Ynol Ethers from Dichloroenol Ethers: Mechanistic Elucidation Through $^{35}$Cl Labeling

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Supporting Information

$((1R,2S)-2-(E)-1,2$-dichloroprop-1-enyloxy)cyclohexyl)benzene (2):
S2

$((1R,2S)-2-(chloroethynyloxy)cyclohexyl)benzene (3)$:
S2

$((1R,2S)-2-(E)-1,2$-dichlorovinylloxy)cyclohexyl)benzene (1-35):
S2

(1S,2R)-2-phenylcyclohexyl 2-chloroacetate (4):
S3

Computational details:
S3

Video Clip of the metadynamics trajectory
S5

$^1$H and $^{13}$C spectra
S6-S11

Reactions were generally carried out under argon in oven-dried glassware. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Dry THF was obtained by filtration through activated molecular sieves and dry CH$_2$Cl$_2$ by filtration through activated aluminium oxide. Thin-layer chromatography was performed on (0.2 mm) silica sheets, which were visualized under ultraviolet light and by heating the plate after treatment with phosphomolybdic acid in ethanol, a p-anisaldehyde staining solution (80 mL of 95% ethanol, 2.9 mL of sulfuric acid, 0.86 mL of acetic acid, 2.1 mL of p-anisaldehyde), ninhydrin in ethanol, ceric ammonium molybdate in ethanol, or basic, aqueous KMnO$_4$. Silica gel (0.040-0.063 mm) was employed for flash column chromatography. A Fourier transform infrared spectrometer was used to record IR spectra. $^1$H NMR and $^{13}$C NMR spectra were recorded on either an AV 300, 400, or 500 MHz apparatus. All shifts for $^1$H spectra were referenced to the residual solvent peak and are reported in ppm. When ambiguous, proton and carbon assignments were established through COSY, HMQC, and/or DEPT experiments. Mass spectra were recorded using either DCI (ammonia/isobutane 63/37), EI, or ESI techniques. HRMS were recorded on an Orbitrap apparatus (ESI). Microanalyses were performed by the microanalysis service of the DCM.
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(\text{1R,2S})-2-(\text{E})-1,2\text{- Dichloroprop-1-enyloxy)cyclohexyl} \text{benzene (2).} \quad n\text{-BuLi (2.5 M in hexanes, 425 µL, 1.1 mmol) was added dropwise at -78 °C to a solution of 1 (262 mg, 0.97 mmol) in dry THF (5.0 mL) under Argon. After 5 min, MeI (120 µL, 1.93 mmol) and HMPA (1.0 mL) were added. After an additional 30 min at -78 °C, the cooling bath was removed and the solution allowed to warm to 20 °C over 4 h. Water was then added and the resulting mixture was extracted with pentane. The combined organic layers were washed with brine and dried over Na\textsubscript{2}SO\textsubscript{4} and the filtrate concentrated under reduce pressure. Purification of the residue by flash chromatography (SiO\textsubscript{2}/NEt\textsubscript{3} (2.5% v/v), pentane 100%) afforded 2 (252 mg, 91%) as colorless crystals: mp 43–43.5 °C; \([\alpha]_D^{20} +76.8 \quad (c 1.0, \text{CHCl}_3); \quad ^1H \text{ NMR (400 MHz, CDCl}_3) \delta 7.32-7.16 \quad (m, 5H), 4.33 \quad (dt, J = 10.6, 4.3 Hz, 1H), 2.81-2.72 \quad (m, 1H), 2.22-2.13 \quad (m, 1H), 1.98 \quad (s, 3H), 1.96-1.86 \quad (m, 2H), 1.79-1.71 \quad (m, 1H), 1.61-1.29 \quad (m, 4H); \quad ^{13}C \text{ NMR (100 MHz, CDCl}_3) \delta 143.1, 137.5, 128.1, 127.6, 126.3, 110.7, 82.5, 49.7, 34.5, 31.4, 25.7, 24.6, 21.3; \quad IR \quad (neat) 3028, 2930, 2858, 1658, 1448, 1181, 1000 \quad \text{cm}^{-1}; \quad MS \quad (ESI) \quad m/z \quad 291.0 \quad (M+Li)^+; \quad \text{Anal. calcd for C}_{15}H_{18}Cl_2O: C, 63.17; H, 6.37. Found: C, 63.55; H, 6.49.}
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(\text{1R,2S})-2-(\text{Chloroethynyloxy)cyclohexyl} \text{benzene (3).} \quad n\text{-BuLi (2.5 M in hexanes, 1.74 mL, 4.3 mmol) was added dropwise at -78 °C to a solution of 2 (1.07 g, 3.95 mmol) in 20 mL of dry THF under Argon. After 5 min the cooling bath was removed and the temperature allowed to reach -10 °C over 15 min. A saturated solution of NaHCO\textsubscript{3} was then added and the resulting mixture was extracted with pentane. The combined organic layers were washed with brine and dried over Na\textsubscript{2}SO\textsubscript{4} and the filtrate was concentrated under reduce pressure. Purification of the residue by flash chromatography (SiO\textsubscript{2}/NEt\textsubscript{3} (2.5% v/v), pentane 100%) afforded 3 (765 mg, 83%) as a colorless oil: \(^1H \text{ NMR (400 MHz, CDCl}_3) \delta 7.35-7.29 \quad (m, 2H), 7.27-7.19 \quad (m, 3H), 4.09 \quad (dt, J = 10.9, 4.5 Hz, 1H), 2.76-2.67 \quad (m, 1H), 2.43-2.34 \quad (m, 1H), 1.99-1.89 \quad (m, 2H), 1.80-1.72 \quad (m, 1H), 1.68-1.27 \quad (m, 4H); \quad ^{13}C \text{ NMR (100 MHz, CDCl}_3) \delta 142.2, 128.5, 127.5, 126.8, 89.8, 76.5, 49.1, 33.8, 31.1, 25.4, 24.7, 22.6; \quad IR \quad (neat) 3028, 2934, 2854, 2254, 1452, 1213, 1181 \quad \text{cm}^{-1}; \quad MS \quad (DCI) \quad m/z \quad 235.2 \quad (MH)^+.}
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(\text{1R,2S})-2-(\text{Cl})-1,2\text{-Dichlorovinyloxy)cyclohexyl} \text{benzene (1-35).} \quad \text{To a solution of the chloroynol ether 3 (395 mg, 1.68 mmol) in dry CH}_2Cl_2 (7.0 mL) at 0 °C was added a freshly prepared solution of H\textsuperscript{35}Cl in Et}_2O (≈ 0.8 M) until no triple bond was detected by IR (ca 2.1 mL). A saturated solution of NaHCO\textsubscript{3} was then added and the resulting mixture was extracted with dichloromethane three times. The combined organic layers were washed}
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with brine, dried over Na$_2$SO$_4$, and filtered. The filtrate was concentrated under reduce pressure and purified by flash chromatography (SiO$_2$/NEt$_3$ (2.5% v/v), pentane 100%) to afford 1-35 (249 mg, 55%) as colorless crystals: mp 57–57.5 °C; [α]$_D^{20}$ +95.3 (c 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.33-7.18 (m, 5H), 5.32 (s, 1H), 4.42 (dt, J = 10.6, 4.4 Hz, 1H), 2.84-2.75 (m, 1H), 2.26-2.18 (m, 1H), 1.99-1.88 (m, 2H), 1.80-1.73 (m, 1H), 1.61-1.25 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 142.8, 142.4, 128.2, 127.7, 126.5, 97.9, 83.2, 49.7, 34.4, 31.6, 25.6, 24.6; IR (neat) 3104, 3031, 2941, 2854, 1629, 1452, 1278, 1087 cm$^{-1}$; MS (ESI) m/z 293.0 (M+Na)$^+$. 

