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Computer-aided kinetic network modeling of orthoester metathesis

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Dynamic covalent exchange (DCE) reactions often generate complex mixtures that make quantitative analysis challenging despite involving mechanistically simple individual processes. Here we introduce an integrated workflow combining automated spectral decomposition, mechanistically guided kinetic modeling, and targeted DFT calculations to elucidate the DCE between triethyl orthoformate and ethylene glycol. Tensor-based analysis of time-resolved ¹H NMR data identified ten distinct species, which were incorporated into a refined kinetic model providing excellent agreement with experiments ($R^2 > 0.95$) and strong predictive performance under various conditions ($R^2 > 0.90$). DFT calculations focused on the acid-promoted activation step supported the kinetic parameters and clarified how substrate structure, catalyst identity, solvent, and released alcohols influence activation barriers and catalyst availability. Together, these results deliver a coherent description of the reaction network and establish a generalizable strategy for analyzing and tuning complex dynamic covalent systems.

Introduction

Dynamic covalent chemistry (DCC) describes molecular systems in which components exchange, reorganize, or adapt through reversible bond formation.^{1–3} These processes play important roles in areas such as supramolecular self-assembly,^{4–8} stimuli-responsive and/or biodegradable materials,^{9–15} and biomass valorization (Fig. 1a).^{16–20} In many cases, however, the underlying chemistry is difficult to characterize. Reversible exchanges often produce mixtures containing numerous species with similar structures, overlapping NMR signals, and interconversions occurring on comparable timescales. As a result, even seemingly simple systems can give rise to complex speciation patterns that are not easily described with traditional kinetic tools.

Classical kinetic analysis generally requires a predefined mechanistic model, assignment of spectroscopic signals, or access to isolated intermediates. These requirements are rarely met in dynamic systems where the number of species is not known *a priori* and where reversible processes create multiple competing pathways. Consequently, the kinetic and mechanistic behavior of many dynamic covalent networks remains only partially understood.^{21–23} To address these limitations, we present a data-driven workflow that reconstructs reaction

networks directly from unprocessed NMR kinetic data. The workflow combines two computational elements. First, tensor decomposition (Tucker analysis) is used to estimate the number of spectroscopically distinct species present in the dataset without requiring prior signal assignment. Second, iterative kinetic modeling is performed, with different model hypotheses evaluated using statistical criteria and residual analyses to identify the most plausible network topology and extract meaningful rate constants. Together, these two components minimize assumptions about the reaction system and allow the network architecture to emerge from the data, while providing a quantitative basis for comparing models of increasing complexity. Although metadynamics^{24,25} and NAMFIS-type^{26,27} analyses could offer complementary information, the present problem is centered on resolving a reactive network of chemically distinct, short-lived intermediates under experimental conditions, rather than on the conformational analysis of a single stable species.

We apply this strategy to a dynamic covalent exchange (DCE) between an orthoester and a simple polyol, namely, ethylene glycol (1). This reaction is well suited as a test case: it generates a broad distribution of acyclic and cyclic orthoesters whose concentrations evolve over time under Brønsted acid catalysis (formic acid). Similar orthoester-based DCE reactions have been examined previously, yet a comprehensive kinetic and mechanistic description of these systems is still lacking (Fig. 1b).^{28,29} The growing availability of computational tools now offers an opportunity to go beyond empirical approaches.^{30–32} While several open-access Python packages allow simulation of kinetic systems, few are tailored for

