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Theoretical Study on the Mechanism and Regioselectivity of the Macromolecular Substitution Reactions of $[NPCl_2]_n$ with Bifunctional Nucleophiles by a Combination of Quantum Mechanical and Molecular Dynamics Calculations

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ABSTRACT: A combination of molecular dynamics simulations and quantum chemistry calculations affords a good understanding of the reaction between $[NPCl_2]_n$ and the bifunctional nucleophile aminophenol $HO-C_6H_4-NH_2$ in THF solution and in the presence of alkali carbonates. This reaction is regiospecific at room temperature favoring the attack by the NH_2 group, and only at higher temperatures the attack by the OH is activated. It is also explained why the reaction of $HO-C_6H_4-NH_2$ with $\{[NP(O_2C_{12}H_8)]_{1-x}[NPCl_2]_x\}_n$ and Cs_2CO_3 at reflux proceeds exclusively by the OH giving aryloxyphosphazenes with terminal NH_2 substituents. Molecular dynamics simulations have been performed on model systems consisting on $[NPCl_2]_n$ chains surrounded by aminophenol molecules or ions obtained by deprotonation of either the OH or NH_2 groups. Quantum mechanics calculations consisted in density functional theory (DFT) computation of the reaction mechanism of aminophenol with the phosphoranimine $(NH_2)Cl_2P(=NH)$ as a simple model for the $NPCl_2$ phosphazene units, using B3LYP approximation with 6-31G(d). Our results provide evidence to support that the macromolecular substitution reactions of poly(dichlorophosphazene) with aryloxide ions are diffusion controlled and governed by the atomic charges, while the reaction with amino-arenes are directed by hydrogen interactions between the NH_2 hydrogens and the phosphazene nitrogen atoms that initiate a lower activation energy stepwise mechanism competing with a concerted mechanism. The combined methodology employed in this work seems to be useful to address the regiochemistry of the macromolecular substitution on polyphosphazenes with heterobifunctional nucleophiles which is a central issue in the design of polymers with predetermined chemical composition and structure.

Introduction

Since Allcock's rediscovery of polyphosphazenes,[1] the field has experienced an outstanding expansion.[2,3] Several factors have significantly contributed to the interest of those inorganic polymers, but they were made attractive mainly by the early perception that they could have almost unlimited possibilities in the design of new materials with controlled properties.[4] In recent years, the broad scope of properties attainable with functional polyphosphazenes has resulted in their implementation in a variety of applications.[2,3,5] This chemical and structural versatility of polyphosphazenes actually lies in the enormous variety of substituents and combination of substituents than can be incorporated to the phosphazene chains by means of a well-established synthetic methology.[2−6]

Most polyphosphazenes are actually copolymers, and recently attention has been paid to achieve well-defined two substituent polyphosphazenes $[NPA_{2-x}B_x]_n$ with a high degree of chemical regularity.[7] A significant part of these polyphosphazenes are random copolymers obtained by the so-called macromolecular substitution[8] from the linear soluble $[NPCl_2]_n$ (Scheme 1), using various proportions of two different nucleophiles (sequential macromolecular substitution). The use of functionalized nucleophiles A−F is an interesting alternative to the chemical modification of the substituents for the incorporation of chemical functions (F) to the polymer (Scheme 1) which is most typically employed for the functionalization of phosphazenes in the main chain or on to the material surface.[9] However, the reaction of the A−F nucleophile must be regiospecific with F not interfering or not competing with A for the chlorine replacement. Therefore, it is crucial to have a good understanding of the macromolecular reaction mechanisms and the factors controlling the nature of the products, particularly with hetero-bifunctional nucleophiles that can span different regiochemistries.

