Chemistry—A European Journal
Research Article
doi.org/10.1002/chem.202404720
Chemistry Europe
European Chemical Societies Publishing
www.chemeurj.org

Odd–Even Effects Leading to Alternating Polymerization and Macrocyclization in Nitroaldol Reaction Systems

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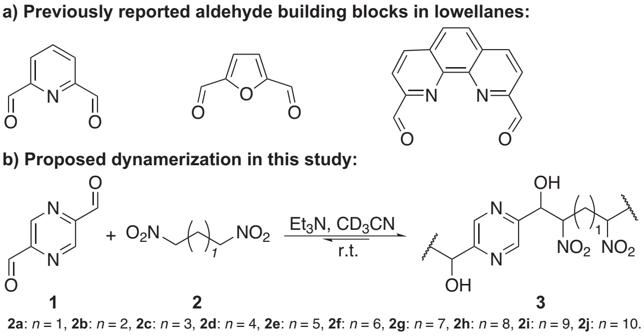
Alternating macrocyclization and polymerization was observed in dynamic nitroaldol reaction systems. The reaction of an aromatic dialdehyde reacting with linear α,ω-dinitroalkanes with even numbers of carbon atoms favored the formation of lowellane macrocycles, while the reactions involving dinitrocompounds consisted of odd numbers of carbon atoms promoted polymerization. The folding patterns of the alkyl chains played an important factor in determining the outcome of the reactions.

1. Introduction

It has been known since the 19th century that the thermodynamic properties of simple linear molecules, such as the boiling points, do not follow a linear trend with the length of the carbon chain. Instead, structures with even numbers of carbon atoms are generally distinguishably different from those with odd numbers of carbons.[1] For instance, many physical properties of linear fatty acids, n-alkanes, and their α-substituted and α,ω-disubstituted derivatives demonstrate an odd–even chain-length dependency.[2–5] Furthermore, molecules with similar structures, such as cyclic alkanes,[6] macrocycles,[7–11] and, linear polymers,[6,12,13] also demonstrated odd–even effects on their formation and properties. The effects are usually attributed to contributions by different folding and stacking behaviors between the "odd" and "even" molecules.

In many systems and processes, the odd–even effect plays a major role in determining the final outcome and the product structures, such as in polymerization,[12,14] catenane and cage formation,[15–19] supermolecule construction,[20–22] and ionic liquid systems.[23–25] In systems based on dynamic covalent reactions, being under thermodynamic control, the influence of the chain length difference can be amplified by the self-sorting and proof-reading abilities. Odd–even effects have thus been observed in a variety of dynamic systems, such as in imine/hydrazone structures,[15,16,18,26,27] boronate vitrimers,[28] and nitroalcohol organogels.[29] Our previous report revealed that even-numbered α,ω-dinitroalkanes could easily gelate with an aromatic trialdehyde in organic solvents, while the odd-numbered counterparts could either not form gels, or result in very long transformation times.[29]


a) Previously reported aldehyde building blocks in lowellanes:

b) Proposed dynamerization in this study:

2a: $n = 1$, **2b**: $n = 2$, **2c**: $n = 3$, **2d**: $n = 4$, **2e**: $n = 5$, **2f**: $n = 6$, **2g**: $n = 7$, **2h**: $n = 8$, **2i**: $n = 9$, **2j**: $n = 10$.

Figure 1. a) Dialdehydes in previous reports; b) proposed dynamerization systems in this work.

To further elucidate the nature of nitroaldol dynamer systems, and how the building-block chain length affects the outcome of the reactions, we explored a dynamer system composed of building blocks that would promote the generation of dynamers with linear topology. The dynamerization outcome was evaluated with respect to the lengths of the component chain lengths. Herein, we report a dynamic covalent polymerization system consisting of an aromatic dialdehyde and α,ω-dinitroalkanes, in which the odd–even effects led to an alternating macrocyclization and polymerization pattern.