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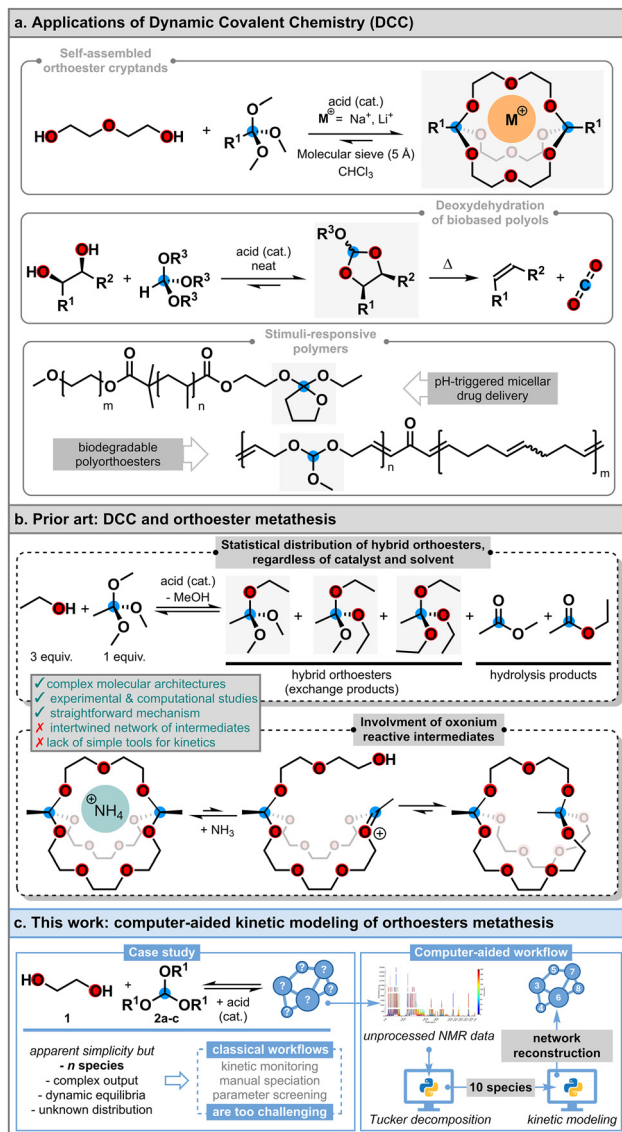


Fig. 1 (a) Representative applications derived from dynamic covalent exchanges (DCE) of orthoesters with diols, including the design of supra-molecular architectures for cationic encapsulation,^{5–7} drug delivery systems,^{12,14} biomass valorization to olefins^{16–20} and stimuli-responsive polymers;^{13,15} (b) literature background on orthoester metathesis: acid-catalyzed orthoester exchange reaction between ethanol and trimethyl orthoacetate and resulting product distribution;²⁹ oxonium reactive intermediates are important intermediates for the rearrangement of an ammonium orthoester cryptate through DCE;²⁸ (c) this work: computer-aided kinetic network modeling of complex orthoester–diol dynamic covalent exchanges. Orthoesters: **2a** ($R^1 = \text{OMe}$); **2b** ($R^1 = \text{OEt}$) and **2c** ($R^1 = \text{OiPr}$).

experimental data fitting, model discrimination, or visualization of complex multidimensional datasets.^{33–38} Moreover, estimating the number of species in equilibrium mixtures remains a major bottleneck.

Using a data-driven workflow (Fig. 1c), we identify ten distinct species, reconstruct their interconnections, and determine how the reaction network responds to changes in solvent, catalyst, and parent orthoester structure. Targeted experiments and supportive DFT calculations were used to rationalize

observed trends in reactivity. Overall, this work demonstrates a general and transferable methodology for analyzing complex dynamic covalent systems. Although illustrated here with an orthoester–polyol exchange, the approach is broadly applicable to any system that can be monitored by time-resolved spectroscopy.

Results and discussion

We examined the DCE between triethyl orthoformate (**2b**) and ethylene glycol (**1**) (equimolar ratio) in the presence of formic acid as a catalyst (10 mol%) in acetonitrile (Fig. 2a). Early alcohol-exchange events generate hybrid orthoesters (SI, Section S5), which undergo sequential substitution and cyclization to yield cyclic species and higher-order DCE intermediates. The continuous evolution of this network produces substantially overlapping ^1H NMR signals, making the system an ideal but demanding benchmark for quantitative kinetic extraction (Fig. 2b). Although high-field ^1H NMR (700 MHz) captures the time-resolved changes, the level of spectral congestion hampers reliable manual identification of the number of species present at any given time.

