) are formed if the reaction occurs in solution using dehydration agents[19–21] (Scheme 1).

Theoretical assumptions on the mechanism of cyclodehydration (CDH) of maleamic acids using dehydration agents were presented for the first time in 1961 by Cotter *et al.*,[19] who proposed that the reaction occurs by a cyclic reaction intermediate. Two years, later Roderick[20] described a possible addition reaction intermediate and suggested that cyclization takes place in the last step of the reaction. Paul and Kende[22] used O^{18}-labeled maleamic acids and the latter reaction route was supported and a reaction mechanism was proposed. However, the formation of IM and M at various rates was not fully explained.



Scheme 1. General cyclodehydration (CDH) route from maleamic acids (MA) to isomaleimides (IM) and maleimides (M)

**Correspondence to:* D. Ivanov, 'P. Poni' Institute of Macromolecular Chemistry, 41A Gr. Ghica Voda Alley, RO-6600 Iasi, Romania.
E-mail: dani@icmpp.tuiasi.ro

This paper reports a theoretical study of the cyclic dehydration of maleamic acids in order to determine the elementary steps of reaction on the basis of computational chemistry calculations.

METHODS

The strategy of the study took into account two different substituents (R) of maleamic acids (Scheme 1): an electron-releasing substituent of alkyl type (butyl, Bu) and an electron-withdrawing substituent of aryl type (phenyl, Ph). Two different reaction procedures were also considered, namely direct cyclodehydration (without dehydration agent) in various solvents (CH_2Cl_2, C_6H_6, CH_3COOH) and cyclodehydration with *N*,*N*′-dicyclohexylcarbodiimide (DCC) as the dehydration agent, in CH_2Cl_2 as the solvent.

The geometries of the reactants, reaction intermediates and products were fully optimized by the PM3/AMSOL (SM5.4P) computational method including the solvation effect[23] on an INTEL P4 1.7 GHz personal computer. Transition states (TS) were calculated from the progress of the reaction energy. The length of a newly created bond was selected as the reaction coordinate and the other reaction parameters were minimized. The maximum of the energy profile represented the nearest TS and it was used as input for the Eigenvector Following (EF) algorithm to calculate the TS. The optimized reacting structures were supposed to evolve via several mechanisms. Among these, the path with the lowest TS energy was selected. A monotonic increase in energy indicated that TS could not be located; therefore, the reaction cannot take place and another mechanism had to be considered.

RESULTS AND DISCUSSION

Theoretical direct cyclodehydration (without a dehydration agent) of MA in different solvents was first considered. Solvents were selected on the basis of experimental reasons: acetic acid is used as the solvent in MA synthesis (a solution that could be further utilized for CDH reactions), C_6H_6 is a selective recrystallization solvent for IM, and CH_2Cl_2 is recommended in the literature as the solvent for CDH reactions. The energy variation during the reaction progress, for instance from MA to IM, as obtained from our calculations, is represented in Fig. 1.

All attempts to locate the TS for the reaction in CH_3COOH as solvent were unsuccessful, meaning that the reaction could not take place; therefore, the corresponding curve is not presented in Fig. 1. For both CH_2Cl_2 and C_6H_6, the energy profile exhibits a maximum that corresponds to a transition state. As for CH_2Cl_2, the process leads to a lower activation energy (E_a) and lower final state energy, this seemed to be a better solvent, in good agreement with experimental reports.[19,24] Even when dichloromethane is used, the heat of reaction (ΔH) are positive; therefore, the direct cyclodehydration is an endothermic process. Moreover, the activation energy is about 50 kcal mol^{-1} (1 kcal = 4.184 kJ), a fairly high value, indicating that high temperatures are required for the reaction to take place. According to reported data, these conditions lead to significant amounts of undesirable resinous by-products (*N*-substituted maleimide has a reactive double bond that can readily polymeriz)[11] and thus decrease the reaction yield. This process is disadvantageous and a new route with a lower activation energy and, therefore, requiring milder conditions is to be preferred. Such a purpose is ensured by the presence of a dehydration agent.

