Computational investigation of thermal decomposition mechanism of 5-nitro-5-R-1,3-dioxane compounds

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Abstract
This paper features the results of the computational study of thermal decomposition reaction of 5-nitro-5-R-1,3-dioxane compounds, with R = H, Br, and CH3. Computational calculations were performed with M06-2X, MPWB1K, PBE0 and ωB97X-D functionals, and 6–311 + G(d,p) basis set in gas phase and also in solution with DMSO, at different temperatures. The kinetic and thermodynamic data obtained indicate a favoring of the reaction when the molecule presents substituent groups in position 5 and when carried out in DMSO, the stability of the molecules in their energetic components was discussed, too. For R = H two different reaction mechanisms were proposed and studied. Wiberg bond indices were obtained for the reactions studied and the results were examined in terms of bond formation and bond breaking progress as well.

Keywords Bronidox · DFT · Nitrous acid · Substituted dioxanes · Thermal decomposition · 5-Nitro-5-R-1,3-dioxanes

Introduction
Compounds of 1,3-dioxane type are involved in industrial processes as by-products, when used as solvents [1], or as reagents in synthesis processes in fine organic chemistry [2]. They have also been reported as biologically active compounds with anti-inflammatory properties, and effective modulators of multidrug resistance [3]. These compounds have also been considered for their enormous potential in terms of structural diversity, especially by substitution at positions 2 and 5 of the molecule [4, 5]. 1,3-Substituted molecules were found to display significant antifungal and antibacterial properties. Within this family of compounds, the most prominent have been the nitro and halonitro derivatives, especially because of their stability at a wider pH range (5–9). For instance, 5-bromo-5-nitro-1,3-dioxane (bronidox) exhibits a broad spectrum of antimicrobial activity [5] and is an important reagent for ion-radical and oxide-reduction type reactions [2–6].

5-Bromo-5-nitro-1,3-dioxane is used as a preservative in rinses, cosmetics, and toiletries such as make-up, perfumes, toothpastes, soaps, shampoos, hand creams, and facial scrubs. [7].

Compounds derived from 1,3-dioxane can thermally decompose and release nitrous acid (HNO2) or nitrogen oxides (NOx) depending on the reaction mechanism [8, 9].

There is an experimental study of the thermal decomposition of 5-nitro-5-R-1,3-dioxane type compounds (Fig. 1 represents their general structure), in which the authors proposed a thermal decomposition mechanism for nitrous acid formation, similarly as represented in Fig. 2 [10].

Although there are computational studies on the formation of 1,3-dioxane compounds [11], we are not aware of published theoretical studies on their thermal decomposition.

The development of this project sought to computationally study the thermal decomposition of a series of 5-nitro-5-R-1,3-dioxane compounds at different temperatures. The findings obtained allowed to deepen in the reaction mechanism of their decomposition, to obtain the kinetic and thermodynamic parameters of the reaction as well as to correlate the activation energy with the structural characteristics of the molecules studied.
Methods

All calculations for this study were carried out in the Gaussian 09 computational package [12]. The geometrical parameters for all reactants, transition states, and products of the reaction studied were optimized using the density functional theory (DFT), with the functional M06-2X [13] and 6–311+G(d,P) basis set [14]. (See Table S1 in supporting information). Pre-calculations were performed on the molecules studied, but there were no significant differences in the results with larger basis set, see Table S2 in supporting information).

Vibrational frequency calculations at M06-2X [13], MPWB1K [15], PBE0 [16], and ωB97X-D [17] were conducted to obtain the kinetic and thermodynamic parameters of the reactions, which also allowed to characterize each structure as a minimum or saddle point within the potential energy surface. Scaling factors of 0.9658 and 0.9812 to M06-2X and PBE0, respectively, were used to correct the zero-point vibrational energy (ZPE), as previously recommended [18].

Computational calculations were accomplished at four different temperatures within the range of 503–563 K and 1 atm of pressure. Enthalpy and entropy values were evaluated according to the standard thermodynamics equations [19]. Calculations in solution with dimethyl sulfoxide (DMSO) were achieved by the polarizable continuum model, using the integral equation formalism (IEFPCM) [20].

Calculations of the intrinsic reaction coordinate (IRC) [21] were performed on each of the localized transition state structures to verify that they connect to the corresponding stationary minimum points corresponding to the reactants and products. An example of IRC is shown in Fig. S1 in the supporting information.