To obtain an unbiased estimate of the number of species in the DCE, we evaluated a range of matrix- and tensor-based factorization methods (SI, Section S6.1). Tensor approaches were particularly attractive because they retain the relationships between chemical shift, signal intensity, and time across the entire dataset. We therefore applied Tucker decomposition to the unprocessed time-resolved ^1H NMR spectra, organized as a third-order tensor, in which the first mode contains chemical-shift values, the second mode holds signal intensities, and the third corresponds to the time dimension. This representation, widely used in multivariate spectral analysis,^{38,39} has seen limited application in time-resolved ^1H NMR studies of organic reaction mixtures. Here, Tucker analysis provides a fully data-driven means to estimate the number of species contributing to the evolving mixture, which is not readily achievable with conventional peak-based approaches. A Python implementation of the Tucker workflow allows direct upload of raw spectra and evaluates model quality as a function of the assumed number of species (SI, Section S6). Statistical assessment of Tucker models of increasing rank (*i.e.*, number of species considered) was evaluated based on the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), explained variance, and reconstruction-error profiles. As shown in Fig. 2c, the information-criterion (AIC) curve displays a minimum at ten components. Taken together, these metrics converge on ten components as the most robust estimate of the number of spectroscopically distinct species contributing to the reaction mixture: 8 hybrid orthoesters, in addition to starting materials **1** and **2b**, are thus expected to be involved in this DCE network.

With the estimated number of contributing species established, we next assigned the signals in the ^1H NMR spectra using literature precedents and standard structural correlations. Although prior structural assignment of the individual

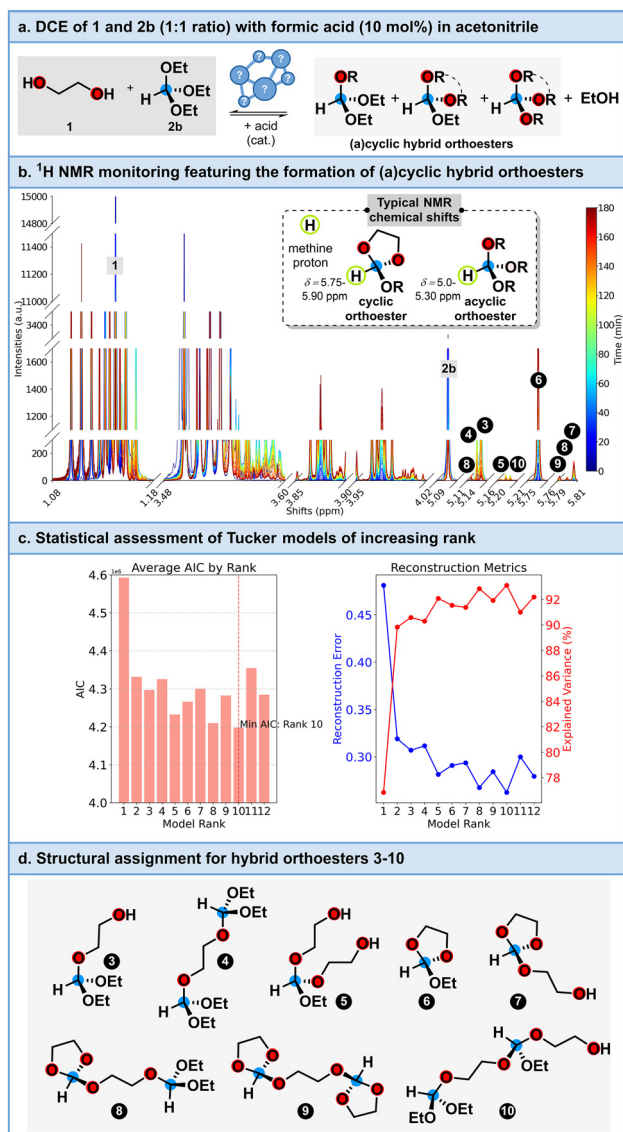


Fig. 2 (a) Model DCE reaction involving ethylene glycol (**1**) and triethyl orthoformate (**2b**) in the presence of formic acid (10 mol%) in acetonitrile; (b) reaction monitoring with high-field ¹H NMR (700 MHz) over time (180 min) showing a high level of spectral congestion; (c) evaluation of the computer assisted data fitting to determine the number of compounds in solution. Comparative analysis of dimensionality reduction performance for ranks 1–12 including the AIC, the reconstruction error and the explained variance ratio (SI, Section 6.2); (d) structures of hybrid orthoesters **3**–**10**.