(1S,2R)-2-Phenylcyclohexyl 2-Chloroacetate (4). To a solution of the chloroynol ether 3 (124 mg, 0.53 mmol) in 3.0 mL of THF at 0 °C was added a solution of 95% H$_2$SO$_4$ (0.3 mL, 5.3 mmol) in 0.5 mL of water. After 25 min a solution of NaHCO$_3$ was then added and the resulting mixture was extracted with pentane. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and filtered and the filtrate was concentrated under reduce pressure. Purification of the residue by flash chromatography (SiO$_2$, 96/4:pentane/Et$_2$O) afforded 4 (88 mg, 66%) as a colorless oil: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.30-7.13 (m, 5H), 5.03 (dt, J = 10.6, 4.6 Hz, 1H), 3.71 (dd, J = 32.5, 14.8 Hz, 2H), 2.74-2.62 (m, 1H), 2.22-2.08 (m, 1H), 2.00-1.73 (m, 3H), 1.66-1.26 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.4, 142.4, 128.3, 127.4, 126.6, 78.1, 49.5, 40.7, 33.5, 32.0, 25.6, 24.6; IR (neat) 3024, 2937, 2858, 1759, 1737, 1292, 1192 cm$^{-1}$; HRMS (ESI) calcd for C$_{14}$H$_{17}$ClO$_2$Na (M+Na)$^+$: 275.0809. Found: 275.0815.

Computational details:
The *ab initio* Born-Oppenheimer dynamics calculations were performed using the CP2K-QuickStep program.$^1$ QuickStep is an implementation of the Gaussian Plane Waves (GPW) method based on the Kohn-Sham formulation of the density functional theory (DFT). The GPW approach is a hybrid method using a linear combination of Gaussian type orbitals to describe the Kohn-Sham orbitals; an auxiliary plan waves basis set is employed to expand the electronic charge density. The BLYP$^2$ functional was used and the basis set was a double zeta polarized set of Gaussian orbitals$^3$ in conjunction with the Goedecker-Teter-Hutter$^4$ pseudopotentials. The auxiliary PW basis set was defined by a cubic box of (20Å)$^3$ and by a density cutoff of 300 Ry. The Gaussian hills with a height of 0.3 kcal.mol$^{-1}$ were added every 20 fs with a time step of 1 fs for the dynamics. A constant temperature of 200K has been enforced by velocity rescaling.

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Two different sets of collective variables have been used. The first set uses two coordination numbers: one between the two chlorine atoms and the lithium atom, and one between the carbon atom and lithium atom. This set of collective variables introduces no discrepancy between the two chlorine atoms, since the coordination number between atoms a and atoms b is defined as

\[ c_{ab} = \frac{1}{N_a} \sum_a \frac{1}{N_b} \sum_b \frac{1}{p} \left( \frac{r_{ab}}{r_0} \right)^p \left( \frac{r_{ab}}{r_0} \right)^q, \]

where \( r_{ab} \) is the distance between the two atoms and \( p \) and \( q \) are set equal to 3 and 6, respectively. To study the alpha elimination, it is necessary to use an artificial “wall” of Gaussians to prevent the system from visiting the regions of the PES (potential energy surface) corresponding to the \( \beta \)-elimination. Thus, a second set of 3 collective variables has been defined: the \( ^6\text{Cl-Li} \) bond distance, the \( ^4\text{Cl-Li} \) bond distance, and the \( ^6\text{Cl}^4\text{C} \) bond distance. The wall of Gaussians prevents the \( ^6\text{Cl-Li} \) bond distance from being smaller than 2.6 Å.

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Video Clip of the metadynamics trajectory (using the first set of collective variables):