Ab initio SCF-MO study of the Staudinger phosphorylation reaction between a phosphane and an azide to form a phosphazene †

Mateo Alajarin,[a] Carlota Conesa[ab] and Henry S. Rzepa *[b]

[a] *Departamento de Quimica Organica, Facultad de Quimica, Campus de Espinardo, Universidad de Murcia, E-300071 Murcia, Spain*
[b] *Department of Chemistry, Imperial College of Science, Technology and Medicine, London, UK SW7 2AY*

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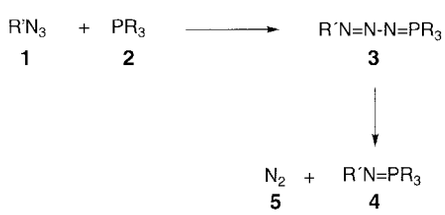
The lowest energy pathway for a Staudinger reaction between a phosphane and an azide is predicted at the RHF and DFT *ab initio* SCF-MO level to proceed *via* an s-*cis* intermediate **7**, followed by cyclisation and elimination of N_2 to form a phosphazene. When suitable stabilising substituents are present, **7** can instead isomerise to the isolable s-*trans* intermediate **9**. Natural bond orbital perturbation theory analysis has been employed to identify the factors influencing the relative stability of the s-*cis* phosphazide and the s-*trans* isomers.

The Staudinger reaction, discovered in 1919,[1] consists of a two-step process that involves the formation of a phosphazide intermediate **3** by nucleophilic attack from the phosphorus atom of an alkyl or aryl phosphane on the terminal nitrogen atom of an azide (Scheme 1). The subsequent elimination of a



Scheme 1

nitrogen molecule yields the corresponding phosphazene **4**. The final product is often the primary amine which results from hydrolysis of the phosphazene.

The structure of the phosphazide intermediate **3** was the subject of some controversy [1d,2] until X-ray structural data became available.[1d,3] Although they are not usually stable, some phosphazides have been isolated.[4] Most of these stable phosphazides present distinctive characteristics such as a) the presence of electron withdrawing substituents on the azido end and/or electron donating substituents on the phosphorus atom, b) the presence of very bulky substituents (R and/or R′), and c) the presence of acidic hydrogen atoms capable of forming intramolecular hydrogen bonds with the N atoms of the PN_3 unit.

Herein, we present the results of *ab initio* Hartree–Fock and density functional theory calculations which provide insight into the mechanism of this reaction, and which can offer suitable explanations for some of the experimental facts.

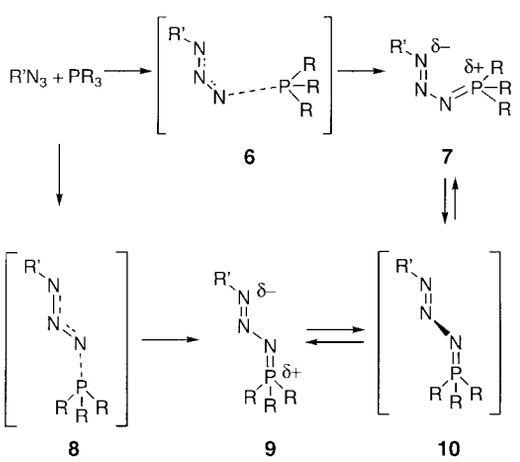
Computational procedure

Approximate geometries were initially optimized at the PM3 level using the MOPAC V6.0 program[5] implemented on CAChe workstations. The transition structures were located using an eigenvector following routine (TS). This procedure was followed by *ab initio* calculations performed using the GAUSSIAN94 and 98 program systems,[6] transition states being located using the Berny algorithm[7] or the synchronous transit-guided quasi-Newton (STQN) methods implemented by Schlegel.[8] A natural bond orbital (NBO) analysis[9] was invoked using the population keyword in GAUSSIAN94/98. Molecular co-ordinates in the form of pdb files for located stationary points are integrated into this article in an enhanced on-line form, together with animations of all important imaginary modes showing the form of the eigenvectors, at the following URL: http://www.rsc.org/suppdata/p2/1999/1811.