It has been shown[10] that the reaction of $[NPCl_2]_n$ with $HO-C_6H_4-NH_2$ in THF in the presence of K_2CO_3 is regiospecific at room temperature occurring by the NH_2 group giving soluble un-cross-linked aminophosphazenes. A similar regiocontrol was also observed with the bifunctional L-tyrosine ethyl ester $[NH_2CH(C_6H_4-OH)CH_2COOEt]$ having amino and phenolic groups that also reacted selectively with $[NPCl_2]_n$ by the NH_2 terminal group.[11] In the reaction of the $HO-C_6H_4-NH_2$ however, at the refluxing temperature the selectivity was lost and the $HO-C_6H_4-NH_2$ attacked the $NPCl_2$ units also by the oxygen site, causing cross-linking.

In order to gain a better understanding of this reaction and to improve the knowledge of the regiochemistry of the macromolecular substitution with heterobifunctional nucleophiles, we have carried out molecular dynamics simulations on the model systems shown in Chart 1 and summarized in Table 1 and density functional theory (DFT) calculations to compute the reaction mechanism of $HO-C_6H_4-NH_2$, or the ions generated by

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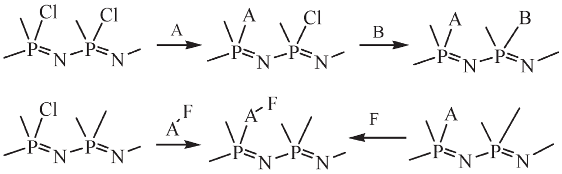
Scheme 1. Macromolecular Substitution and Chemical Derivation of Polyphosphazenes[a]



[a] A and B are nucleophiles replacing chlorines. F is a generalized functional group.

Chart 1. Model for the $[NPCl_2]_n$/Aminophenol System Showing the Distances between Reactant O and N Atoms and the Polymer Chain P Atoms That Are Computed by MD Simulations

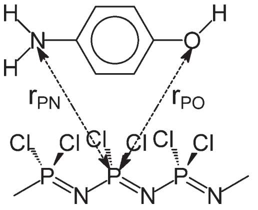
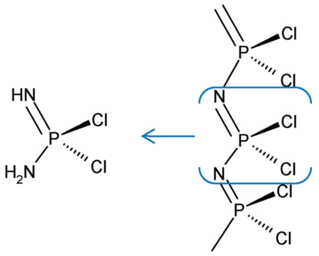


Chart 2. $(NH_2)Cl_2P(=NH_2)$ Molecule Employed as a Model for the $NPCl_2$ Repeat Unit



deprotonation at either the HO or the NH_2 groups, with the phosphoranimine $(NH_2)Cl_2P(=NH)$ as a simple model for the $NPCl_2$ phosphazene unit. Chart 2 shows the structure of the polymer chain (right) and the corresponding minimal system model used for the study of the reaction mechanism (left).

The results of our calculations provide a plausible explanation of all the experimental facts and open a way to design more reliable synthetic methodologies for well-defined mixed phosphazene copolymers with functionalized substituents having a high degree of chemical and structural regularity. Although DFT calculations have been successfully applied to support the mechanisms for the formation of polyphosphazenes from tris(amino)phosphine via its phosphazene tautomer,[12] to the best of our knowledge no calculations of this kind have been used to study the macromolecular substitution in $[NPCl_2]_n$.

Computational Methods

The Amber molecular modeling package,[13] including the Amber force field, was employed for all the molecular dynamics simulations presented below. Both the force field and all the computational procedures described here have been previously used in the analysis of the same kind of molecules studied in the present work.[14-17] Coulombic potentials were computed by the Ewald sum procedure.[13] Partial charges were assigned to every atom by means of the MOPAC package and the AM1 procedure.[18] A time step $\delta = 1$ fs (i.e., 1×10^{-15} s) was employed for the integration algorithm.

All the MD simulations were performed on periodic boundary conditions (PBC) systems under NVT conditions (i.e., canonical ensemble), with the temperature being kept constant by means of the Berensen[13,19] thermostat with a coupling factor of 1000 fs. Several exploratory calculations were performed at different temperatures ranging from 300 to 500 K. Finally, it was decided to perform all the calculations at 500 K in order to increase the atomic velocities, thus facilitating the passage over energetic barriers and consequently improving the statistical sampling of all the configurational space.