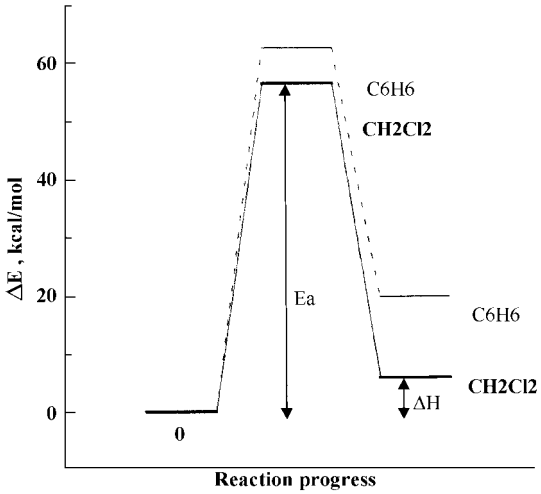


Figure 1. Solvent influence on the energetic profile of direct CDH reaction

A literature survey on dehydration agents for the cyclodehydration of maleamic acids to maleimides and/or isomaleimides showed that the following reagent can be efficiently carbodiimide, especially *N*,*N*′-dicyclohexylcarbodiimide (DCC),[4,19,25] acetic anhydride with or without sodium acetate,[26,27] trifluoroacetic anhydride without an acid acceptor[28] or in the presence of triethylamine,[2,20,21] acid halides (ethyl chloroformate and triethylamine),[1,19,24] halogenated acyl halides (acetyl chloride),[3,29] acyl halides of heterocyclic nitrogen or sulfur compounds[30,31] and phosphorus oxychloride.[29]

DCC, a commercial solid reagent, is widely used in organic synthesis as a dehydration agent because is not very expensive and it is active under mild conditions. Sheehan and co-workers[32,33] proposed it for the first time as a reagent leading to amide bond formation. Bodansky[34] showed that DCC acts as a coupling reagent when it is added to a solution of carboxyl and amine components. The reagent activates the carboxyl group through its addition to the N═C double bond, followed by nucleophilic attack of the amino component on the *O*-

acylisourea intermediate. DCC fulfils the prerequisite of inertness towards primary and secondary amines because under the reaction conditions this possible secondary reaction is too slow to compete with the rapid addition to the carboxyl group. Another advantage of this agent comes from *N*,*N*′-dicyclohexylurea formation as the secondary product, which is insoluble in most organic solvents (except in alcohols) and thus readily removable from the reaction mixtures as a filter cake.

Two different possible mechanisms for maleamic acid cyclodehydration using DCC as the dehydration agent and CH_2Cl_2 as the solvent have been reported. Cotter *et al.*[19] suggested the formation of a five-membered cyclic anion that by further attack of protonated DCC on the amide oxygen leads to a quasi-six-membered ring TS as depicted in Scheme 2. The experiment yields were about 50% in IM for *N*-alkyl-substituted MA and 89–100% in IM for *N*-aryl-substituted MA. The authors mentioned that the cyclic TS leads to the exclusive formation of *N*-substituted IM and they supposed that M also obtained in the system comes from the rearrangement of the former isomaleimide. The attack of DCC on an anionic cyclic structures with the formation of six-membered ring intermediates was also proposed by Kozyrev *et al.*[35] in the synthesis of emeraldins.

Paul and Kende[22] studied the reaction using O^{18}-labeled maleamic acid and reported equal amounts of O^{18} in the main (IM and M) and secondary (*N*,*N*′-dicyclohexylurea, SP) products, as depicted in Schemes 2 and 4. These results contradict the mechanism proposed by Cotter *et al.*, whose cyclic intermediate would lead only to O^{18}-labeled main products. The authors proposed a reaction mechanism involving the formation of an acyclic internal addition intermediate between MA and DCC, which theoretically explain the experimental results.