Results and discussion

Factors influencing the relative stability of 7 and 9

Our first aim was to reconcile why almost all the reported X-ray structural data of phosphazides **3** revealed a species with a central N–N bond with the s-*trans* configuration **9** (Scheme 2),



Scheme 2

whereas the subsequent extrusion of nitrogen and the formation of an N–P bond requires an s-*cis* configuration **7**.

Our results predict the unsubstituted s-*cis* isomer **7** (R = R′ = H) to be more stable[10] than the s-*trans* isomer **9**, by

† An enhanced version of this article is available as supplementary data at the URL: http://www.rsc.org/suppdata/p2/1999/1811.

Table 1 Absolute and relative (to **1** + **2**) energies and transition wavenumbers for the stationary point structures in the transformation **1** + **2** to **4** + **5** (Fig. 3)

Stationary point	RHF/6-31G*		B3LYP/6-31G*		B3LYP/6-311G**	
	Energy/Hartree (relative to **1** + **2**, kcal mol^{-1})	ν/cm^{-1}	Energy/Hartree (relative to **1** + **2**, kcal mol^{-1})	ν/cm^{-1}	Energy/Hartree (relative to **1** + **2**, kcal mol^{-1})	ν/cm^{-1}
R = R′ = H						
1	−342.44795		−343.14027		−343.17284	
2	−163.83869		−164.78288		−164.83053	
6	−506.22902 (36.17)	499.4i	−507.88812 (21.61)	325.2i	−507.96675 (22.98)	339.2i
7	−506.26216 (15.37)		−507.89731 (15.83)		−507.97511 (17.73)	
8	−506.18812 (61.84)	573.8i				
9	−506.25172 (21.92)		−507.8818 (25.50)		−507.96130 (26.40)	
10	−506.24131 (26.70)	176.5i	−507.87110 (32.29)	200.5i	−507.94970 (33.68)	211.4i
11	−506.23611 (31.78)	350.4i	−507.88096 (27.1)	228.8i	−507.95697 (29.12)	251.2i
13	−506.24157 (28.29)		−507.88159 (25.70)		−507.95829 (28.29)	
14	−506.23536 (32.19)	663.2i			−507.95704 (29.07)	542.0i
4	−397.42731		−398.44640		−398.49981	
R = OMe, R′ = H						
6	−847.967545		−851.50187		−851.67384	
7	−848.02835		−851.56220		−851.73372	
8	−847.92777					
9	−848.03012		−851.56164		−851.73393	
10	−848.02083		−851.55290		−851.72518	
R = H, R′ = CN						
7	−597.98427		−600.13067		−600.22866	
9	−597.97486		−600.11701		−600.21617	

6.6 kcal mol^{-1} at the HF level and 9.4 and 8.7 kcal mol^{-1} at the B3LYP/6-31G* and 6-311G** levels respectively (Table 1). A simple rationalisation is in terms of favourable electrostatic interactions between the partially positive phosphorus atom (Mulliken charge +0.54/B3LYP/6-31G*) and the partially negatively charged nitrogen atom (−0.37/B3LYP/6-31G*) in the s-*cis* isomer **7**. The geometry of the s-*trans* isomer also shows a significant double bond character for the N–P bond. This bond distance is longer for the s-*cis* isomer, which also shows a shortening of the central N–N bond (Fig. 1).