The kinetic parameters were evaluated using classical transition state theory (TST), according to the Eyring-Polanyi equation [22, 23].

The population partitioning technique, natural bond orbital (NBO) [24, 25], has been used using the NBO program [26] implemented in the Gaussian 09 computational package [12]. Bond characteristics were obtained through Wiberg bond indices [27]. They are interpreted as a measure of bond order and bond strength among atoms. Processing these values generates additional indicators of both the bonds and the reaction. The percentage of evolution (%EV) is an indicator of the relative variation of the bond in the transition state, and has been calculated as:

\[
%EV = \delta \beta_i \times 100
\]

where

\[
\delta \beta_i = \frac{\beta_i^{TS} - \beta_i^R}{\beta_i^P - \beta_i^R}
\]

\[
\delta \beta_{av} = \frac{1}{n} \sum \delta \beta_i
\]

where \( n \) is the number of bonds to be considered in the reaction. The value obtained allows inferring characteristics of the transition state and is interpreted as a measure of the degree of progress of the transition state along the reaction coordinate.

The reaction is characterized by absolute synchronicity \([28]\)(\( S_y \)), calculated from the Wiberg bond indices, according to the following expression:

\[
S_y = 1 - \left[ \frac{1}{2n-2} \sum \frac{|\delta \beta_i - \delta \beta_{av}|}{\delta \beta_{av}} \right]
\]

\( S_y \) is an indicator ranging from 0 to 1; high values for \( S_y \) imply that the reaction is highly synchronous.
Results and discussion

Mechanism of the decomposition reaction

The thermal decomposition reaction of a series of 5-nitro-5-R-1,3-dioxane compounds with R = H, CH₃, and Br, was computationally modeled to observe the effect of the substituent group on the reaction parameters and mechanism.

The reactions were carried out under conditions simulating the gas phase and also in solution with DMSO as solvent. The mechanisms postulated in Figs. 2 and 3 were used as a starting point.

Figure 2 represents a reaction mechanism that proceeds through a 5-atom cyclic transition state and involves the breaking of the carbon–nitrogen bond and the migration of a hydrogen from carbon 6 to one of the oxygens of the nitro group, thus leading to the subsequent formation of the alkene: 5-R-4H-1,3-dioxine and a nitrous acid molecule.

Alternatively, when R = H, the two-stage mechanism depicted in Fig. 3 is also followed, where the reaction starts with the breaking of the C4–O3 and N9–C5 bonds and the formation of new bonds between C6–O3 and C4–N9. This leads to the formation of the intermediate compound 4-(nitromethyl)-1,3-dioxolane, which in a later stage decomposes through a cyclic transition state of 5 atoms. This involves the migration of hydrogen from carbon 5 and the detachment of the nitro group. The alkene 4-methylene-1,3-dioxolane is also produced by the formation of double bonds at carbons 4 and 5.

Computational optimization of the molecules was accomplished at M06-2X/6–311 + G(d,p). Figure 4 depicts the optimized geometry of the reactants, transition states (TS1-5-H-M1, TS1-5-methyl-M1, and TS1-5-Br-M1) and products (P1-H, P1-methyl, and P1-Br) involved in the decomposition reactions, following the one-stage mechanism.

Kinetic and thermodynamic parameters

The vibrational frequency data in the temperature range of 503.15–563.15 K obtained with some DFT functionals allowed to calculate the kinetic values are shown in Table 1. It is worth noticing that the lowest activation Gibbs energies (∆G°) for the decomposition reaction are given in their order for the PBE0, oB97X-D, M06-2X, and MPWB1K functionals.

The results obtained with the PBE0 functional have less overestimation in comparison with the other functionals that were used. Table 2 shows the complete kinetic data calculated with the PBE0 functional and the linearization of the Arrhenius equation.

The two-stage mechanism turned out not to be feasible for the decomposition reaction 5-nitro-1,3-dioxane compared to that occurring in a single-stage mechanism. We see that the first stage is the limiting of the speed with a free energy of activation of 280.6 kJ∙mol⁻¹, which is 96.6 kJ∙mol⁻¹ higher than the activation free energy in the reaction occurring according to the single-stage mechanism in gas phase.

When the reactions are carried out in solution with DMSO, the energy barrier in each of them is lowered and as a result the decomposition rate increases. The most important solvent effect occurs in the decomposition reaction of 5-methyl-5-nitro-1,3-dioxane, where the activation Gibbs energy is decreased in 17.6 kJ·mol⁻¹. It is also observed that when the substituent is a bromine atom, solvent stabilization is very little.