Table 1. Composition of the Systems Studied in This Work by Means of Molecular Dynamics Procedures[a]

	system A	system B	system C
oligomers: $Cl[PCl_2-N-]_{102}-H$	5	5	5
solvent: THF	2000	2000	2000
neutral reagent: $HO-C_6H_4-NH_2$	500	0	0
phenoxy reagent: $^-O-C_6H_4-NH_2$	0	500	0
amido reagent: $HO-C_6H_4-NH^-$	0	0	500
counterion: K^+	0	500	500

[a] Each system was contained in a cubic box having periodic boundary conditions and side length $L_9 = 7.540$ nm (density of ca. 1 g cm^{-3}).

The polymer simulated in this section was an oligomer containing 102 repeat units of poly(dichlorophosphazene). Five such oligomers were packed into a cubic box having PBC together with 2000 molecules of THF as solvent and 500 molecules of the nucleophile reagent. Three systems were thus generated whose composition is summarized in Table 1.Thus, systems A, B, and C contain neutral, phenoxy, and amide anions reagents, respectively. 500 K^+ were included as counterions in systems B and C in order to achieve electrical neutrality. However, it should be pointed out that all the results presented below remain unchanged when Cs^+ instead of K^+ is employed as counterion.

The final side of the PBC box was $L = 7.54$ nm (density of ca. 1 g cm^{-3}). However, each system was initially built within a box having approximately twice the final side length. The size of these initial boxes was progressively decreased by a combination of MD and energy minimization steps performed as follows:[16,17] After each decrease of the side box, a 60 ps (i.e., 60×10^{-12} s) MD simulation was performed, during which the system was slowly warmed up from 0 to 500 K, equilibrated at this temperature for ~20 ps, and then slowly cooled to 0 K. Then, the energy of the system was minimized with respect to all internal coordinates with a combination of steepest descendent and conjugated gradient algorithms.[13] Once the system has reached the desired volume, it was slowly warmed up from 0 to 500 K employing 100 ps in this process. Finally, the production stage was started which consisted in 4×10^6 integration cycles (i.e., a time span of 4000 ps) during which the coordinates of the system were recorded at intervals of 1 ps, thus producing a total of 4000 configurations of the system that were employed in the posterior analysis. Results obtained during the warming step were not used in the analysis.

The goal of the MD simulations was to detect possible differences among the approximation of the active sites of the reagent molecule to the P atom of the polymer chain to which eventually they will be linked (see Chart 1). Thus, distance from N and O atoms of every reagent molecule contained in each system to all the P atoms of each oligomer were computed for all the configurations recorded during the production stage of the MD trajectory. These distances were employed to compute the radial correlation function $g(r)$ defined as the ratio between the probability of finding two particles at a distance $r \pm \delta r$ and the same probability computed assuming that the particles are randomly distributed. A value $\delta r = 0.01$ nm was employed in the present work.

We have used density functional theory (DFT) For the study of the chemical reaction pathways. All the quantum mechanical calculations were performed using B3LYP approximation with 6-31G(d) basis set as implemented in Gaussian 03 suite of programs.[20] All the structures were optimized (vanishing gradient)

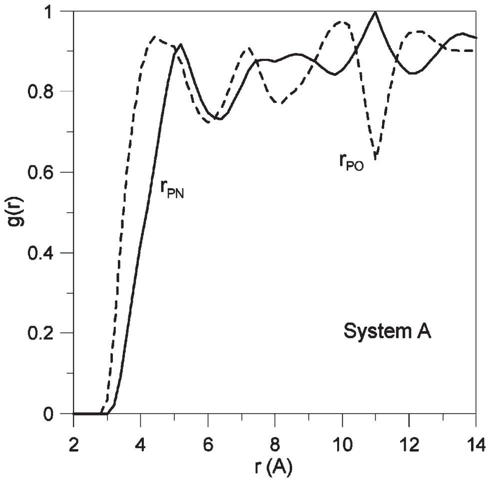


Figure 1. Radial correlation function $g(r)$ for the distances between P atom of the oligomers contained in system A to N and O atoms of the reagent molecules computed from molecular dynamics trajectories performed at 500 K (see text for details).

by computing analytical gradient and have been characterized as either minima or transition states by performing analytical frequency calculations at the optimized geometries, identifying a single imaginary frequency mode for transition states and all positive frequency modes for minima. In order to study the reaction pathways, it has been also computed the intrinsic reaction coordinate (IRC) from each transition state structure, linking each minimum on the potential energy surface by the corresponding transition state.