DCE products is not strictly required for the next step of the computer-aided workflow (kinetic analysis), it provided valuable chemical insight into the evolving network. Several cyclic hybrid orthoesters reported previously (*e.g.*, **6**, **7**, **9**) were readily recognized by the characteristic singlet of the orthoformate methine proton in the 5.75–5.90 ppm region.^{40,41}

In contrast, cyclic species such as **8** and the acyclic orthoesters **3**, **4**, and **5** had been scarcely described, or not reported at all. These compounds displayed a distinct singlet between 5.00 and 5.30 ppm, which we attributed to their orthoformate methine protons (Fig. 2b). Unambiguous assignments (Fig. 2d)

were obtained by 2D HMBC analysis, which connected each methine resonance to the relevant vicinal methylenoxy groups. For example, parent orthoester **2b** showed a single correlation to an ethoxy methylene, whereas acyclic hybrid orthoester **3** displayed an additional correlation to the ethylene glycol moiety (SI, Section S4). The identities of acyclic species **3**, **4**, and **5** were further confirmed by preparative isolation followed by NMR and GC-MS analysis (SI, Section S12).

Concentrations of the detected species were then quantified using an internal standard and used to construct time-dependent speciation profiles. Kinetic modeling was performed using a Python code based on the chemical kinetics framework developed by Boudoire.^{36,42} The script solves the differential equations governing the time evolution of each species and provides quantitative and graphical diagnostics to evaluate model performance. Our strategy involved sequential construction of kinetic networks that incorporate an increasing number of experimentally detected species, in order of decreasing abundance. For each iteration, forward and reverse rate constants were fitted to the speciation curves, and reactions with negligible kinetic contributions were removed. The resulting model served as the starting point for the next refinement step, allowing the progressive addition of new species and reversible pathways until a high-quality global fit was achieved (SI, Section S7). This procedure led to the construction of kinetic models with increasingly improved fit (Models I–X) describing the DCE network and its evolution under the reaction conditions (Fig. 3a).

Model I incorporated the fundamental equilibria connecting ethylene glycol (**1**) and triethyl orthoformate (**2b**) to the primary hybrid orthoester **3**, together with its downstream conversion into **5** and cyclic orthoester **6** (SI, Section S7.4). All steps proceed with the concomitant release of ethanol (1 or 2 equiv.). The fitted equilibrium constants indicated that formation of **3** is reversible but thermodynamically favored ($K \approx 3$), whereas its conversion to **6** proceeds under essentially irreversible conditions ($K_5 \approx 165$). This initial model provided a baseline representation of the earliest DCE events.

To account for the formation of dimeric species **4**, Model II introduced two plausible routes: reaction between **2b** and **3** (thus releasing ethanol), and self-condensation of **3** (thus releasing **1**). Statistical comparison of the resulting fits showed that only the self-condensation pathway produced an accurate description of the transient concentration of **5**, while alternative formulations resulted in systematic deviations (SI, Section S7.5). This outcome refined the plausible connectivity within the network and guided subsequent model development.

Model III expanded the reaction network by including formation of species **7** through two possible processes: cyclization of **5** and reversible exchange between **6** and **1**. The kinetic analysis distinguished these pathways clearly. Cyclization of **5** proceeded irreversibly, whereas the exchange between **6** and **1** remained reversible ($K \approx 0.5$). An experiment increasing the concentration of **1** (**1/2b** 100:1) shifted the distribution toward **7**, providing experimental validation of the reversible pathway (SI, Section S7.7).