2. Results and Discussion

In our previous reports,[29–31] we observed polymerization and macrocyclization in several nitroaldol systems in which the dialdehyde building blocks displayed acute angles between the aldehyde groups (2,5-, 2,6-, or 2,9-orientation, Figure 1a). This orientation between the connecting points may have promoted the formation of macrocycles owing to the close proximity of the terminal functional groups after two reaction steps, thereby

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202404720

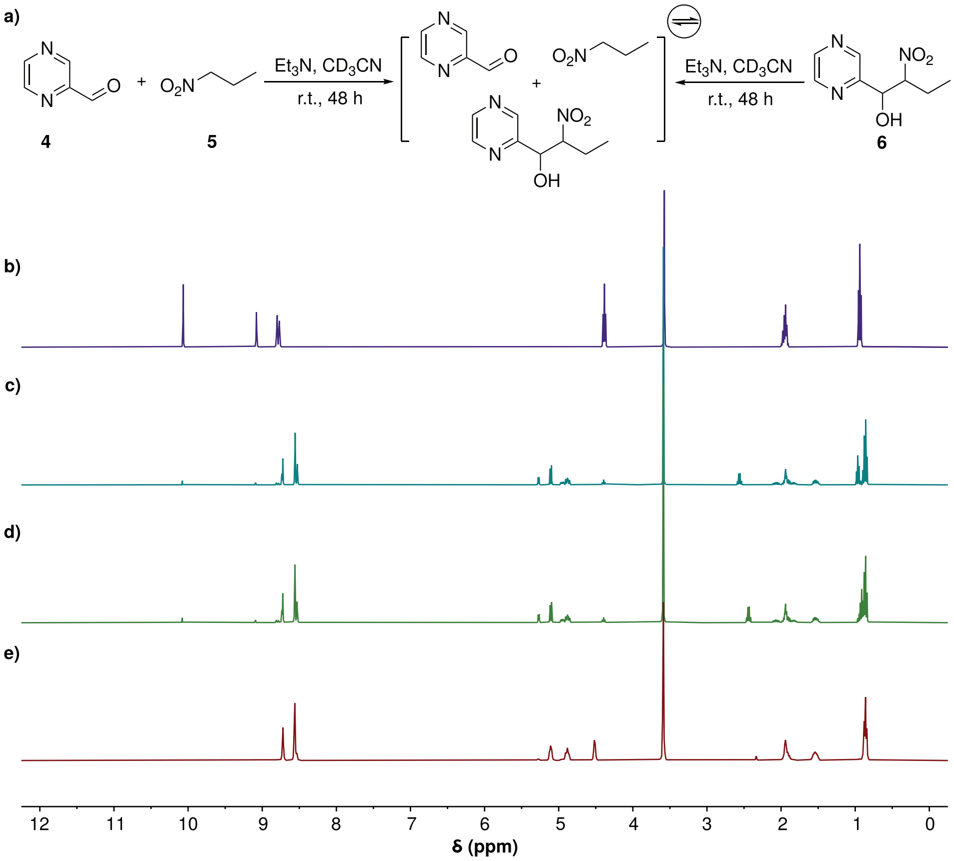
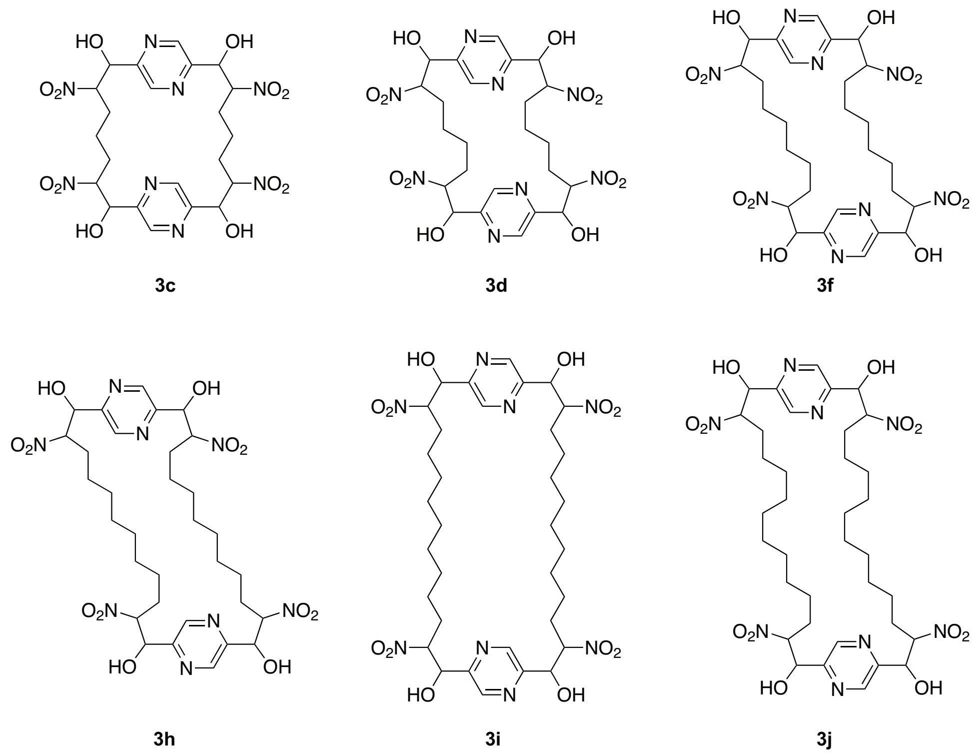


