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#### Paper

# Experimental and Theoretical Study of the Reaction Kinetics of 2,5-Dimethylterephthalonitrile Bromination Compared to 1,4-Dimethylbenzene Bromination

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Received: 30.11.2017 Accepted after revision: 01.12.2017 Published online: 29.01.2018 DOI: 10.1055/s-0036-1591750; Art ID: ss-2017-z0564-op

**Abstract** Experimental and theoretical studies showed the differences observed in the benzylic tetrabromination reactions in 2,5-dimethyl-terephthalonitrile compared to 1,4-dimethylbenzene. It was observed that the compound containing the nitrile substituent underwent a slower bromination reaction, with the formation of four intermediate compounds, while for the compound without substituents, the reaction was faster and only two intermediate compounds were observed.

**Key words** bromination reactions, 1,4-dimethylbenzene, 2,5-dimethylterephthalonitrile,  $\alpha, \alpha, \alpha', \alpha'$ -tetrabromide-*p*-xylene,  $\alpha, \alpha, \alpha', \alpha'$ -tetrabromide-2,5-dicyano-*p*-xylene

Aromatic compounds that are brominated either in the side chain or ring, have been synthesized and studied for a long time. These compounds are interesting because of their applications, primarily as intermediates in syntheses to later reach functions and complex organic structures.<sup>1,2</sup> They are also used in the synthesis of materials, agrochemicals, antioxidants and pharmaceuticals.<sup>3–5</sup>

Different methods of syntheses have been studied to obtain such compounds. Electrochemical bromination methods<sup>6</sup> as well as other brominations with solvents such as 1,2-dichlorobenzene,<sup>1</sup> ionic liquid,<sup>7</sup> and water,<sup>8</sup> among others, have been performed.

In this study, benzylic tetrabrominations were performed in *p*-xylene (1,4-dimethylbenzene) and in 2,5-dicyano-*p*-xylene (2,5-dimethylterephthalonitrile) by using the Wohl–Ziegler Reaction,<sup>9</sup> which has been the most commonly used method. The reaction is performed under heating with light provided by a light bulb. The compound to be brominated is added to a flask along with benzoyl peroxide as radical initiator, and N-bromosuccinimide (NBS) in carbon tetrachloride solvent as source of bromine.<sup>9</sup>

The *p*-xylene compound was converted into the  $\alpha, \alpha, \alpha', \alpha'$ -tetrabromide-*p*-xylene compound, which has been studied so that its pharmaceutical applications can be explored; studies have shown interesting properties in trials for the treatment of Alzheimer's, and for medications against AIDS and cancer.<sup>10</sup> Moreover, it is used to obtain PPV polymers (polyphenylenevinylene) through electrosynthesis; such polymers have been drawing the attention of researchers since the 1990s because their properties allow them to be used in organic light-emitting diodes (OLEDs), organic photovoltaic films (OPVs), and in photovoltaic cells.<sup>11</sup> The 2,5-dicyano-*p*-xylene compound was converted into  $\alpha, \alpha, \alpha', \alpha'$ -tetrabromide-2,5-dicyano-*p*-xylene, which has been studied as part of the search for conducting polymers with well-defined properties to be used in photovoltaic devices<sup>12</sup> and photoluminescent materials, among others.13

In this study we aimed to compare the bromination reactions that occur in 1,4-dimethylbenzene and in 2,5-dimethylterephthalonitrile. To do so, the experimental synthesis of both compounds was completed using the Wohl– Ziegler reaction.<sup>9</sup> The synthesis was monitored for 10 hours, and the formation of mono-, di-, tri- and tetrabrominated compounds over time was assessed by <sup>1</sup>H NMR spectroscopic analysis. Furthermore, a theoretical study was carried out wherein density functional calculations were performed to understand the electronic changes in the methylene groups during the addition of bromine atoms to the reactants and, thus, explain the experimental data obtained.

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A kinetic study of the bromination reaction of 1,4-dimethylbenzene and 2,5-dimethylterephthalonitrile was undertaken to explain the differences in the rate of incorporation of bromine atoms in the methyl groups when the compound has CN substituents on the ring and when it does not.

The Wohl-Ziegler reaction is radical. In its mechanism, NBS generates molecular bromine (Br<sub>2</sub>), which reacts with the initiating agent (benzoyl peroxide, which is broken homolytically in the presence of light/heat). Thus, the bromine radical is produced. This radical removes a hydrogen atom from the allylic or benzylic position of the compound to be brominated, generating a benzylic radical (stabilized by resonance) and HBr. HBr reacts with NBS and forms more Br<sub>2</sub> and succinimide. The benzylic radical removes a bromine atom from the Br<sub>2</sub> compound, yielding the brominated compound.9

The presence of six compounds, the structures of which are shown in Figure 1, was found during the reaction of 2,5dimethylterephthalonitrile.