Both the Cotter and Paul–Kende mechanisms were considered in the calculations in this paper. On the basis of the Dewar statement of normally prohibited synchronous multibond processes,[36] we assumed that reaction takes place in distinct steps, each involving the formation and/or breaking of one bond. Therefore, we supposed that the reaction system evolved from the initial state (marked as **0** in Scheme 2 and Figs 2 and 3) to the Cotter or Paul–Kenede intermediates through an ion pair state (**I1** in Scheme 2).

Calculations supported the formation of intermediate **I1** by donation of the carboxylic proton in MA to the double-bonded nitrogen atom in DCC (Figs 2 and 3). The resulting MA anion could pass into a cyclic form that reacts further with DCC via the Cotter mechanism. On the other hand, the positive charge in protonated DCC is

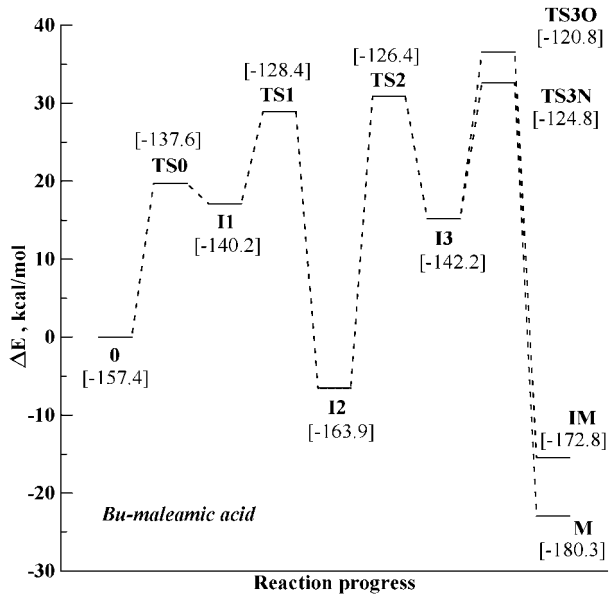
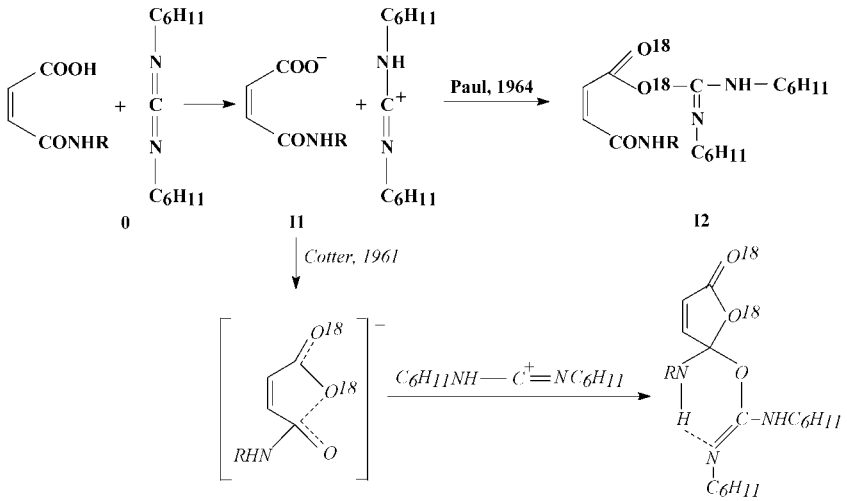


Figure 2. Energy profile (relative energy given on *y*-axis; heats of formation, kcal mol^{-1}, in brackets) for CDH of *N*-Bu-maleamic acid with DCC in CH_2Cl_2; maleimide (M) is kinetically favoured: *E*(**TS3N**) < *E*(**TS3O**)



Scheme 2. Mechanisms of CDH as suggested in the literature[19,22]