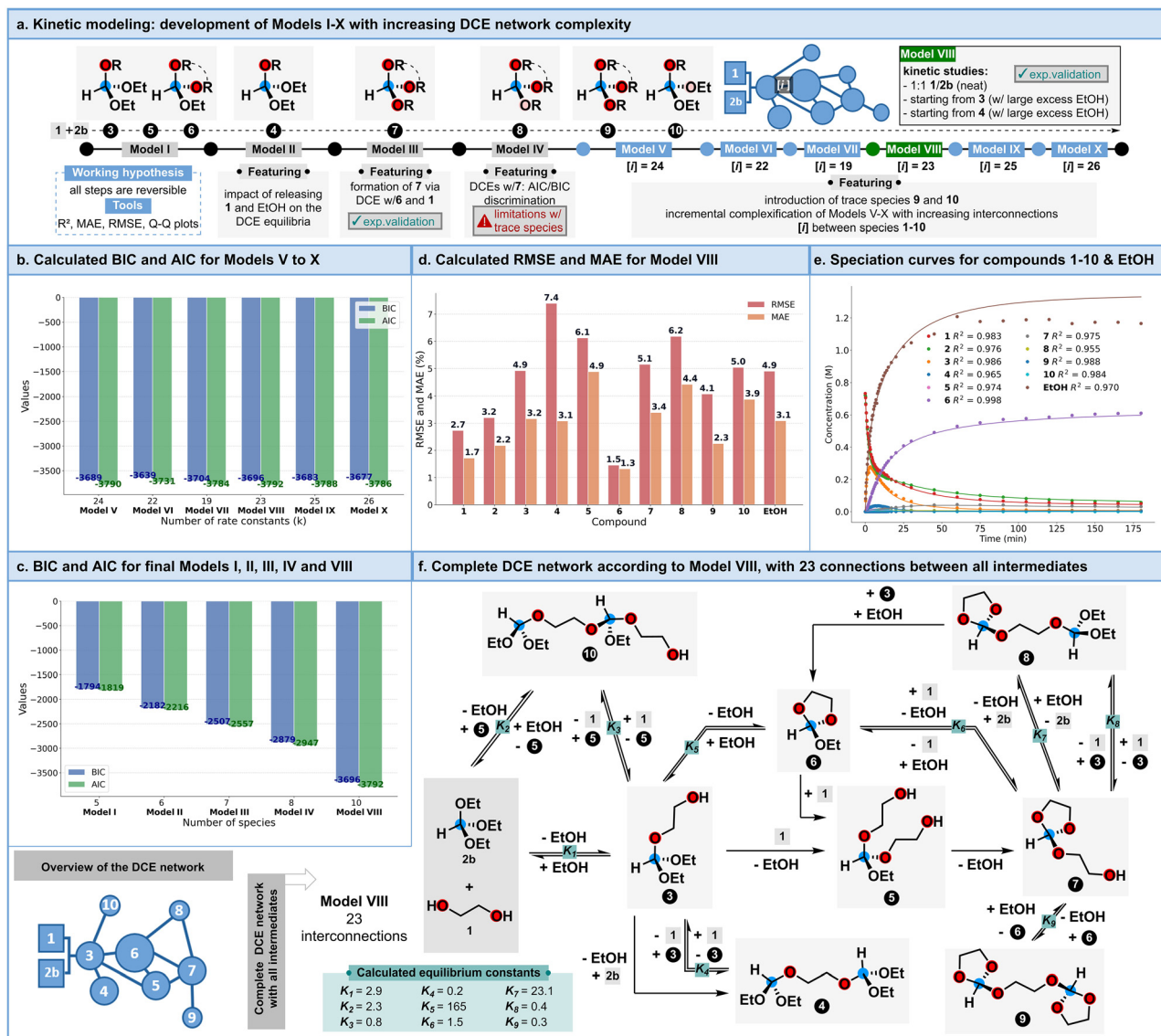


Fig. 3 (a) Strategy toward the complexification of the model according to the number of species and the number of interconnections [i]; (b) calculated BIC and AIC for Models V to X; (c) calculated BIC and AIC for final Models I, II, III, IV and VIII. Model VIII was validated through kinetic studies under neat conditions, and applications to other experimental conditions (kinetic studies starting from **3** or **4** in presence of an excess of EtOH); (d) calculated root means square error (RMSE) and mean average error (MAE) for Model VIII; (e) speciation curves for compounds **1** to **10** and EtOH and their corresponding coefficients of determination (R^2) using Model VIII; (f) finalized DCE network according to Model VIII, featuring all intermediates. Equilibrium constants are given (K_{1-9}), and calculated kinetic constants are provided in the SI (Section S7.11.4).

Model IV introduced the formation of species **8** through several competing routes involving combinations of **3**, **6**, **7**, and **2b**. Because **8** remained at low steady-state concentration, several pathway combinations yielded comparable statistical metrics. AIC and BIC analysis offered modest preference for routes involving **7**, although the differences were small (SI, Section S7.8). These results indicated the limits of model discrimination for low-intensity species. Species **9** and **10**, each detected at low concentrations, were incorporated by evaluating a series of expanded network topologies (Models V–X, Fig. 3b). Comparison based on AIC and BIC identified Model VIII as the most appropriate representation, balancing model complexity with the quality of the fit (Fig. 3b and c).