Figure 1 Bromination of 2,5-dimethylterephthalonitrile

The percentage of each compound present in the reaction mixture during 10 hours was calculated (Figure 2). Such calculations were performed based on the integral related to the signals of each compound in the <sup>1</sup>H NMR spectra.

It was observed that, in the beginning of the reaction, first, the formation of approximately 40% CN 2 was necessary for two bromine atoms to enter the methyl groups (CN 3 and CN 4). It is seen that the entrance of bromine atoms into opposite methyl groups or into the same methyl group occurs in almost the same proportion, but with a slight preference for the opposite methyl group due to the greater number of effective collisions provided by its geometry. For the formation of structures with three bromine groups to increase significantly, it is necessary that there be approximately 20% of structures with two bromine atoms (CN\_3 and CN\_4). The formation of structures with four bromine atoms (CN\_6) only starts to occur after the relative percentage of the structures with three bromine groups also increases to approximately 20%. Meanwhile, the relative percentages of the structures with two bromine atoms start to decrease. The reaction continues for 10 hours and an increase in the percentage of tetrabrominated compound CN\_6, occurs.





For the 1,4-dimethylbenzene, the formation of only two intermediate compounds, H 3 and H 5, was observed (Figure 3).



Figure 3 Bromination of 1,4-dimethylbenzene

The formation of the compound with only one bromine atom (H\_2) was not observed, with the first sample (withdrawn after 15 minutes of reaction) indicating the formation of 100% of compound H\_3, with two bromine atoms one at each methyl group (Figure 4). Increased relative percentage of the compound with three bromine atoms (H\_5) was then observed with a decrease in the relative percentage of the **H\_3** compound. When the relative percentage of H\_5 was approximately 30%, an increased relative percentage of  $\alpha, \alpha, \alpha', \alpha'$ -tetrabromide-*p*-xylene (**H\_6**), with four

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bromine atoms, was observed. The relative amount of **H\_6** increases throughout the reaction time until all the NBS is consumed.



The reactions observed for the 1,4-dimethylbenzene, with and without substituents on the ring, differed with respect to velocity. After 1 hour of reaction, the 1,4-dimethylbenzene already had a relative percentage of 20% of the tetrabrominated compounds. Meanwhile, the compound containing substituents (**CN\_1**) presented a slow reaction; after 10 hours of reaction, it had only ca. 15% tetrabrominated compounds. It is believed that the reaction of 2,5-dimethylterephthalonitrile requires a higher energy of activation and, thus, is slower.

Calculations on the electronic structure were performed to better explain what happens in each structure. Potential energy surface calculations were performed and all minima were optimized, but some conformations obtained in this preliminary analysis converged to more stable conformations. The electrostatic potential maps of the most stable conformations of the derivatives of the two compounds were studied. It was observed through the map of electrostatic potential that the higher the number of bromine atoms bonded to the methyl group, the greater the positive character of the carbon to which they were attached.

The atomic charge was determined with three different methods to verify this observation: charge analysis through the natural bond orbital method (NBO),<sup>14</sup> Mulliken charges, and ATP charges. Since the atomic charge is not a quantum observable, all methods to compute it are necessarily arbitrary.<sup>15</sup> In this discussion, the results of Mulliken charges will not be presented due to the restrictions on the distribution of atomic charges in the molecules.

Table 1 and Table 2 show the values of the ATP and NBO charges obtained for the C7 and C8 carbon atoms for both compounds (Figure 5).



Figure 5 Structures of 1,4-dimethylbenzene (H\_1) and 2,5-dimethylterephthalonitrile (CN\_1)

 
 Table 1
 ATP and NBO Atomic Charges for the Derivatives of 2,5-Dimethylterephthalonitrile Calculated at M06-2X/6-311++G(2d,2p)

	C7 (ATP)	C8 (ATP)	C7 (NBO)	C8 (NBO)
CN_1	0.01543	0.01543	-0.63483	-0.63483
CN_2	0.33954	0.00405	-0.43337	-0.60722
CN_3	0.33186	0.33186	-0.43696	-0.43696
CN_4	0.65489	-0.00094	-0.38264	-0.60578
CN_5	0.64519	0.32272	-0.38349	-0.43936
CN_6	0.63763	0.64231	-0.41465	-0.38510

 Table 2
 ATP and NBO Atomic Charges for the Derivatives of 1,4-Dimethylbenzene Calculated at M06-2X/6-311++G(2d,2p)

