Conformer-specific photochemistry imaged in real space and time

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Conformational isomers (conformers) of molecules play a decisive role in biology and organic chemistry. However, experimental methods for investigating chemical reaction dynamics are typically not conformer-sensitive. We report on a gas-phase megaelectronvolt ultrafast electron diffraction investigation of α-phellandrene undergoing an electrocyclic ring-opening reaction. We directly imaged the evolution of a specific set of α-phellandrene conformers into the product isomer predicted by the Woodward-Hoffmann rules in real space and time. Our experimental results are in quantitative agreement with nonadiabatic quantum molecular dynamics simulations, which provide considerable detail of how conformations influence the time scale and quantum efficiency of photoinduced ring-opening reactions.

Conformational isomers, or conformers, can interconvert via rotations around single chemical bonds. Interconversion between conformers represents an important step in many biomolecular reactions, where reactant species must encounter one another not only in a particular orientation but also in a specific structural conformation (1). Moreover, conformer dynamics arise naturally in self-ordering of macromolecular structures (e.g., protein folding) (2). However, investigation of conformer-specific dynamics on their natural time and length scales of femtoseconds and angstroms is hindered by the insensitivity of established experimental methods to conformers.

The influence of conformers on photochemical reactivity is well known, such as from electrocyclic reactions according to the Woodward-Hoffmann (WH) rules (3). These rules predict them to be concerted and conformer-specific (i.e., leading to different reaction products depending on the reactant conformer). Moreover, the WH rules predict an inverted conformer specificity for electrocyclic ring opening in the electronically excited state versus the ground state of a molecule. Electrochemical reactions play an important role in chemical synthesis (4) and vitamin D production in human skin (5).

An instructive example of conformer specificity is the photochemical ring opening of the monoterpene α-phellandrene (αPH) (6), which is produced by plants and used in the fragrance, food, and pharmaceutical industries (7). α-Phellandrene consists of a 1,3-cyclohexadiene (CHD)-like ring moiety with two substituents: an isopropyl group at its sp3-hybridized C1 position and a methyl group at the C8 position (Figs. 1 and 2). The substitution gives rise to two conformers with the isopropyl group being in either quasi-axial (ax) or quasi-equatorial (eq) orientation (i.e., approximately perpendicular or parallel to the ring plane, respectively). The WH rules predict the ring opening to take place in a concerted, conrotatory motion; that is, both ends of the newly formed open-ring molecule rotate away from each other in the same clockwise or counterclockwise direction (Fig. 1A). This motion leads to different photoproducts depending on the reactant conformer: the isomers (3Z,5E)-3,7-dimethyl-octa-1,3,5-triene (ZEDOT; from eq-αPH) and (3Z,5Z)-dimethyl-octa-1,3,5-triene (ZZDOT; from ax-αPH) (Fig. 1).

Evidence for the conformer specificity of the ring opening in αPH (6) and other reactants (8, 9) has been observed in solution-phase measurements of photoproduct ratios. Moreover, resonance Raman investigations revealed evidence for the importance of conrotatory motion in the depopulation of the Franck-Condon region of the reactant excited state (10). The photochemical dynamics leading from the Franck-Condon region to the ring-opened photoproducts of αPH have been investigated by several ultrafast spectroscopic studies in both the gas and condensed phase, although largely without sensitivity to the structural dynamics, reactant conformers, or photoproduct isomers (11–15).

Here, we report on a combined megaelectronvolt ultrafast electron diffraction (UED) and ab initio multiple spawning (AIMS) (16–18) study of conformer-specific dynamics in the photochemical ring opening of gas-phase αPH with unambiguous conformer sensitivity, confirming but going far beyond the qualitative orbital symmetry–based WH rule predictions. In both our static diffraction measurements and quantum chemical calculations, we found the eq-αPH conformer to dominate in our gas-phase sample (text S1). As opposed to other studies of electrocyclic reactions, our time-resolved measurements directly image concerted and exclusive formation of the ZEDOT photoprotein predicted by the WH rules on the femtosecond time scale with sub-angstrom resolution and in quantitative agreement with AIMS simulations of the photochemical dynamics.