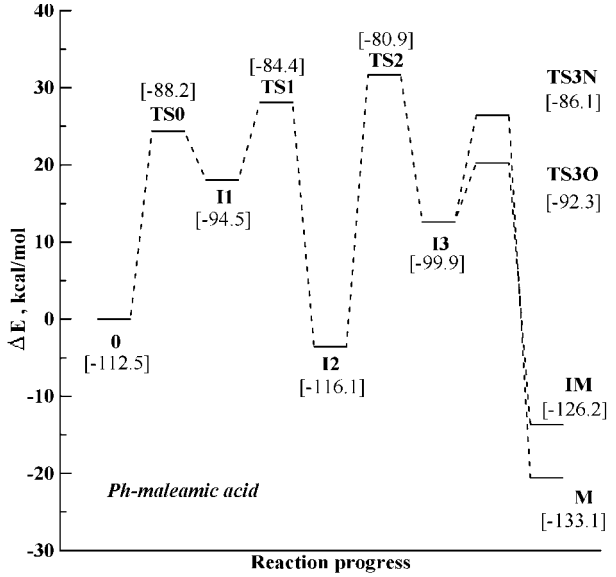
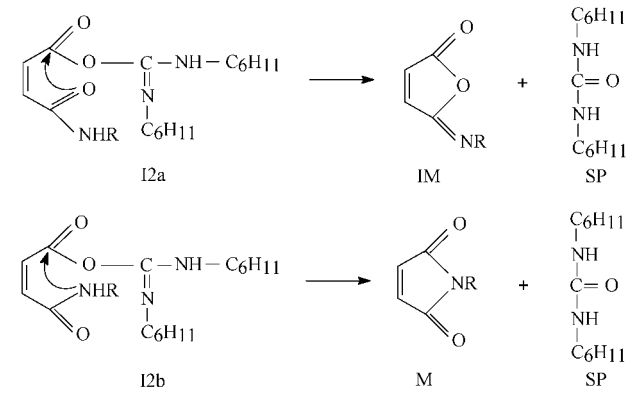


Figure 3. Energy profile (relative energy given on *y*-axis; heats of formation, kcal mol^{-1}, in brackets) for CDH of *N*-Ph-maleamic acid with DCC in CH_2Cl_2; isomaleimide (IM) is kinetically favoured: *E*(**TS3O**) < *E*(**TS3N**)

displaced from the initial nitrogen atom and is delocalized in an N—C—N conjugated system[37] with significant localization on the C atom that could react with either the cyclic anion (Cotter mechanism) or the MA acyclic anion leading to the intermediate **I2** (Paul–Kende mechanism).

The computational results did not indicate a stable energy level corresponding to the cyclic anion structure proposed by Cotter *et al.* and the energy evolution of the system showed a convenient value of the activation energy for the formation of the intermediate **I2** (Figs 2 and 3). Therefore, the Paul–Kende assumption is supported computationally and the structure **I2** was considered for subsequent calculations to elucidate the reaction mechanism.

Three possible reactions for intermediate **I2** were taken into account, as shown below. Cyclization could take

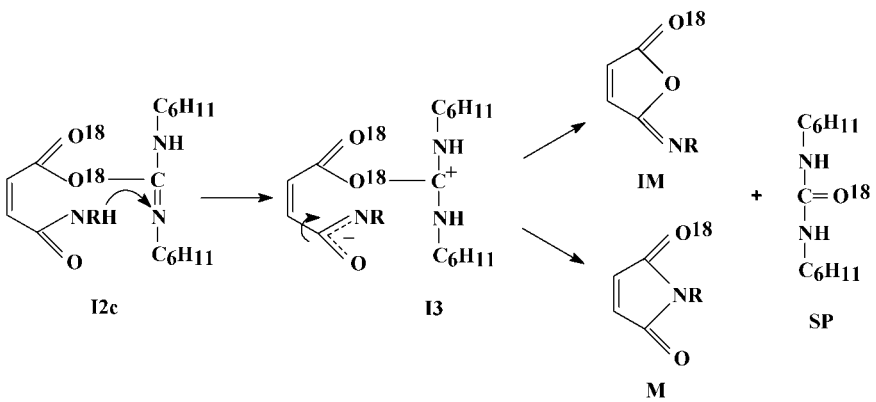


Scheme 3. Possible internal cyclization of intermediate **I2** by amide O (**I2a**) or N (**I2b**) attack