Results and Discussion

The same methodology previously employed by us to explain the hydrolytic resistance of $\{[NP(O_2C_{12}H_8)_{1-x}][NPCl_2]_x\}_n$ containing high chlorine contents,[16] and the acidic degradation of the $[NP(O_2C_{12}H_8)]_n$ homopolymer[17] was applied in this work to calculate the spatial disposition of the reagent molecules $HO-C_6H_4-NH_2$ around a polymeric $NPCl_2$ chain in THF solution by means of the radial correlation function $g(r)$ computed as explained.

Values of $g(r)$ corresponding to the distances from the P phosphazene atoms to the N atom of the NH_2 (r_{PN}) and the O atom of the OH (r_{PO}) are represented in Figure 1 for system A (i.e., neutral $HO-C_6H_4-NH_2$ reagent). They clearly show that the aminophenol molecules are statistically distributed without any preferential orientation of amine of phenol groups relative to the phosphazene units.

The same kinds of results are shown in Figure 2 for system B (i.e., phenoxy $^{-}O-C_6H_4-NH_2$ reagent which is the most stable tautomer of the deprotonated aminophenol). As Figure 2 indicates, there is an outstanding maximum of probability in the radial correlation function for the distances from the phosphazene P atom to the oxygen atoms of the reagent ion (r_{PO}).

Figure 3 shows the results of $g(r)$ computed for system C which contains the unfavorable $HOC_6H_4-NH^-$ ion. This ion is preferentially oriented with the NH^- group pointing to the P atom of the phosphazene chain although the difference with respect to the other group is much smaller than in the previous case.

In brief, molecules of the neutral aminophenol do not show any particular preference for orientations placing either OH or NH_2 groups pointing to the polymer chain. On the contrary, ionized reagents tend to point the ionic group toward the P atoms of the polymer, although the preference is smaller in the case of NH^- than in O^-. It is important to point out that the same conclusions are obtained through examination of the correlation functions computed with the distances from the P, Cl, and N atoms of the chains to the H, N, or O atoms of the NH_2, OH, NH^-, and O^- groups, which are not shown here. It seems that interactions among electrical charges play an important role in the preferred orientation of the reagent molecules with respect to the polymer chain.

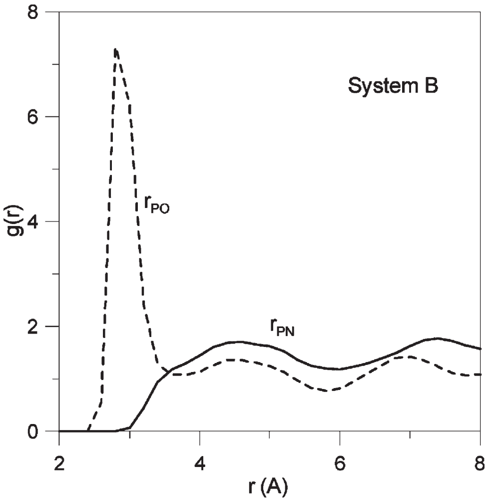


Figure 2. Radial correlation function $g(r)$ for the distances between P atom of the oligomers contained in system B to N and O atoms of the reagent molecules computed from molecular dynamics trajectories performed at 500 K (see text for details).