The simulations reveal that after photoexcitation into the lowest excited state (S0) with ππ* character, αPH nonadiabatically relaxes to the electronic ground state (S0) through three different conical intersection (CI) geometries (19). Only one of them yields ring-opened photoproducts; the other two form vibrationally “hot” reactants. The presence of the isopropyl group redirects significant (40 ± 4%) amounts of the S0 population toward the non-WH CIs, substantially reducing the WH-photoprotein yield relative to CHD (20). Additionally, the rotational orientation of the isopropyl group gives rise to three rotational conformers (rotamers) for each of the eq- and ax-αPH structures, labeled as gauche+/− (G+/G−) and trans (T) (Fig. 2), which were simultaneously present in our sample. These rotamers show different ring-opening time scales.

Identification of the reactant conformer

Figure 2A shows the extracted static atomic pair distribution function (PDF) from a gas-phase sample of randomly oriented αPH molecules. For comparison, we plotted simulated PDFs of all six ax-αPH/eq-αPH rotamer geometries. We analyzed the structural information contained in the PDFs in terms of carbon coordination shells, which are additionally plotted as bars for the eq-αPH (blue) and ax-αPH (red) conformers in Fig. 2A: The many C-C bonds (first carbon coordination shell, labeled as α) in the system give rise to a strong maximum in all PDFs at 1.4 Å. A second peak at 2.4 Å corresponds to the second carbon coordination shell (distances between carbon atoms two atomic sites away from each other; β in Fig. 2A) with some contributions from the third coordination shell (distances of carbons three atomic sites apart from each other). The signatures above 3 Å belong to the third and higher coordination shells.

We found the strongest differences between the PDFs within the third coordination shell (γ in Fig. 2A). All eq-αPH rotamers, the ax-G–αPH rotamer, and the experimental PDF exhibit a minimum around 3.5 Å, in contrast to the two remaining ax-αPH rotamers that produce a shoulder. The minimum results from a splitting of the third coordination shell in the eq-αPH and ax-G–αPH rotamers into
distances between carbons in cis configuration (small dihedral angles, 3c in Fig. 2A) (e.g., the C3–C6 distance) and in trans configuration (large dihedral angles, 3t in Fig. 2A) (e.g., the C3–C10 distance). The splitting collapses for the ax-G+ and ax-T rotamers because one of the methyl groups of the isopropyl substituent is directly below the carbon ring and thereby moves many of the ring carbon–methyl carbon distances into the γ region (see structures in Fig. 2). The high level of agreement of the experimental PDF with those of eq-αPH and disagreement with some of the ax-αPH PDFs suggest that the sample is dominated by eq-αPH rotamers, in agreement with our quantum chemical calculations (text S1) and previous results (2J).

**Evolution into the Woodward-Hoffmann predicted product isomer**

Figure 2B shows an experimental ΔPDF 260 fs after photoexcitation with an ultrashort 266-nm optical pulse (experimental instrumental response function: 150 fs full width at half maximum; see supplementary materials). Atomic distance changes appear in ΔPDFs as a combination of a negative contribution at the initial atomic distance and a positive contribution at the delay-dependent distance. Accordingly, the experimental ΔPDF in Fig. 2B shows signatures from ring opening. The negative signature in the α region directly follows from breaking the C1–C4 bond. The negative signature in the β region mainly results from increases in the C1–C2, C2–C6, and C7–C4 distances. Positive signatures in the γ region suggest that at least some of these distances increase to values close to 3.5 Å. The structural implications of these distance changes can be qualitatively understood by comparison to “simple” ΔPDF simulations generated from single photoproduct and reactant geometries. Such simulations for the WH-predicted photoproducts of eq-αPH → ZEDOT (blue line) and ax-αPH → ZZDOT (red line) are plotted in Fig. 2B. Additionally, the WH-forbidden reactant → photoproduct ΔPDF simulations of eq-αPH → ZZDOT (blue dashes) ax-αPH → ZEDOT (red dashes) are shown. Similar to the static PDFs, experimental and simulated ΔPDFs show the most prominent differences in the γ region. Differences between experimental and simulated ΔPDFs in the α and β regions are due to the approximation of the photoproduct by a single geometry. The WH-allowed photoproduct of the eq conformers shows good qualitative agreement with a strong positive signature in the γ-region of the experimental ΔPDF, whereas all other photoproduct ΔPDFs show essentially zero or negative amplitude.

The difference between the simulated photoproduct ΔPDFs can be explained by steric effects from the bulky isopropyl group: In eq-αPH, it points away from the carbon ring. The WH-predicted conrotatory motion (Fig. 1A) rotates it farther away, favoring smaller atomic distance changes into the γ region in the photoproduct (e.g., the cZc-EDOT geometry in Fig. 1B). In ax-αPH, the WH-predicted conrotatory motion rotates the isopropyl group into the carbon ring. This is sterically unfavorable, forcing larger atomic distance changes beyond the γ region in the photoproduct (e.g., the tZt-ZDOT geometry in Fig. 1B). Thus, both effects—the positive signature of eq-αPH → ZEDOT and the negative signature of ax-αPH → ZZDOT—are direct results of the orientation of the isopropyl group in the reactant conformer and therefore an unambiguous signature of conformer-specific ring opening.