	C7 (ATP)	C8 (ATP)	C7 (NBO)	C8 (NBO)
H_1	0.05079	0.05079	-0.59260	-0.59260
H_2	0.45798	0.03560	-0.40475	-0.59465
H_3	0.44700	0.44699	-0.41002	-0.41001
H_4	0.79655	0.02910	-0.34447	-0.59587
H_5	0.77433	0.42480	-0.35150	-0.41391
H_6	0.77066	0.77069	-0.35369	-0.35367

Based on the positive character of carbons C7 and C8, a comparison between these theoretical values and experimental data can be made. Thereby, an explanation for the distinct behavior of both reactions can be suggested. The reactions occur with the formation of radicals; the carbon with greater charge deficiency (higher charge) causes a weakening of the carbon-hydrogen bond, making removal of the hydrogen easier, thus, facilitating the formation of the benzylic radical. It is suggested that because of the observed charge differences, the formation of the **H\_3** compound, containing a bromine atom in C7 and C8, is very fast, and the **H\_2** compound cannot be detected in the first sample withdrawn at 15 minutes of reaction. What is observed at this time is the formation of 100% of **H\_3** and, afterwards, other compounds appear.

When observing the ATP charge for **CN\_2**, it can be seen that the values for C7 and C8 are quite different because the charge of C8 has a very low value due to the entrance of a

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bromine atom on the opposite side. For **H\_2**, the charge values observed are not so different. In this case, the charge of C8 is only a little less positive than the charge of C8 in **H\_1**. Such behavior of the charges is significant, because, when compared with the other experimental data, it can be noted that 1,4-dimethylbenzene (**H\_1**) is completely dibrominated right at the beginning of the reaction and, later, other compounds appear, whereas the 2,5-dimethylterephthalonitrile (**CN\_1**) first has 40% of its structure monobrominated and, only then, other dibrominated structures appear.

For **CN\_2**, entrance of the second bromine atom does not occur so fast because of the effect of the ATP charges of carbons C7 and C8, and also for steric reasons. Therefore, the relative percentage of the dibrominated compounds formed (**CN\_3** and **CN\_4**) is only 20–30%, after a reaction time of approximately 250 minutes, with **CN\_3** being formed in greater quantity.

The third bromine atom can add to either the C7 or the C8 atom in the structure without substituents. Therefore, the structures containing two bromine atoms (**H\_3**) are quickly converted into **H\_5** and stabilize after 60 minutes from the beginning of the synthesis.

The energy between the dibrominated structures **CN\_3** and **H\_3** (two bromine atoms on different methyl groups) and **CN\_4** and **H\_4** (two bromine atoms on the same methyl group) can be compared. The **CN\_3** and **H\_3** compounds are more stable than the **CN\_4** and **H\_4** compounds. The difference between **CN\_3** and **CN\_4** is 2.22 kcal mol<sup>-1</sup> and the difference between **H\_3** and **H\_4** is 3.63 kcal mol<sup>-1</sup>. The opposite is found for radicals that lead to the formation of the second bromination. The radical on the methyl group that has already undergone monobromination is more stable than the radical on the methyl group without bromine atoms. However, the difference in energy was greater for the radicals of the derivative of 2,5-dimethylterephthalonitrile (2.51 kcal mol<sup>-1</sup>) than for radicals of the derivative of 1,4-dimethylbenzene (1.44 kcal mol<sup>-1</sup>).

The entrance of a third bromine atom can occur after 75 minutes of reaction for the structure with substituents (**CN\_3** or **CN\_4**). It can be promoted by the insertion of a bromine atom in the C7-Br, forming the C7-Br<sub>2</sub>, or in the C8-H, leading to C8-Br.

The entrance of the fourth bromine atom into both structures is determined by the amount of steric hindrance as well as by the character of the radical reaction. The percentage of formation of the **H\_6** structure becomes constant when it reaches approximately 18% after 75 minutes of reaction. The **CN\_6** structure is only detected at 150 minutes, with a percentage of 0.44%, has a gradual percentage increase, and, even with no stabilization after 600 minutes, it reaches a value of only 14.93%.

In conclusion, we observed that the bromination reactions in the compound without substituents are faster. It is believed that this is due to the lower activation energy reIt took longer for four bromine atoms to enter the structure containing the nitrile substituents, and four intermediates were observed.