Model VIII reproduced the experimental speciation profiles with excellent accuracy, yielding R^2 values between 0.95 and 0.99 and residual distributions within acceptable confidence intervals (Fig. 3d and e; SI, Section S7.9.2). To assess its generality, Model VIII was applied to three additional datasets: reactions initiated from isolated **3**, from isolated **4**, and reactions performed under neat conditions (Fig. 3a). In all cases, the model reproduced the data with R^2 above 0.90, demonstrating both robustness and transferability. Under neat conditions, additional minor species were detected, including several singlets in the 5.00–5.30 ppm region consistent with the formation of further acyclic orthoesters. Nonetheless, Model VIII continued to describe the major components well, with only species **8**

affording a limited fit ($R^2 = 0.5$), likely due to the increased complexity of the system.

Attempts to incorporate speculative additional pathways did not improve the fit (SI, Section S7.11), indicating that the validated model already captures the dominant features of the network (Fig. 3f). Examination of Model VIII highlights the roles of **3** and **7** as structurally versatile intermediates. Both contain free hydroxyl groups that enable multiple dynamic covalent exchanges, giving them high interconnectivity within the network. Species **6** accumulates because its onward reactivity depends on the availability of ethylene glycol, which becomes depleted early in the reaction, and because its activation is comparatively slower (see below). In contrast, species **4** and **5** are only transiently formed, while **9** and **10** appear only in low concentration due to their dependence on short-lived precursors. While the kinetic model defines the connectivity and relative rates of exchange processes (Fig. 3e), it does not on its own explain the molecular basis for the observed rate differences.

To support kinetic interpretation, a DFT study was performed focusing on the acid-promoted activation step, which was identified as rate-determining across the network (SI, Sections S10 and S11). The principal computational conclusions are summarized in Fig. 4. The calculations indicated that

activation proceeds through protonation of an alkoxy group and polarization of the adjacent C–O bond. Species containing a free hydroxyl group (e.g., **3**, **5**, and **7**) stabilize this activated layout through hydrogen bonding, resulting in lower activation barriers than for fully substituted species such as **6**, which may account for the greater persistence of the latter under the reaction conditions (Fig. 4a). This provides a molecular rationale for the central roles of **3** and **7** and the persistence of **6**. By contrast, the subsequent nucleophilic substitution step was calculated to be fast and exergonic for all substrates, consistent with the kinetic observation that activation through the formation of carbocationic species, rather than nucleophilic attack, limits the rates of most transformations. The full computational dataset is provided in the Supporting Information, while the main text focuses on the mechanistic conclusions most directly relevant to the proposed workflow and experimentally observed reaction behavior.

A limited exploratory screening was performed in which selected reaction parameters were varied, including the nature of the Brønsted acid catalyst (other than formic acid), the solvent, and the orthoester substrate (**2a–c**) (SI, Sections S8 and S9). Although this screening was not intended to be exhaustive, the observed variations in kinetics and product distributions were sufficiently pronounced to reveal trends.