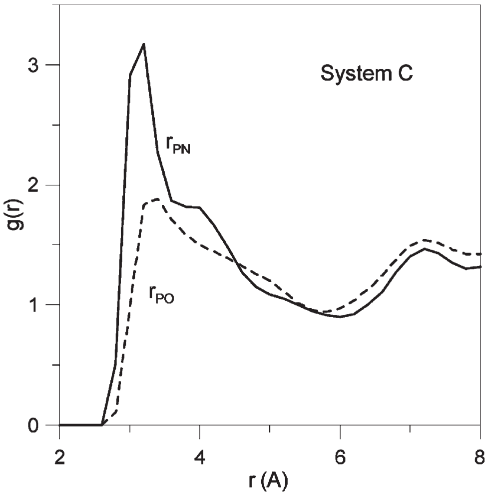


Figure 3. Radial correlation function $g(r)$ for the distances between P atom of the oligomers contained in system C to N and O atoms of the reagent molecules computed from molecular dynamics trajectories performed at 500 K (see text for details).

The results shown above, in particular those of Figure 2, could explain the experimental results obtained for the reaction of polydichlorophosphazene with aminophenol in the presence of K_2CO_3 under reflux which indicates that the reaction takes place through the O atom of the reagent while its amine N atom does not react. Thus, the experimental conditions will deprotonate the aminophenol, producing mainly the most stable tautomer $^{-}O-C_6H_4-NH_2$ whose O^- group will have quite a high probability of coming into distances of ca. 2−3 Å to the skeletal P atoms. This interpretation could also explain why the reaction of $\{[NP(O_2C_{12}H_8)_{1-x}][NPCl_2]_x\}_n$ with $HO-C_6H_4-NH_2$ and Cs_2CO_3 at reflux proceeds exclusively by the OH giving aryloxyphosphazenes with terminal NH_2 substituents.[10]

However, the results shown in Figure 1 suggest that, when the reagent is the neutral aminophenol molecule, reactions through

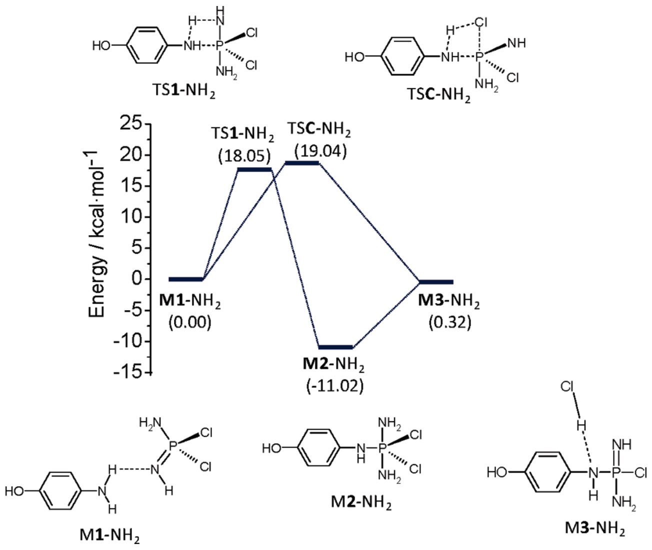


Figure 4. Energy profile for the two possible reaction mechanisms when the amino group is the reacting center. As it can be seen, although the stepwise mechanism has lower energy of activation, the concerted mechanism could be a competitive reaction mechanism.

the OH and NH$_2$ groups should be produced roughly to the same extent. This conclusion is in evident contradiction with experimental results obtained at room temperature when no deprotonation of the reagent molecule takes place, which indicates a strong regioselectivity through the NH$_2$ group.[10] It seems that the regiochemical effects observed in this reaction should be originated by the reaction mechanism rather than being produced by a preferential orientation of the reagent molecule before the reaction onset.

This was successfully demonstrated by performing density functional theory (DFT) calculations on a simple molecular model presenting the main features of the real system to allow reliable computational predictions and yet being affordable from a computational point of view. The model takes into account only a single phosphorus of the polymer chain linked to two chlorine and two nitrogen atoms which, in turn, are linked to H in order to avoid free valences (see Chart 2). Therefore, the computed reaction takes place between $HO-C_6H_4-NH_2$ and the phosphoranimne $(NH_2)Cl_2P(=NH)$.