An important contribution to the decrease of the free energy of activation can be noticed in the activation entropy with the highest value 33.3 J∙mol⁻¹∙K⁻¹ for bromine as a
substituent group in gas phase, which is also evident when looking at the values of the frequency factor (A).

Although the reaction of the molecule with the substituent bromine has higher activation energy (Ea) than the molecule with methyl group substituent, the former has a higher value in the frequency factor (A); therefore, its reaction rate is higher.

It is also worth noting that the Gibb energy of activation for the bromine substituent is smaller compared to the corresponding ones for the hydrogen and methyl groups in the gas phase; however, in solution with DMSO, the activation energy becomes smaller for the molecule substituted with a methyl group in position 5.

Figure 5 features the optimized structures involved in the reaction by the proposed two-stage mechanism. Table 3 summarizes the experimental values reported for the modeled decomposition reactions.

The computational findings obtained present some discordance with the experimental values reported by Stepanov et al. [10]. For example, the computational activation energy for the decomposition reaction of the studied compounds are 18, 10, and 16% above the experimental values for the substituent groups H, methyl, and Br, respectively. However, the results reported by the authors indicate that the greatest favorability for decomposition reactions occurs with the bromine atom at position 5, followed by substitution by the methyl group and the

**Table 1** Gibbs activation energies for the decomposition reaction of 5-R-5-nitro-1,3-dioxane by the one-stage reaction mechanism at 523 K

| R group     | ΔG° (KJ·mol⁻¹) |
|-------------|----------------|
|             | M06-2X | ωB97X-D | MPWB1K | PBE0 |
| H (gas)     | 204    | 192     | 209     | 184  |
| H (DMSO)    | 198    | 181     | 200     | 176  |
| CH₃ (gas)   | 194    | 177     | 198     | 183  |
| CH₃ (DMSO)  | 175    | 154     | 176     | 165  |
| Br (gas)    | 199    | 180     | 201     | 173  |
| Br (DMSO)   | 197    | 173     | 194     | 167  |
hydrogen atom at position 5. The computational results indicate the same.

The free energy profile for the reaction in gas phase and in DMSO is shown in Fig. 6.

From the graphical representation, it can be observed that the decomposition reaction of 5-bromo-5-nitro-1,3-dioxane generates the most stable products, additional to that kinetically, it is the most favored reaction among the reactions observed. The reactions in DMSO solution occur with a lower activation free energy value; however, the thermodynamics of the reaction are not significantly favored.

Population analysis (NBO)

The natural bond orbital (NBO) population partitioning technique was used to obtain the Wiberg bond index values and by means of them to follow in depth the processes of bond breaking and bond formation throughout the chemical reaction.

The findings obtained from the NBO analysis and the other indicators that were calculated with Eqs. (1), (2), (3), and (4) are depicted in Table 4.

When the reaction is carried out with DMSO solvent, it occurs more quickly, and this is more evident with the methyl group as a substituent.

### Table 2

| R    | ΔG° (kJ mol⁻¹) | Ea (kJ mol⁻¹) | Log A | ΔS° (J mol⁻¹ K⁻¹) |
|------|---------------|---------------|-------|-------------------|
| H    | 184.0 (176.1) | 204.2 (197.4) | 15.1  | 30.1 (32.2)       |
| Methyl | 182.9 (165.3) | 188.3 (174.2) | 13.6  | 2.2 (9.9)         |
| Br   | 172.9 (167.6) | 194.8 (191.7) | 15.2  | 33.3 (37.6)       |

| R  | Ea (kJ mol⁻¹) | Log A | ΔS° (J mol⁻¹ K⁻¹) |
|----|---------------|-------|-------------------|
| H  | 173.1         | 12.81 | −12.7             |
| Methyl | 170.1      | 13.40 | −1.4              |
| Br | 167.7         | 13.42 | −1.0              |

### Table 3

| R      | Ea (kJ mol⁻¹) | Log A | ΔS° (J mol⁻¹ K⁻¹) |
|--------|---------------|-------|-------------------|
| H      | 173.1         | 12.81 | −12.7             |
| Methyl | 170.1         | 13.40 | −1.4              |
| Br     | 167.7         | 13.42 | −1.0              |

The average relative variation of the bond indices, δRi, with values of 0.49 and 0.51 for the reactions, indicates symmetric transition states whose structure is intermediate between reactants and products.