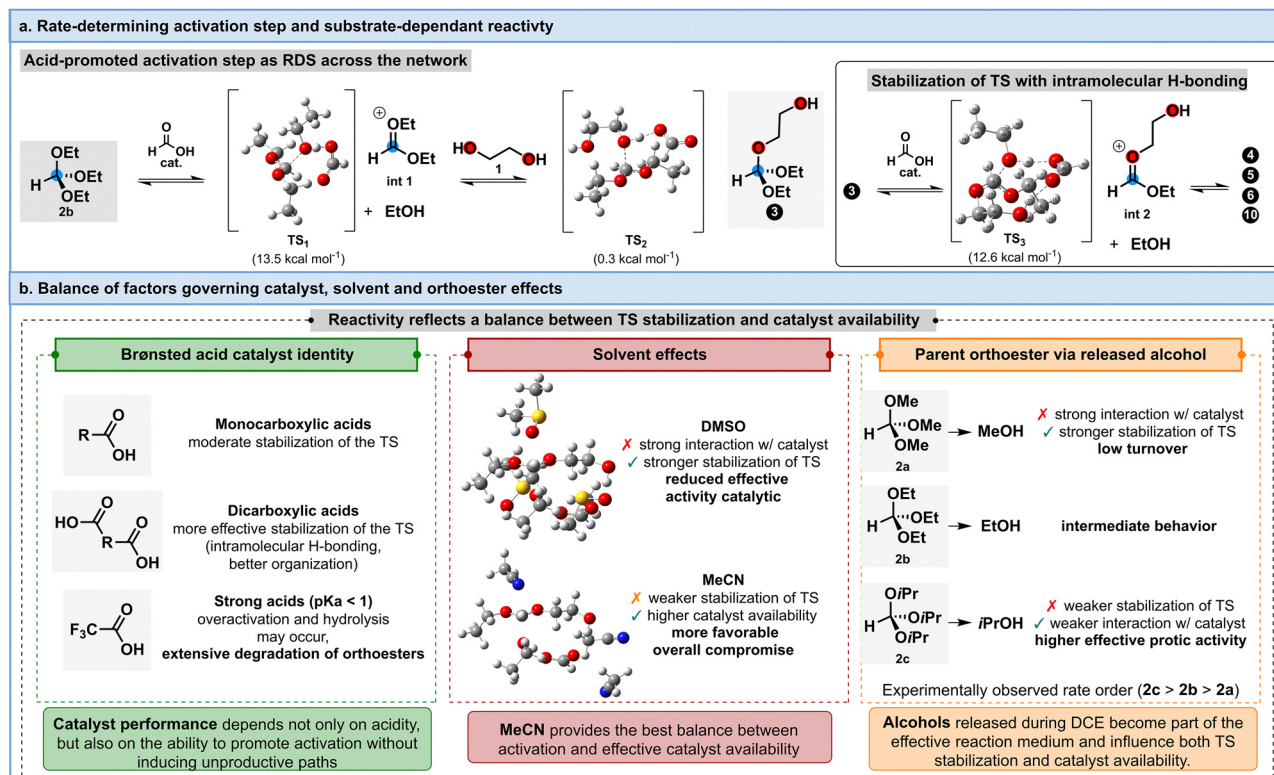


Fig. 4 Computational summary of the mechanistic factors governing the orthoester metathesis network. (a) The acid-promoted activation step to carbocationic intermediates (e.g., **int 1** and **int 2**) is identified by DFT as the rate-determining step (RDS) of the network. Free-hydroxyl-containing intermediates (e.g., **3**) stabilize TS through intramolecular hydrogen bonding, lowering the activation barrier. (b) Reactivity is governed by a balance between TS stabilization and catalyst availability. This framework rationalizes the effects of Brønsted acid identity, solvent, and parent orthoester structure, including the influence of alcohols released during exchange on the effective reaction medium and the observed rate order **2c** > **2b** > **2a**.

These preliminary results already provide valuable mechanistic insight and are therefore discussed below, while also indicating that a comprehensive investigation of these parameters would call for a dedicated future study. The influence of reaction conditions, specifically the nature of the catalyst and the solvent, was examined using experimental screening supported by DFT calculations of activation barriers (Fig. 4b and SI, Section S11.6).

With respect to solvation, the computations were primarily conducted using the implicit SMD model in order to provide a consistent framework for comparing a broad range of intermediates, catalysts, and reaction environments. In addition, selected cluster-based calculations were examined to probe explicit solvation effects and to refine the interpretation of solvent and substituent effects. This point is particularly relevant in the present system because the alkoxy substituents initially attached to the parent orthoesters are progressively released as alcohols during the development of the DCE network. These alcohols therefore become part of the effective reaction medium and can influence both stabilization of transition states and catalyst availability (Fig. 4b). While the present approach was designed to capture the principal mechanistic trends governing the observed reactivity in a form compatible with the broader workflow presented here, a more exhaustive treatment of explicit solvation would represent a valuable direction for future computational study.