Figure 2. a) Model nitroaldol system; ^{1}H-NMR spectra of b) initial mixture of compounds **4** and **5**; c) mixture of compounds **4**, **5**, and Et$_3$N after 48 hours of incubation at RT; d) mixture of compound **6** and Et$_3$N after 48 hours of incubation at RT; e) compound **6** (400 MHz, CD$_3$CN).

resulting in a high probability of cyclization. In consequence, this would also be one of the factors causing the limited degree of polymerization observed. To address this possibility, we opted for an alternative dialdehyde possessing a straight angle between the reacting aldehyde centers, in order to reduce the probability of short-chain end-groups reacting with one another at the expense of forming acyclic polymers. Thus, a highly reactive aromatic dialdehyde, 2,5-pyrazinedicarboxaldehyde (**1**), was used in the reactions with α,ω-dinitroalkanes (**2a**–**2j**; Figure 1b).

Before proceeding to the polymerization study, model reactions were first investigated to assess the dynamicity of the proposed system (Figure 2a). A mixture of 2-pyrazinecarboxaldehyde (**4**) and 1-nitropropane (**5**), in the presence of Et$_3$N, afforded a mixture of nitroalcohol **6** alongside the residual starting materials (Figure 2c). Starting from the product side, pure nitroaldol adduct **6** partially decomposed into its aldehyde and nitroalkane building blocks after incubation with base (Figure 2d). As shown in Figure 2c and 2d, the compositions resulting from the different starting points demonstrated high similarity, thereby indicating systemic reversibility. This dual-entrypoint analysis thus suggested that the proposed polymerization reaction (Figure 1b) would give rise to dynamic covalent polymers under these conditions.[29,31]

Subsequently, dynamerization reactions between 2,5-pyrazinedicarboxaldehyde (**1**) and α,ω-dinitroalkanes **2a**–**2j** were carried out. In the reactions with short dinitroalkanes, including 1,3-dinitropropane (**2a**) and 1,4-dinitrobutane (**2b**), only short oligomers were produced in solution, likely due to the steric hindrance caused by the limited chain length in the building blocks (Figure S10–S13, Figure S30–S31). On the other hand, the reaction of compound **1** with 1,5-dinitropentane (**2c**) resulted in a low extent of precipitation, which upon analysis could be identified as lowellane[31] macrocycle **3c** with two repeating units (Figure 3, Figure S40–S43). A considerable amount of oligomers was in this case still present in solution, indicating limited macrocyclization (Figure S14–S15, S32). However, this was not the case in the system consisting of compound **1** and 1,6-dinitrohexane (**2d**), where a large amount of product precipitated out from the reaction system with almost no oligomers left in solution (Figure S16–S17). The solid product was characterized as lowellane macrocycle **3d**, having a similar structure as other lowellanes (Figure 3, Figure S44–S47, S33).[30,31] In contrast, in the reaction with dialdehyde **1** and 1,7-dinitroheptane (**2e**), no signs of precipitation could be detected and all products remained in solution. NMR and GPC analyses revealed that the products were polymers with a degree of polymerization of 23 (Figure S18–S19, S34). Adding another methylene group to the nitroalkane chain, in the system based on compound **1** and 1,8-dinitrooctane (**2f**), again yielded precipitation with formation of lowellane macrocycle **3f** (Figure 3, Figure S20–S21, S35, S48–S51). Moving further up the carbon ladder, 1,9-dinitrononane (**2g**) yielded longer polymers (DP = 21, Figure S22–S23, S36) while



3c 3d 3f

3h 3i 3j

Figure 3. Structures of obtained lowellane macrocycles.