Figure 3 shows a comparison of experimental ΔPDFs with those computed from AIMS simulations (18) using a state-averaged complete active-space self-consistent field theory (α-CASSCF) (22). Experimental ΔPDFs are shown as lineouts in Fig. 3B and as a false-color plot in Fig. 3E. The simulated ΔPDFs of the individual G–, T, and G+ rotamers are averaged assuming roughly equal contributions at room temperature and plotted analogously to the experimental ΔPDFs in Fig. 3, A and D, for eq-αPH and in Fig. 3, C and F, for ax-αPH. Additionally, the delay-dependent integrated experimental ΔPDFs in the α, β, and γ regions

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**Fig. 1. Conformer-specific photochemistry in α-phellandrene. (A)** Woodward-Hoffmann predictions for the conformer specificity of photoinduced electrocyclic ring opening in α-phellandrene. Its isopropyl substituent (R) can be in axial or equatorial orientation with respect to the carbon ring. Axial and equatorial conformers are in thermal equilibrium in solution phase (A). (B) The Woodward-Hoffmann rules predict a concerted, conrotatory ring-opening motion (orange arrows) yielding isomers with R in different positions depending on the reactant conformer. (B) Schematic based on ab initio multiple spawning simulations of the photoinduced ring opening. Equatorial and axial conformers are photoexcited from their respective ground-state (S0) energy minima to the first excited state (S1); they evolve along an out-of-plane (OOP, green) coordinate toward conical intersections CI-1 and CI-2 or along the ring-opening coordinate (purple) toward CI-3. CI-1 and CI-2 lead to reformation of α-phellandrene, whereas CI-3 leads to both αPH reformation and ring opening. Several different conformers of the ZZDOT/ZEDOT photoproduct minima (cZc, cZt, and tZt) are accessible in the ground state. The two pie charts visualize the photoproduct distribution for axial and equatorial conformers as well as the distribution among the CI geometries CI-1 to CI-3; errors representing 68% confidence intervals were obtained from bootstrap analysis.
Fig. 2. Comparison of experimental and simulated structural information. (A) Experimental (black) and simulated pair distribution functions PDF(r) of six α-phellandrene (αPH) conformers, which are depicted below together with the dihedral angles defining the rotation of the isopropyl group [two gauche orientations (G+/G−) and one trans (T) orientation of the marked isopropyl hydrogen with respect to the marked ring carbon]. Carbon-carbon coordination spheres for axial (red) and equatorial (blue) conformers are shown as bars. Additionally, the α, β, and γ ranges of Fig. 3 are shown. The inset shows the carbon atom numbering used in the text. (B) Experimental difference PDF |PDF(r)| at a pump-probe delay of 0.26 ps (black) and simple simulations of the signature of Woodward-Hoffmann (WH)—allowed and WH-forbidden reaction product signatures of the equatorial (eq-αPH) and axial (ax-αPH) reactant conformers and (3Z,5E)-3,7-dimethylocta-1,3,5-triene (ZEDOT) and (3Z,5Z)-dimethylocta-1,3,5-triene (ZZDOT) product isomers. Shaded areas represent a 68% confidence interval obtained from bootstrap analysis.

Fig. 3. Comparison of experimental and simulated time-dependent difference pair distribution functions (ΔPDF) of equatorial and axial conformers. (A to C) ΔPDFs at different pump-probe delays. (D to F) False-color plots of ΔPDF over the whole investigated time window of 1.2 ps. Simulated ΔPDFs are based on ab initio multiple spawning simulations (see supplementary materials) and represent the averaged dynamics of the G+, G−, and T rotamers. Shaded areas [(A) to (C)] represent a 68% confidence interval obtained from bootstrap analysis. For the simulations, these error bars reflect convergence with respect to initial condition sampling.

are compared in Fig. 4 with the corresponding curves for the averaged and individual eq-αPH rotamer contributions. The averaged AIMS ΔPDFs of the eq conformers show quantitative agreement with the experimental data within their limited signal-to-noise level. The averaged AIMS ΔPDFs of the ax conformers qualitatively disagree with the experimental data in the γ region. The experimental time-dependent signatures are clearly dominated by the eq-αPH rotamers (>80%; see text S1). Thus, we unambiguously observed exclusive formation of the WH-predicted photoproducts of the eq-αPH conformer within a few hundred femtoseconds after optical excitation. Our results constitute direct observation of conformer-specific photochemical reaction dynamics in real space and time.