A study of the potential energy surface for the formation of **3** revealed that not only was the s-*cis* isomer **7** route the most stable but also corresponded to the pathway with the lowest energy barrier. The transition state **8** for N–P bond formation has an energy barrier of 61.8 kcal mol^{-1}, which is 25.9 kcal mol^{-1} larger than the alternative **6** at the RHF level, whilst **8** could not even be located at the DFT level. A further study of the potential energy surface allowed us to locate another transition structure **10**, corresponding to the isomerization of the phosphazide molecule by rotation of the central N–N bond. The location of this transition structure meant that the s-*trans* isomer could be formed from the s-*cis* isomer by isomerization, with a readily accessible energy barrier (Table 1) of 20.8 kcal mol^{-1} (HF) or 16.46 kcal mol^{-1} (B3LYP).

Our results for R = R′ = H did not explain why only the s-*trans* configuration is found for those exceptionally stabilised phosphazides which have been isolated. To identify why such stabilization has a greater effect on the s-*trans* isomer than on the s-*cis*, we calculated systems with either a cyano substituent on the nitrogen atom (R′ = CN, R = H) or a π electron-donating substituent on the phosphorus atom (R′ = H, R = OMe). In the first case, the difference between the energy of the s-*cis* and s-*trans* isomers was reduced from 9.4 (R = R′ = H) to 5.9 kcal mol^{-1} at the RHF level. In the second case (R′ = H, R = OMe) the s-*trans* isomer was indeed found to be very slightly more stable than the s-*cis* isomer at the RHF/6-31G* and B3LYP/6-311G** levels (Table 1). The energy barrier for the formation of the phosphazide for R′ = H, R = OMe was still lower for the s-*cis* isomer. We suggest therefore that the formation of stabilised s-*trans* isomers takes place *via* the formation and subsequent isomerisation of the s-*cis* phosphazide by rotation of the central N–N bond.

In order to get a deeper insight into the factors that control the relative stability of the s-*cis* and s-*trans* isomers, we made use of the natural bond orbital (NBO) analysis, a method which has been previously employed in the study of the *cis*-effect in 1,2-difluoroethene and other organic molecules.[11] We note firstly that for the case of R = R′ = H, the NBO (RHF/6-31G* level) shows a one-centre π lone pair $n_\pi(N_\alpha)$ on the N atom connected to the P, rather than a two-centre π bond between the N_α and P atoms. The most significant difference between the two isomers is that the term corresponding to the interaction $n_\pi(N_\alpha)$ to $\pi^*(N_\beta{=}N_\gamma)$ is 58.8 kcal mol^{-1} for the s-*trans* isomer and 95.5 kcal mol^{-1} for the s-*cis*. The difference is due to the differences in energy between both orbitals (0.47 Hartree for s-*cis* and 0.50 Hartree for s-*trans*) and in the Fock matrix element (0.195 Hartree for s-*cis* and 0.161 Hartree for s-*trans*). In addition, the antiperiplanar contributions also favour the s-*cis* isomer. Thus the antiperiplanar interaction $n_\sigma(N_\beta)$ to $\sigma^*(N_\alpha{-}P)$ is large for the s-*cis* whereas it is insignificant for a synperiplanar s-*trans* interaction (16.7 kcal mol^{-1} *vs.* 0.7 kcal mol^{-1}). The interaction $n_\sigma(N_\alpha)$ to $\sigma^*(N_\beta{=}N_\gamma)$ is analogous (8.2 kcal mol^{-1} *vs.* 0.7 kcal mol^{-1}). For the substituted system (R = OMe, R′ = H) the NBO shows in contrast a π orbital between N_α–P rather than an n lone pair on N_α, although the contribution to this orbital is mainly from the N (93%). In this case, the term for the interaction $\pi(N_\alpha{=}P)$ to $\pi^*(N_\beta{=}N_\gamma)$ is 50.2 kcal mol^{-1} for the s-*trans* isomer and 41.75 kcal mol^{-1} for the s-*cis*. The Fock matrix element is the same for both isomers and the difference is due to both orbitals being closer in energy for the s-*trans* isomer (0.67 Hartree *vs.* 0.57 Hartree). Although the antiperiplanar contributions are still in favour of the s-*cis* isomer, *e.g.* $n_\sigma(N_\beta)$ to $\sigma^*(N_\alpha{-}P)$ is 13.70 kcal mol^{-1} for s-*cis and* 0.5 kcal mol^{-1} for s-*trans* and similarly $n_\sigma(N_\alpha)$ to $\sigma^*(N_\beta{=}N_\gamma)$ is 9.2 kcal mol^{-1} for s-*cis vs.* 1.0 kcal mol^{-1} for s-*trans*, they do not seem to be enough to make the s-*cis* isomer more stable.