Two different reaction mechanisms, namely stepwise and concerted (see Figures 4 and 5), were considered: for both possible reaction centers (hydroxyl and amino groups) of the reacting molecule. We found that in both cases the stepwise mechanism is more efficient (lower energy of activation) than the concerted one. Nevertheless, the concerted pathway could play a significant role as a competitive reaction pathway in the case of the amino group. The concerted pathway implies a transition state of four centers. For both reacting centers (hydroxyl and amino groups) two bonds are being broken (N−H or O−H in the reagent molecule and P−Cl) and two others are being formed (N−P or O−P and H−Cl) simultaneously in a single transition state (TS**C**). On the other hand, the stepwise mechanism involves a first transition state (TS**1**) of three centers, connecting the **M1** and **M2** species on the potential energy surface (see Figures 4 and 5). In this transition state (TS**1**) two sigma bonds are being formed (N−P or O−P and the H−NH) while one σ bond is being broken (the N−H or O−H), but also the P═N double bond becomes a P−N single bond through this transition state. In summary, for the **TS1**, two sigma bonds are formed as one sigma and one pi bonds are broken. This situation implies that this transition state structure is lower in energy than the corresponding concerted transition state for each reaction center.

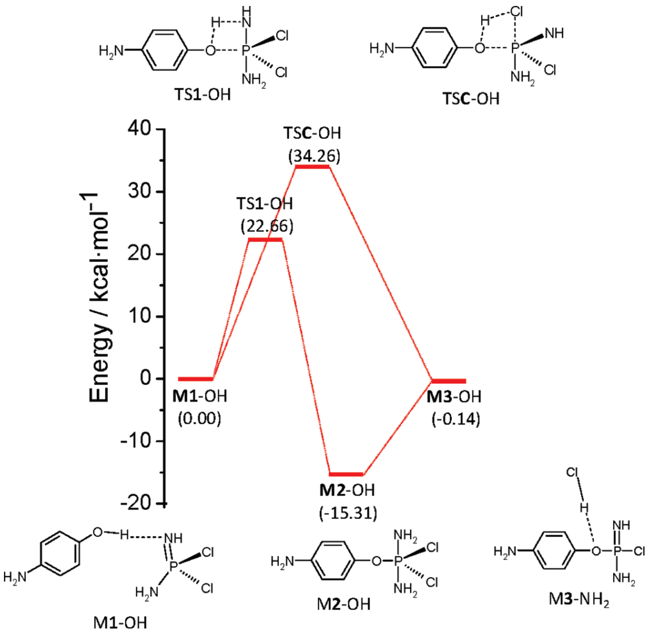


Figure 5. Energy profile for the two possible reaction mechanisms when the hydroxyl group acts as the reacting center. The stepwise mechanism is more efficient than concerted mechanism, being the only effective pathway for the reaction.

After forming the **M2** intermediate, the second and last step of the mechanism, consisting in the elimination of HCl, takes place. This step implies a continuous increase of the energy as the HCl molecule separates, reaching an energy plateau at infinite distance. Nevertheless there is a shallow minimum (which has been represented in the energy profile plot in Figures 4 and 5) due to the formation of the Cl−H···N or Cl−H···O hydrogen bond.

The stepwise mechanism is the more efficient pathway in terms of energy of activation when the reacting center is the amino group. On the other hand, molecular dynamics simulations predict a similar distance distribution for amino and phenoxy groups (see Figure 1) which suggest that the preexponential factor of the rate constant for both groups should also be similar. By applying transition state theory, it is possible to predict that the substitution reaction is controlled by the activation energy, and therefore, the most favored reaction product with a yield of ca. 100% at room temperature is the amino derivative due to the lower activation energy (ca. 18 kcal/mol, see Figure 4) as compared with the hydroxyl group (ca. 23 kcal/mol, see Figure 5).