Among the carboxylic acids evaluated, DFT calculations showed that dicarboxylic catalysts capable of intramolecular hydrogen bonding (*e.g.*, oxalic and succinic acid) stabilized the transition state more effectively than monocarboxylic acids of similar acidity, correlating with higher experimental conversion. Experimentally, strong acids led to overactivation and hydrolysis, consistent with their strong association with the substrate predicted computationally. DFT evaluation of solvent effects reflected a balance between transition-state stabilization and catalyst availability (SI, Section S11.6). DMSO stabilized the transition state more strongly than MeCN, but also formed stronger complexes with the acid catalyst, effectively reducing catalytic activity. MeCN provided a more favorable compromise, which experimentally was reflected by faster reaction rates. Finally, the nature of the parent orthoester influenced reactivity principally through the alcohol released during exchange (SI, Sections S9 and S11). DFT showed more polar alcohols (*e.g.*, MeOH from **2a**) stabilized the transition state but also formed stronger interactions with the acid catalyst, decreasing turnover. Bulkier alcohols (*e.g.*, *i*PrOH from **2c**) had weaker interactions with the catalyst, maintaining higher effective acidity even though they offered less transition-state stabilization. This balance explains the experimentally observed rate order (**2c** > **2b** > **2a**). Overall, the combined kinetic and computational analyses provide a coherent description of the DCE network and the factors governing its evolution under reaction conditions (Fig. 4b). The results highlight the importance of substrate structure, catalyst properties, and solvent effects in modulating activation barriers and directing the distribution of species within the network.

Conclusion

Kinetic analysis is central to understanding and optimizing chemical reactivity, providing the basis for catalyst selection, efficient process design, and the identification of productive mechanistic pathways. However, extracting quantitative kinetic information from complex reaction mixtures remains challenging, particularly when multiple, structurally related species evolve concurrently and generate highly congested NMR datasets. To address this problem, we implemented two complementary Python tools designed to assist in the analysis and interpretation of dynamic covalent exchange (DCE) processes. The first script performs automated preprocessing and tensor-based decomposition of time-resolved spectral data, enabling a statistical assessment of the number of spectroscopically distinct species present in a reaction mixture. Application of this workflow to the exchange between triethyl orthoformate and ethylene glycol identified ten contributing species, which were independently confirmed by NMR analysis and GC-MS. A second script was developed to facilitate kinetic modeling through automated fitting of experimental speciation profiles to mechanistically informed reaction networks. This approach enables rapid evaluation of alternative kinetic scenarios and provides a practical framework for model refinement. The resulting model reproduced the evolution of all ten species with high accuracy ($R^2 > 0.95$) and was transferable across several experimental conditions, yielding similarly strong agreement ($R^2 > 0.90$). To support the interpretation of the kinetic results, a DFT study was carried out to examine the acid-promoted activation step central to the DCE network. The computational analysis served to rationalize the relative reactivities observed experimentally. The calculations highlighted the influence of substrate structure, particularly the presence of free hydroxyl groups, on the stabilization of transition states, consistent with the roles inferred from the kinetic model. Complementary computational and experimental screening of catalysts, solvents, and parent orthoesters further clarified how medium composition modulates activation barriers and catalyst availability.

By integrating automated spectral analysis, mechanistically guided kinetic modeling, and targeted computational support, this study provides a generalizable framework for dissecting complex reaction networks. The workflow offers a practical route to extract kinetic information from congested datasets, evaluate mechanistic hypotheses efficiently, and identify how medium composition influences dynamic reactivity. Such integrated approaches have the potential to inform the rational design of dynamic covalent networks and related chemical systems.

Author contributions

Claire Muzyka: conceptualization, experimental work, writing – original draft. Diana Silva-Brenes: writing – original draft; writing – review & editing. Jean-Christophe M. Monbaliu:

project administration, supervision, funding acquisition, writing – original draft; writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

This manuscript is accompanied by comprehensive supplementary information (SI), which includes structural characterization of the identified compounds, all processed kinetic data and derived models, computational data, and detailed experimental protocols. Python scripts 1 and 2 are provided free of charge on GitHub (<https://github.com/CiTOS-ULiege/KineticFitToolkit.git> and https://github.com/CiTOS-ULiege/nmr_tensor_analysis.git, respectively) and on Zenodo with the following DOI: <https://doi.org/10.5281/zenodo.15584403>. See DOI: <https://doi.org/10.1039/d6cp00391e>.

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