The reaction that occurs for the molecule with the methyl substituent presents an imbalance between bond formation and bond breaking events, evidenced by a value of 0.83 for the reaction synchronicity. Perhaps that is why the effect of the solvent is more important for the decomposition of 5-methyl-5-nitro-1,3-dioxane.
Conclusions

Computational calculations with the M06-2X, MPWB1K, PBE0, and ωB97X-D functionals were performed to model the decomposition reaction of 5-nitro-5-R-1,3-dioxane compounds. According to the computationally obtained data for R = H, methyl, and Br two possible reaction mechanisms for the thermal decomposition of 5-nitro-1,3-dioxane were considered. The findings of the computational calculations indicate that the two-stage mechanism for this reaction is not feasible with respect to the single-stage mechanism. When this compound is substituted at the carbon 5 position by a methyl group or a bromine atom, the rate of the reaction becomes higher, mainly with the bromine group, and if the reaction is also carried out in solution with a solvent such as DMSO, the activation energy decreases with respect to the reaction in the gas phase.

The values of kinetic and thermodynamic parameters obtained in this study and through the density functional theory, depart from the experimental values previously reported by Stepanov et al. [10]. However, there is an agreement regarding the effect of substituent groups on the reaction.

The analysis of the Wiberg bond indices for the reaction studied allowed us to define carbon–nitrogen and nitrogen–oxygen bond breaking as the most and least advanced processes in each of the reactions, respectively.

Table 4 Wiberg bond indices for reactants, transition states, and products ($B^R$, $B^{TS}$, and $B^P$) for gas-phase decomposition reactions using the one-stage mechanism

|       | $C_5-C_6$ | $C_6-H_7$ | $H_7-O_8$ | $O_8-N_9$ | $N_9-C_5$ |
|-------|-----------|-----------|-----------|-----------|-----------|
| $B^R$ (1) | 0.9793    | 0.9217    | 0.0022    | 1.5178    | 0.8763    |
| (2)    | 0.9633    | 0.9203    | 0.0025    | 1.5147    | 0.8451    |
| (3)    | 0.9862    | 0.9083    | 0.0008    | 1.5339    | 0.8408    |
| $B^{TS}$ (1) | 1.3882    | 0.4261    | 0.3176    | 1.372     | 0.278     |
| (2)    | 1.3524    | 0.4393    | 0.3006    | 1.3743    | 0.1187    |
| (3)    | 1.3527    | 0.4249    | 0.3183    | 1.371     | 0.2694    |
| $B^P$ (1) | 1.8559    | 0.0000    | 0.752     | 1.0947    | 0.0000    |
| (2)    | 1.8092    | 0.0000    | 0.752     | 1.0947    | 0.0000    |
| (3)    | 1.795     | 0.0000    | 0.752     | 1.0947    | 0.0000    |
| %EV (1) | 46.65     | 53.77     | 42.06     | 34.46     | 68.28     |
| (2)    | 46.00     | 52.27     | 39.77     | 33.43     | 85.95     |
| (3)    | 45.31     | 53.22     | 42.27     | 37.09     | 67.96     |

%EV percentage of evolution, $\delta\beta_{av}$ average relative variation, $S_\text{abs}$ absolute synchronicity of the reaction

Two possible reaction mechanisms for the thermal decomposition of 5-nitro-1,3-dioxane were considered. The findings of the computational calculations indicate that the two-stage mechanism for this reaction is not feasible with respect to the single-stage mechanism. When this compound is substituted at the carbon 5 position by a methyl group or a bromine atom, the rate of the reaction becomes higher, mainly with the bromine group, and if the reaction is also carried out in solution with a solvent such as DMSO, the activation energy decreases with respect to the reaction in the gas phase.

The values of kinetic and thermodynamic parameters obtained in this study and through the density functional theory, depart from the experimental values previously reported by Stepanov et al. [10]. However, there is an agreement regarding the effect of substituent groups on the reaction.

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Author contribution The contribution of each author listed is based on Silvia Quijano and Pablo Ruiz, who made a substantial contribution to the conception and design, data acquisition and analysis, and interpretation of the data; Pablo Ruiz and Jairo Quijano drafted the article and
critically reviewed the intellectual content. All the authors read and approved the final manuscript.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Competing interests The authors declare no competing interests.

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