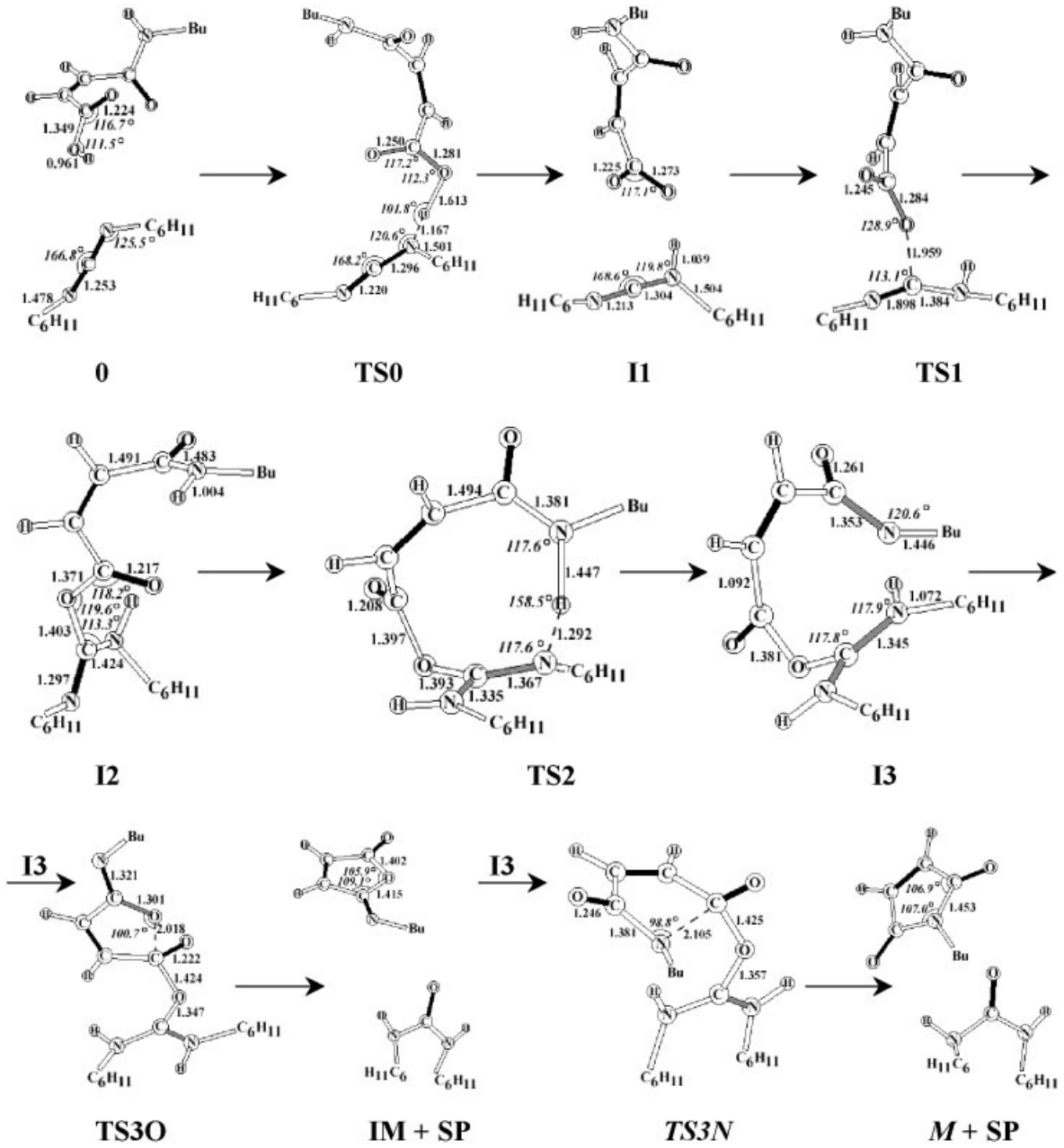
place by attach of either amide oxygen (**I2a**) or amide nitrogen (**I2b**) on the activated carbonyl carbon, leading to IM or M, respectively, as depicted in Scheme 3. All attempts to locate the TS for both cases were not successful, indicating that the reaction cannot correspond to such presumptions.