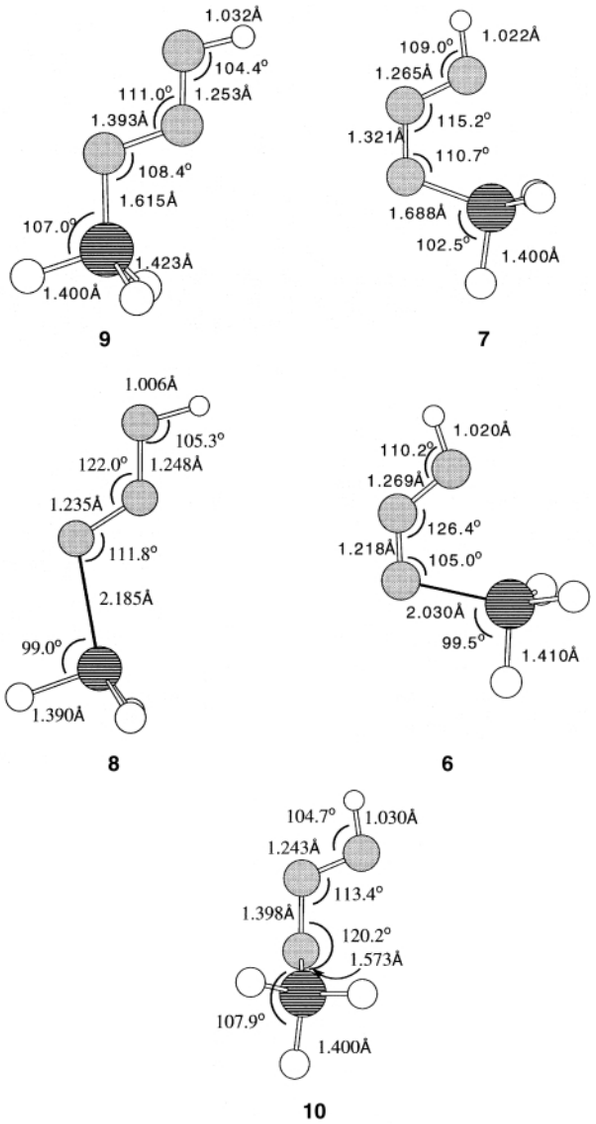
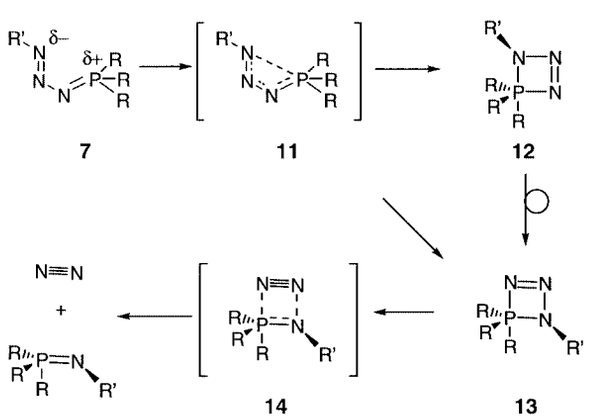


Fig. 1 B3LYP/6-311G** geometries for ground states **9** and **7**, and transition states **6**, **8** and **10**.