The reactions were carried out by using the Wohl-Ziegler<sup>9</sup> method (Scheme 1) to perform the kinetic study. CCl<sub>4</sub> (30 mL), 2,5-dicyano-pxylene (1.65 g), NBS (8.25 g) and benzoyl peroxide (1.5 mg) were added to a flask. A reflux condenser was connected to the flask. After reflux started, the reaction was run for 10 h under strong stirring and lighting with a 500 W incandescent bulb. Samples (0.6 mL) were collected for the kinetic study. The same procedure was carried out for the reaction with *p*-xylene, substituting 2,5-dicyano-*p*-xylene for *p*xylene (1.92 mL). In the first 2 h, samples were collected every 15 min; in the next 2 h, every 30 min; in the next 3 h, every 1 h, and, subsequently, every 2 h, with a total of 16 samples. The samples were filtered and redissolved in chloroform so that the <sup>1</sup>H NMR spectrum could be acquired to determine the percentage of each compound formed during the reaction. The theoretical studies were conducted with workstations running in a Linux environment using the Gaussian 09 software package<sup>16</sup> for the electronic structure calculations and the NBO 5.9 module<sup>17</sup> for analyses involving natural bond orbital theory.



Scheme 1 Bromination reaction of 1,4-dimethylbenzene and 2,5-dimethylterephthalonitrile

Potential energy surface calculations related to the C-C-C-Br dihedral angles were performed at the M06-2X/6-31G level of theory for each compound, with 24 steps of 15°. The minima were minimum points then optimized with the DFT (Density Functional Theory) method M06-2X<sup>18</sup> and basis set  $6-311++G(2d,2p)^{19}$  in a vacuum. The M06-2X hybrid functional method is suitable for obtaining thermochemical and kinetic data, and for cases in which noncovalent interactions are important in systems involving atoms of the main group.<sup>20</sup> Calculations of frequency with the same level of theory were performed to characterize the obtained structures as stationary points or transition states, and to obtain thermodynamic properties and the zero-point energy (ZPE).<sup>21</sup>

## **Funding Information**

We thank the Capes and CNPq for financial support.

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## **Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591750.

## References

- (1) Lee, S.; Ra, C. S. Clean Technol. 2016, 22, 269.
- (2) Jakhar, K.; Makrandi, J. K. Green Chem. Lett. Rev. 2008, 1, 219.
- (3) Forsch, R. A.; Wright, J. E.; Rosowsky, A. Bioorg. Med. Chem. 2002, 10, 2067.
- (4) Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K. V. Tetrahedron Lett. 1994, 35, 7055.
- (5) Ventosa-Andrés, P.; González-Vera, J. A. Bioorg. Med. Chem. 2008, 16, 9313.
- (6) Raju, T.; Kulangiappar, K. Korean J. Chem. Eng. 2014, 31, 365.
- (7) Alimenla, B.; Kumar, A.; Jamir, L.; Sinha, D.; Sinha, U. B. Acta Chim. Slov. 2009, 56, 457.
- (8) Podgoršek, A.; Stavber, S.; Zupan, M.; Iskra, J. Tetrahedron Lett. 2006, 47, 1097.
- (9) Kürti, L.; Czakó, B. Strategic Applications of Named Reactions in Organic Synthesis; Elsevier Academic Press: San Diego, 2005, 758.
- (10) Manzoor, A. M.; George, G.; Ramalingam, S.; Periandy, S.; Gokukakrishnan, V. J. Mol. Struct. 2016, 1106, 37.
- (11) Kin, T.; Park, S. Electrochimica Acta 2005, 50, 1461.
- (12) Garcia, J. R.; Gehlen, M. H.; de Oliveira, H. P. M.; Nart, F. C. J. Braz. *Chem. Soc.* **2008**, *19*, 1678.
- (13) Xie, W.; Li, Y.; Li, F.; Shen, F.; Ma, Y. Appl. Phys. Lett. **2007**, 90, 141110.

(14) Glendening, E. D.; Landis, C. R.; Weinhold, F. WIREs Comput. Mol. Sci. 2012, 2, 1.

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- (15) Foresman, J. B.; Frisch, Æ. Exploring Chemistry with Electronic Structure Methods; Gaussian Inc: Pittsburgh, **1996**, 2nd ed..
- (16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, Jr. J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. P.; Dannenberg, J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09 revision b.01; Gaussian Inc: Wallingford CT, 2009.
- (17) Reed, A. E.; Glendening, E. D.; Badenhoop, J. K.; Carpenter, J. E.; Bohmann, J. A.; Morales, C. M.; Weinhold, F. *NBO* 5.9; Theoretical Chemistry Institute, University of Wisconsin: Madison, **2011**, http://www.chem.wisc.edu/~nbo5.
- (18) Zhao, Y.; Truhlar, D. G. Theor. Chem. Acc. 2008, 120, 215.
- (19) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. J. Chem. Phys. **1980**, 72, 650.
- (20) Zhao, Y.; Truhlar, D. G. Acc. Chem. Res. 2008, 41, 157.
- (21) Jensen, J. H. *Molecular Modeling Basics*; CRC Press: Boca Raton, **2010**.