Another path is internal migration of the amide proton to the unsaturated nitrogen (**I2c**) with formation of reaction intermediate **I3** (Scheme 4). The computational results supported this route as the only one energetically favored (Figs 2 and 3). In the zwitterionic intermediate **I3**, the negative charge in the amide group increases its basicity and therefore its reactivity in nucleophilic attacks. In the meantime, the electrophilicity of the carbon atom of the carboxyl group increases, owing to the net positive charge vicinity making the cyclization possible only in intermediate **I3** and not in the **I2a** or **I2b** type. Internal rotation in **I3** could explain the formation of both IM and M by nucleophilic attack of either the amide oxygen or amide nitrogen over the activated carbonyl carbon (Scheme 4).

The path from intermediate **I3** to the reaction products supposes a quasi-five-membered cyclic transition state, **TS3O** or **TS3N**, as depicted in Scheme 5 for Bu-



Scheme 4. Internal amide proton migration in intermediate **I2** leading to isomaleimide (IM) and maleimide (M)



Scheme 5. Geometric parameters (distances in Å, angles in degrees) of intermediates and TS involved in CDH of *N*-Bu-maleamic acid; single, double and partial double bonds are represented as white, black and gray sticks, respectively; newly forming bonds are marked as dotted black lines

substituted maleamic acid. If one considers the bond length and the value of angles, no significant difference appears between the two structures; therefore, they have similar ring strain. This is in good agreement with the similar yields in IM and M found experimentally. On the other hand, replacing the Bu substituent of the initial maleamic acid with Ph did not essentialy modify the geometry of **TS3O** and **TS3N** as well as other reaction intermediates and TS. However, the final product yield was totally different, as mentioned previously. The reaction selectivity cannot be explained by intermediates having similar geometry; therefore, geometric parameters are not essential factors in the reaction mechanism proposed here.

The nucleophilic attack is ruled by the electronic effect of the MA substituent (R) that modifies the electron density of amide heteroatoms. Hence an electron-releasing substituent (Bu) increases the amide nitrogen basicity so that it becomes similar to the amide oxygen basicity. In such an instance, the formation of IM and M occurs with similar probability. An electron-withdrawing substituent (Ph) deactivates the amide nitrogen (the lone pair of the nitrogen atom, with a large p character, is delocalized into the aromatic ring). In such a case,

Table 1. Net atomic charges on reaction centers in intermediate **I3** and differences (Δ) between the absolute values on the reaction centers

R substituent	Carbonyl C	Amide O	Δ(O−C)	Amide N	Δ(N−C)
Bu	+0.5833	−0.6941	0.1108	−0.7545	0.1712
Ph	+0.5792	−0.6473	0.0681	−0.7131	0.1339

cyclization takes place by the amide oxygen atom that is more nucleophilic, leading to IM as the main product.

These assumptions are supported by the principle of hard and soft acids and bases (HSAB). Pearson and Songstad[38] considered that reactions will take place between centers with similar strength. Net atomic charges calculated for the intermediate **I3** were considered as a measure of acid–base strength of the reaction centers: activated carbonyl carbon, amide oxygen and amide nitrogen (Table 1). For the Bu substituent, the amide O and N have a similar basic character that is stronger than the carbonyl C acid character (high positive differences of atomic charge modulus values); therefore, cyclization in **I3** occurs with similar probability on both amide centers, leading to similar amounts of IM and M. For the Ph-substituted amide group, the O charge is very close in absolute values to that on carbonyl C; therefore, they have similar basic and acid strengths respectively; the cyclization will be favored between these two centers and IM will be the major product.

The theoretical assumptions about the mechanism proposed here also have energetic support. The energy evolution of the reaction system (ΔE, considering the energy of initial state **0** as the reference value) calculated for Bu and Ph substituents is represented in Figs 2 and 3, respectively.