Conformer-specific dynamics beyond the Woodward-Hoffmann rules

Our AIMS simulations revealed additional aspects of the relaxation process that could not be easily extracted from the experimental data. α-Phellandrene relaxes via the WH-predicted conrotatory ring-opening motion through a CI (CI-3) yielding both ring-opened photoproducts and the closed-ring reactant (Fig. 1B, Fig. 5A, and fig. S2). As a consequence of its differential nature, the ΔPDF observable is preferentially sensitive to the part of the population undergoing ring opening. Additionally, out-of-plane bending in S1 leads through two Cls (CI-1/CI-2) to the closed-ring reactant (table S1). Furthermore, we observed a hitherto unknown secondary ring-closure reaction in the electronic ground state, yielding 2-ladderane (5-isopropyl-2-methylbicyclo[2.2.0]hex-2-ene).

The ring closure was exclusively observed for the fraction of population undergoing internal conversion through CI-1 in the ground state (text S2). Non-WH relaxation pathways have been observed before for the prototypical CHD molecule (23) but had marginal contributions to the relaxation process. The presence of the isopropyl substituent redirects 40 ± 4% of the eq-αPH S1 population toward non-WH pathways and thus substantially reduces the ring-opening quantum yield (Fig. 1B).

The time dependence of the measured and computed ΔPDFs in the α, β, and γ regions are shown in Fig. 4 and fig. S3B for the eq and ax conformers, respectively. The averaged simulation assuming equal distribution of the three eq rotamers (G+, G−, and T) leads to quantitative agreement with experiment, whereas individual eq rotamer contributions to the ΔPDFs are quite distinct (Fig. 4). Thus, the rotational orientation of the isopropyl group must influence the mechanism and time scale of ring opening. This fact becomes obvious in Fig. 5B, top, where simulated nonadiabatic population transfer events are categorized with respect to their C3–C4 distances at the time of the transfer event—that is, their ability to undergo ring
Fig. 4. Comparison of integrated difference pair distribution functions (ΔPDF) from experiment and simulations in the α, β, and γ regions of Fig. 3. Experimental signals (dots with error bars) are compared to corresponding signals of the averaged (lines) and the individual equatorial rotamer simulations with the isopropyl group in gauche+ (G+, dashed lines), gauche− (G−, dotted lines), and trans (T, dash-dotted lines) orientations. The experimental error bars and the shaded areas around the line plots of the simulations represent a 68% confidence interval obtained from bootstrap analysis. For the simulations, these error bars reflect convergence with respect to initial condition sampling.

opening and thus to contribute to the ΔPDF observable (see above). In the case of the eq–G–rotamer, almost all of the population undergoing ring opening relaxes to S0 within 200 fs after photoexcitation. The other two rotamers show substantially less ring opening in this time frame. Their remaining population undergoes ring opening considerably later, 500 to 700 fs after photoexcitation. The difference in ring-opening time scale is clearly reflected in the time-dependent ΔPDF amplitudes in Fig. 4.

Conclusion
By combining UED with AIMS simulations, we directly observed conformer-specific photochemical reaction dynamics on their natural time and length scales in agreement with the Woodward-Hoffmann rules. Moreover, we observed considerable effects on the efficiency and time scale of the reaction from the presence and orientation of an isopropyl substituent of the molecule. Similar conformer-dependent photochemistry has been observed only in a limited number of studies of photoproduct distributions, mostly after conformer-specific resonance-enhanced photoionization (1, 24–26). Because organic structures are prone to a large number of ground-state conformers and rotamers, our findings could have a large impact on our understanding of photochemical reaction mechanisms. We speculate that the paucity of previous observations of conformer and rotamer specificity is due to the absence of suitable experimental observables and challenges in preparing conformer-pure samples. Our study now demonstrates a suitable experimental observable. The investigation of specific conformers can be facilitated by methodological developments in the area of conformer-selected molecular beams (27, 28) and single-molecule methods such as Coulomb explosion imaging (29) in combination with high-repetition rate x-ray free electron laser sources. Future investigations of photochemical dynamics using such emerging methods will provide general access to conformer-specific photochemistry.

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**SUPPLEMENTARY MATERIALS**

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