Potential surface for the subsequent reaction of 7

The second step of the Staudinger reaction takes place when the s-*cis*-phosphazide undergoes cyclization to form the four-membered cyclic intermediate **13** (Scheme 3). Such cyclisation



Scheme 3

would be expected[11] to take place *via* a nucleophilic apical attack of the terminal nitrogen atom at one of the faces of the

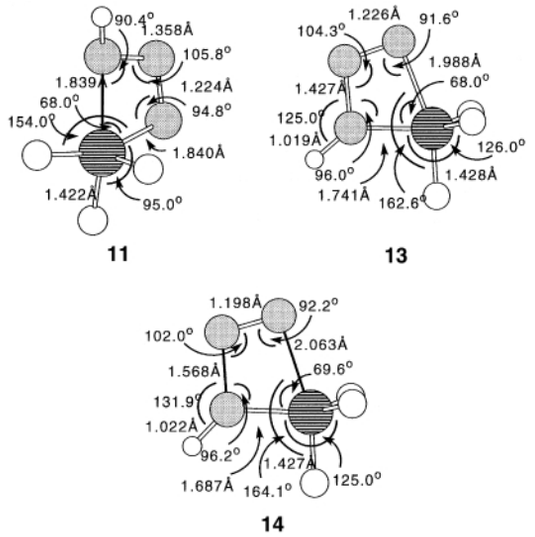


Fig. 2 B3LYP/6-311G** geometries for structures **11**–**14**.

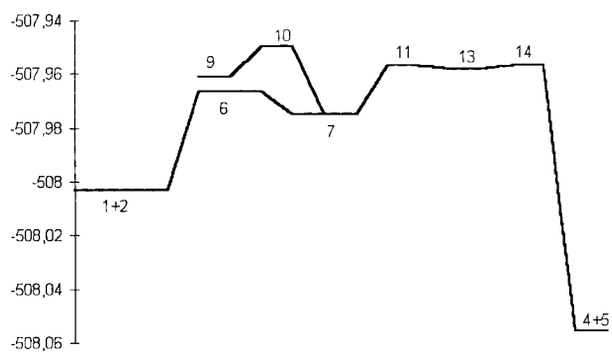


Fig. 3 The overall B3LYP/6-311G** potential energy surface for the Staudinger reaction.

tetrahedral phosphorus. This mechanism would produce cycle **12** with the sp^3 nitrogen atom in an apical position. Given the known[12] apicophobic character of the NH_2 moiety, this species would evolve *via* pseudorotation,[12,13] to the *a priori* more stable isomer **13**, in which the sp^2 nitrogen atom is in an apical position because of the increase in apicophilicity of substituents in pentavalent phosphorus on increasing the electronegative character. However, the cyclisation transition state **11** (Fig. 2), was found to link (*Z*)-phosphazide **7** with the cyclic isomer **13** without the intermediacy of **12**. The vibrational analysis of transition structure **11** shows a rotation of the N–P bond simultaneous to the approach of the nitrogen and phosphorus atoms. The energy of **11**, at least with R = R′ = H is in fact lower than for **10**, which explains why the s-*cis*-phosphazides are not usually isolated. Subsequently, the extrusion of a nitrogen molecule from the cyclic intermediate can take place by fragmentation of the P–N bond in the apical position (transition state **14**) without the need for a pseudo-rotation process. Again, the energy of **14** is lower than **10**, confirming that a low energy route does exist for nitrogen extrusion compared to isomerisation (Fig. 3).

Conclusions

At the *ab initio* RHF and B3LYP levels of theory, we predict that the Staudinger reaction consists of a sequence of reactions shown diagrammatically in Fig. 3. Nucleophilic attack of the phosphane on the terminal nitrogen of an azide forms the corresponding s-*cis*-phosphazide **7**, which in turn can either isomerise to the s-*trans* isomer **9**, which would only be stable and isolable if appropriate substituents are present, or readily cyclise to form the cyclic intermediate **13**. Elimination of a

nitrogen molecule would form the corresponding phosphazene **4**. Results on larger substituted systems of synthetic interest will be reported in a subsequent article.

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