The two energetic profiles indicate that the substituent influences especially the evolution of the last step of reaction mechanism, as expected from the **0** to **I3** reaction study (Schemes 2 and 4). When Bu is considered (Fig. 2), both amide nitrogen attack (**TS3N**) and amide oxygen attack (**TS3O**) have high and not very different activation energies. In such conditions, the reaction of **I3** is not selective, IM and M resulting with similar probabilities. On the other hand, the Ph substituent (Fig. 3) favors amide oxygen attack (**TS3O**) the activation energy of which is low and much smaller than that for nitrogen attack (**TS3N**). Reaction occurs under kinetic control and IM is the main product.

The effect of the R substituent on the activation energy that controls the evolution of the process to the final products was confirmed by results of synthesis in mild conditions, as described by Cotter *et al.*[19] The CDH of *N*,*N*′-hexamethylenemaleamic acid (alkyl-type substituent) did not lead to satisfactory yields even after long reaction times. On the other hand, reaction easily occurred for *p*-tolylmaleamic acid (aryl-type substituent) with good yields of the corresponding IM.

The energy values show that M is the thermodynamically favored form for both Bu- and Ph-substituted isomaleimide, as also reported for *para*-substituted *N*-phenylisomaleimide.[39] There is experimental support that IM rearranges to the corresponding M when heated[8] or treated with small amounts of catalysts.[19,40,41] Sauers[27] noted that even in the presence of catalyst the IM partial rearrangement could not explain the amounts of M obtained experimentally in cyclodehydration reactions. These results confirm the Cotter mechanism, which supposes that IM rearrangement to M during reaction is not valid for the systems studied here.

Performing CDH of MA with other dehydration agents, and Hardwood Pyriadi[42] obtained results opposite to those reported by Cotter *et al.* (yields of IM of 100% for Bu and 63% for Ph). The authors proposed an amide ion intermediate of **I3** type in which they considered the negative charge to be localized on either the amide nitrogen or oxygen in two equilibrated tautomers. On the basis of the relative electron densities of the oxygen and nitrogen ions, they concluded that IM formation was favored by alkyl-type substituents and M by aryl-type substituents, but this has no support considering the electronic effects. Their experimental results led us to conclude that the mechanism presented here is valid only for DCC; in other cases the reaction mechanism might be different.

CONCLUSIONS

This paper has presented a theoretical study of the maleamic acid cyclodehydration mechanism in terms of computational chemistry calculations and reported experimental data.

Theoretical direct cyclodehydration of maleamic acids (Scheme 1) exhibited high activation energies (over 50 kcal mol^{-1}) that can be related to the high temperatures required for reaction to occur (giving undersirable by-products); therefore, a dehydration agent is needed in order to decrease the activation energy. Using different solvents, it was calculated that CH_2Cl_2 favors the reaction as it affords the lowest activation energy (Fig. 1).

The cyclodehydration mechanism of maleamic acids in the presence of DCC as the dehydration agent in CH_2Cl_2 as the solvent was established on the basis of the Paul–Kende mechanism to which new steps were added (Schemes 2–5). Calculations suggested that the cycliza-

tion occurs only in the final step (Fig 2 and 3) depending on the R substituent electronic effect. When R is an alkyl substituent (Bu) the high activation energies with similar values for IM and M formation decreased the process selectivity although M seemed both kinetically and thermodynamically favored. In contrast, if the amide group is aryl substituted (Ph), IM formation has a low activation energy and it represents the main product. These assumptions are supported by net atomic charges and energy values for the last intermediate and transition state, respectively. The theoretical ^{18}O distribution in the products resulting from the mechanism proposed here corresponds to the reported experimental data when labeled maleamic acid was used.