1,10-dinitrodecane (**2h**) favored macrocycles (Figure 3, Figure S24–S25, S37, S52–S55). Thus, an alternating pattern of macrocycle/polymer formation revealed itself in the reactions between dialdehyde **1** and dinitroalkanes **2d**–**2h**. Eventually, with even longer dinitroalkanes, the odd-pattern started to fade out, and the reaction between compound **1** and odd-numbered 1,11-dinitroundecane (**2i**) yielded both lowellane **3i** (Figure 3, Figure S56–S59) and oligomers (Figure S26–S27, S38). However, the even-numbered 1,12-dinitrododecane (**2j**) only produced cyclic molecules **3j** with compound **1** (Figure 3, Figure S28–S29, S39, S60–S63).

Conspicuously, the results indicate that the use of dialdehyde building block **1**, in which the aldehyde functionalities have a *para*-relationship, did not prevent cyclization. Instead, macrocycles were generated in several systems, in which the product formation followed an alternating pattern of linear polymerization/macrocyclization (Figure 4). Oligomers/polymers were thus generally formed with odd-numbered dinitroalkanes, whereas even-numbered building blocks predominantly yielded macrocycles. With shorter (≤5 carbon atoms) or longer chains (≥11 carbon atoms), this odd–even effect became less pronounced and oligomers or mixtures were formed to some degree. Even though the nitroaldol reactions proceeded on opposite sides of the dialdehyde aromatic ring, the flexible nature of the dinitroalkanes allowed for folded structures with two repeating units in which the end groups could undergo a ring-closing nitroaldol reaction. The results show that this folding/ring-closing effect was mainly conceivable with even-numbered dinitroalkane carbon chains, whereas it was less likely with the odd-numbered counterparts. Considering the dynamic nature of the reaction system, potentially funneled by precipitation of the ring-closed entities, macrocyclization could be expected to take place in all cases unless the dinitroalkanes were too short. Similarly, ring-closing would be less likely with long carbon chains, thereby leading to a diminished influence from the folding typologies and leading to a less pronounced odd–even effect.

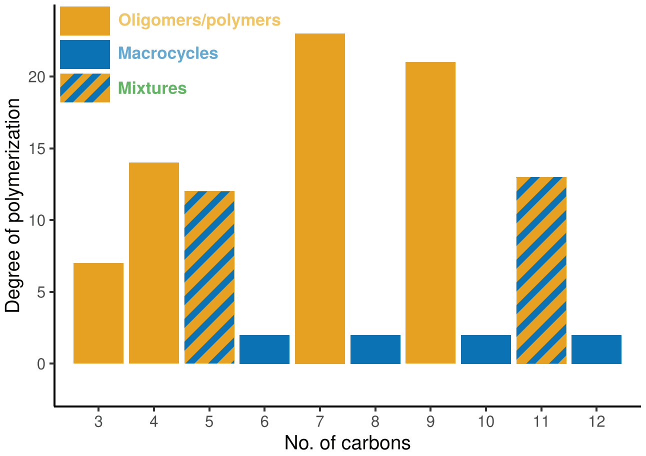


Figure 4. Product formation in reactions between dialdehyde **1** and dinitroalkanes **2a**–**2j** (0.5 M, CD_3CN); compounds **2c** (5 carbons) and **2i** (11 carbons) yielded both oligomers and macrocycles.