Therefore, the amino group of the $HO-C_6H_4-NH_2$ nucleophile has the lower energy of activation for the chlorine replacement leading to the amino-phosphazene product, which is in complete agreement with the experimental reaction with the real $[NPCl_2]_n$ polymer at room temperature. The overall process involves a first diffusion step in which the molecule come close to the polymer chain and a second one in which the chemical reaction is produced. Two possible hydrogen-bonded complexes (**M1** in Figures 4 and 5) may be formed in the first step. However, the relative stability of these complexes does not determine the reactivity of the system due to the diffusion control of this step. On the contrary, the limiting step of the overall process is the chemical process, which consists in a two-step mechanism in which a very stable intermediate is formed in the first step, giving rise after irreversible elimination of HCl to the final substituted polymer.

By contrast, the same calculations with the aryloxide $^{-}OC_6H_4-NH_2$ showed no activation energy for the O−P bond formation. Therefore, the DFT calculations predict that the substitution reaction is barrierless and diffusion controlled, which implies that the $^{-}OC_6H_4-NH_2$ ions react much faster through the alkoxide than through the amino group within the same chemical species, since this last group presents an energy barrier to fulfill the reaction (see above), while the alkoxide does not

It is important to realize that we are seeking for differences among the reaction rates of the dichlorophosphazene chain with the two groups placed at opposite ends of the *p*-aminophenol molecule rather than for the absolute velocity of any of these individual reactions. For this reason, the model compounds that we employed in the calculation include the actual structure of the reactant *p*-aminophenol molecule although the repeat structure of the polymer is drastically simplified in order to keep the computational time within reasonable limits. It is quite obvious that improving the realism of the studied system (for instance, employing a larger oligomer, including solvent effect, etc.) will increase the reliability of the individual activation energies thus obtained, but probably the incidence in the difference that we are looking for will be small.

Conclusions

The combination of results of radial correlation functions of interatomic distances obtained by molecular dynamics with the exploration of reaction mechanisms by quantum mechanical calculations performed on simple model compounds strongly suggest that the neutral bifunctional nucleophile $HO-C_6H_4-NH_2$ reacts with $[NPCl_2]_n$ in THF exclusively through the NH_2 group by a lower energy stepwise mechanism competing with a concerted mechanism, both of which are much more favorable than that for the reaction with the OH group. However, the anion $^{-}O-C_6H_4-NH_2$ reacts through the oxygen, giving aryloxyphosphazenes in a diffusion-controlled process governed by the negative charge.

This picture allows a satisfactory explanation of the experimental results which indicate that the reaction of $[NPCl_2]_n$ with substoichiometric amounts of $H_2N-C_6H_4-OH$ is regioselective by the OH at room temperature, forming linear soluble aminophosphazenes while at reflux cross-linked materials with $NP-NH-C_6H_4-O-PN$ links are formed by the activation of the OH. It is clear that at room temperature the reagent is the neutral molecule while at the refluxing temperature it is the anion $^{-}O-C_6H_4-NH_2$ (the most stable tautomer of the deprotonated aminophenol) formed by proton abstraction by the carbonate. Most likely the equilibrium between the neutral and aryloxy anion is driven further toward the deprotonated form at higher temperatures. This also explains why the reaction of $\{[NP(O_2C_{12}H_8)_{1-x}][NPCl_2]_x\}_n$ with $HO-C_6H_4-NH_2$ and Cs_2CO_3 at reflux proceeds exclusively by the OH giving aryloxiphosphazenes with terminal NH_2 substituents.

Therefore, this combined methodology is useful to address the regiochemistry of the macromolecular substitution on polyphosphazenes which is a central issue in the design of polymers with predetermined chemical composition and structure. Thus, it could be advanced that the reactions of clorophosphazenes with neutral nucleophiles having both arene−OH and arene−NH_2 groups in the presence of mild proton abstractors would give amino derivatives with pendant OH groups unless a significant concentration of aryloxy anions is formed at the temperature needed for the substitution in which case the reaction would give aryloxyphosphazenes with pendant NH_2 groups or cross-linked products.

A more general tentative conclusion is that, while the macromolecular substitution reactions of poly(dichlorophosphazene) with aryl oxide ions are diffusion controlled and governed by the atomic charges, with amino-arenes the process is directed by hydrogen interactions between the NH_2 group and the phosphazene nitrogen atoms that initiate the substitution mechanism.

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