REFERENCES

1. Sauers CK, Cotter RJ. US Patent 2 980 701, 1961.
2. Sauers CK, Cotter RJ. US Patent 2 995 577, 1961.
3. Sauers CK, Cotter RJ. US Patent 2 998 429, 1961.
4. Sauers CK, Cotter RJ. US Patent 3 035 065, 1962.
5. Theodoropulos S. US Patent 4 600 775, 1986.
6. Theodoropulos S. US Patent 4 789 742, 1988.
7. Sauers CK, Cotter RJ. US Patent 2 980 694, 1961.
8. Pyriadi TM, Abdulameer I. *J. Polym. Sci., Part A* 2000; **38**: 3244–3252.
9. Akiyama M, Yanagisawa Y, Okawara M. *J. Polym. Sci., Part A-1* 1969; **7**: 1905–1912.
10. Pyriadi TM, Nabeel A. *J. Macromol. Sci. Chem. A* 1988; **25**: 1683–1688.
11. Sauers CK, Cotter RJ. US Patent 3 018 290, 1962.
12. Sauers CK, Cotter RJ. US Patent 3 018 292, 1962.
13. Sauers CK, Cotter RJ. US Patent 3 144 435, 1964.
14. Imai Y, Ueda M, Kanno S. *J. Polym. Sci., Polym. Chem. Ed.* 1975; **13**: 1691–1698.
15. Hedaya E, Theodoropulos S, Hinman RL. US Patent 3 472 817, 1969.
16. Bargain M. US Patent 3 839 358, 1974.
17. Landis AL, Lau KSY. US Patent 8 902 306, 1989.
18. Searle NE. US Patent 2 444 536, 1948.
19. Cotter RJ, Sauers CK, Whelan JM. *J. Org. Chem.* 1961; **26**: 10.
20. Roderick WR. *J. Org. Chem.* 1963; **28**: 2018–2024.
21. Hedaya E, Hinman RL, Theodoropulos S. *J. Org. Chem.* 1966; **31**: 1311–1316.
22. Paul R, Kende AS. *J. Am. Chem. Soc.* 1964; **86**: 4162–4166.
23. Cramer CJ, Truhlar DG. *Chem. Rev.* 1999; **99**: 2161–2200.
24. Ezzell SA, Hansen RG, Anderson GJ. US Patent 5 744 574, 1995.
25. Rossi RD, Ray-Chaudhuri DK. US Patent 4 581 461, 1986.
26. Kretov AE, Kul'chitskaya NE, Mal'nev AE. *J. Gen. Chem USSR* 1961; **31**: 2415.
27. Sauers CK. *J. Org. Chem.* 1969; **34**: 2275.
28. Tsou KC, Barrnett RJ, Seligman AM. *J. Am. Chem. Soc.* 1955; **77**: 4613.
29. Hoogewerff S, van Dorp WA. *Recl. Trav. Chim. Pays- Bas* 1893; **12**: 12; 1894; **13**: 93; 1895; **14**: 252.
30. Buchwalter SL, Frank ER, O'Toole TR, Thomas RR, Viehbeck A. US Patent 5 187 241, 1993.
31. Anderson GJ, Ezzell SA, Hansen RG. US Patent 5 744 574, 1998.
32. Sheehan JC, Hess GP. *J. Am. Chem. Soc.* 1955; **77**: 1067.
33. Sheehan JC, Goodman, Hess GP. *J. Am. Chem. Soc.* 1956; **78**: 1367.
34. Bodansky M. In *Principles of Peptide Synthesis*, 2nd rev'd edn. Springer Verlag: Berlin, 1980; 40.
35. Kozyrev AN, Zheng G, Lazarou E, Dougherty TJ, Smith KM, Pandey RK. *Tetrahedron Lett.* 1997; **38**: 3335–3338.
36. Dewar MJS. *J. Am. Chem. Soc.* 1984; **106**: 209–219.
37. Khorana HG. *Chem. Ind. (London)* 1955; 1087–1088; Doleschall G, Lempert K. *Tetrahedron Lett.* 1963; **18**: 1195–1199.
38. Pearson RG, Songstad J. *J. Am. Chem. Soc.* 1967; **89**: 1827–1836.
39. Zubkov VA, Iakimanskii AV, Cudriavtzev VV. *Dokl. Akad. Nauk SSSR* 1982; **262**: 612–615.
40. Rubinstein H, Parnarouskis M. *J. Org. Chem.* 1973; **38**: 2166–2169.
41. Roth M. US Patent 4 132 715, 1979.
42. Pyriadi TM, Hardwood HJ. *J. Org. Chem.* 1971; **36**: 821–823.