Geometry optimizations of the potential four-unit structures revealed a relatively visible pattern (Figure 5, Figure S64). For the short dinitroalkanes **2a** and **2b**, although the simulation results suggested possible formation of cyclic entities, their crowded and strained conformation prevents their formation during the

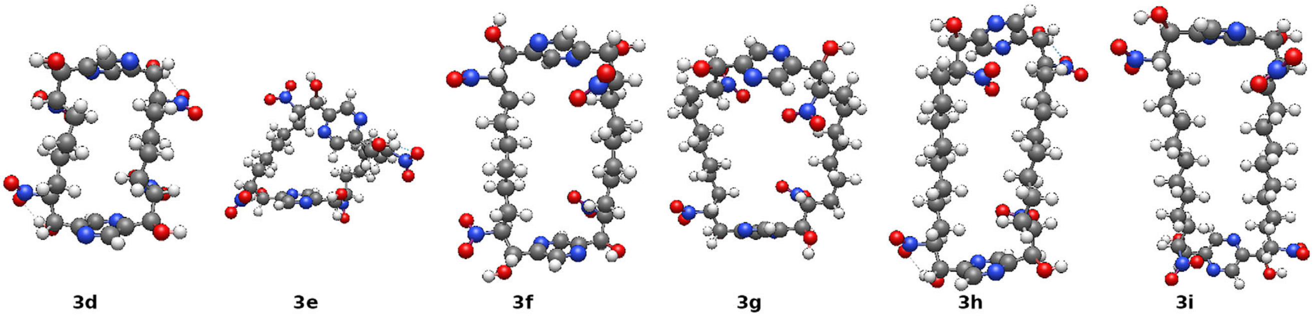


Figure 5. Simulated structures of **3d**–**3i**.

reactions. For the structures that yielded macrocycles (**3c**, **3d**, **3f**, **3 h**, **3i**, and **3j**), the optimized structures were generally symmetric and rectangular in shape, with relatively "straight" alkyl chains on the sides (Table S1). This geometry may have promoted their formation in the process, due to their relatively low energy and probability to yield aggregates. Even-numbered alkyl chains improved the stacking between the macrocycles, thus promoting precipitation that further enhanced macrocyclization. Furthermore, the precipitated macrocycles could work as a second reservoir slowly exchanging with components in the solution. In contrast, for simulated molecules **3e** and **3g** with odd-numbered dinitroalkanes, the structures were more irregular and without apparent symmetry. As a consequence, these cyclic structures would have lower aggregation tendency than the odd-numbered counterparts, thereby resulting in a lower degree of systemic funneling and a higher degree of linear polymerization. On a further note, as many studies suggested,[32–34] cyclic polymer or oligomers are commonly formed in a reversible polymerization reaction, which should also apply in our system. But in large polymer loops, the odd–even effect would generally function the same way as in long linear chains, since the folding behavior would be similar between large linear and cyclic polymers.

3. Conclusion

In summary, an alternating pattern in the formation of linear polymers and macrocycles was observed in nitroaldol reaction systems. The number of carbon atoms in the alkyl chains of the components resulted in a significant influence on the output of the reactions, likely due to the folding geometry of the chains coupled with potential aggregation tendencies and precipitation-driven systemic macrocyclization. This observation shines more light on the complex dynamic processes involved in reversible polymerization systems, yielding different structures with emergent properties. The findings will also improve the rational design of functional dynamer systems, enabling targeted synthesis of specific macrocycles and dynamers, for which the reaction control is generally challenging. Furthermore, we envisage that the obtained pyrazine-based lowellane macrocycles could find applications in sensing and in the construction of advanced supramolecular structures.

Supporting Information

Synthetic procedures, characterization data, NMR spectra, MS spectra, GPC data, equilibration analysis, computational study.

The authors have cited additional references within the Supporting Information.[35–39]

Acknowledgments

We thank Wendy Gavin for NMR and GPC analysis. Mass spectral data were obtained at the University of Massachusetts Mass Spectrometry Core Facility, RRID:SCR_019063. We thank Dr. Steve Eyles and Dr. Cedric Bobst for their kind help on HRMS measurements. The Unity cluster at the Massachusetts Green High Performance Computing Center (MGHPCC) is gratefully acknowledged for providing access to supercomputing resources.

Conflict of Interests

There are no conflicts to declare.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: dynamic covalent · macrocycle · nitroaldol · polymer

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Manuscript received: January 8, 2025
Revised manuscript received: March 24, 2025
Version of record online: April 21, 2025