Supporting Information

Hyperpolarized NMR Reveals Transient Species and Elusive Routes in Acid-Catalyzed Furfural Oxidation at Natural Isotope Abundance

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Supplementary Figures

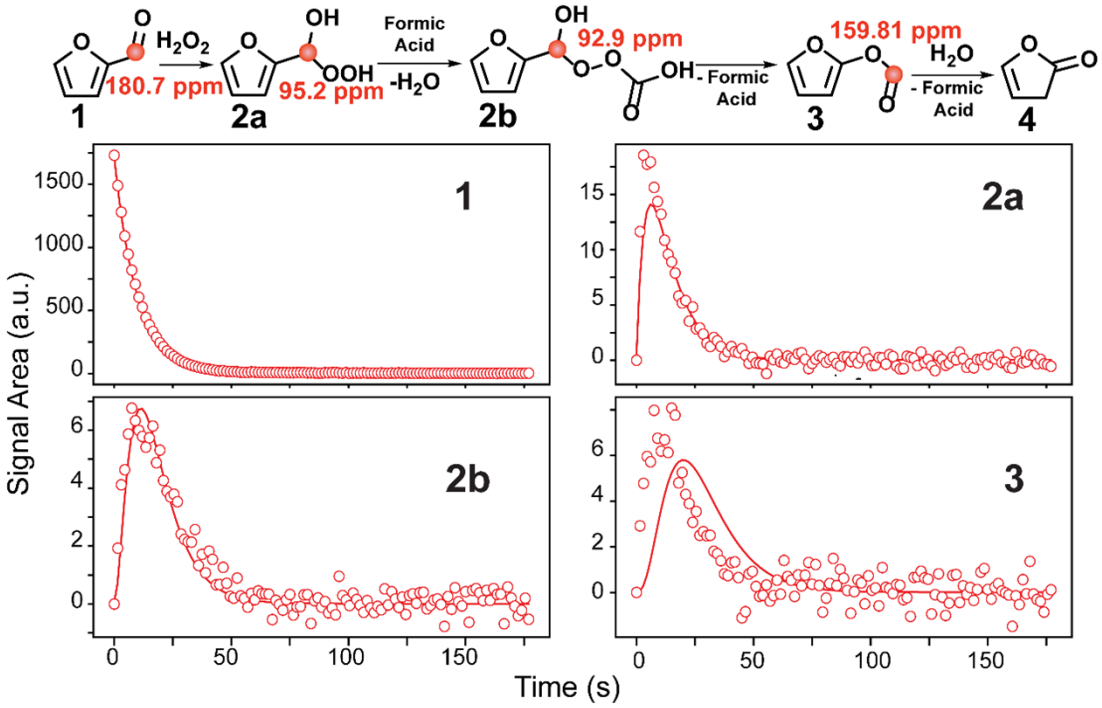

Figure S1. Kinetic fitting of hyperpolarized NMR data to a linear pathway based on the furfural aldehyde position. The kinetic model is not consistent with the hyperpolarized NMR data for the pathway shown on top.

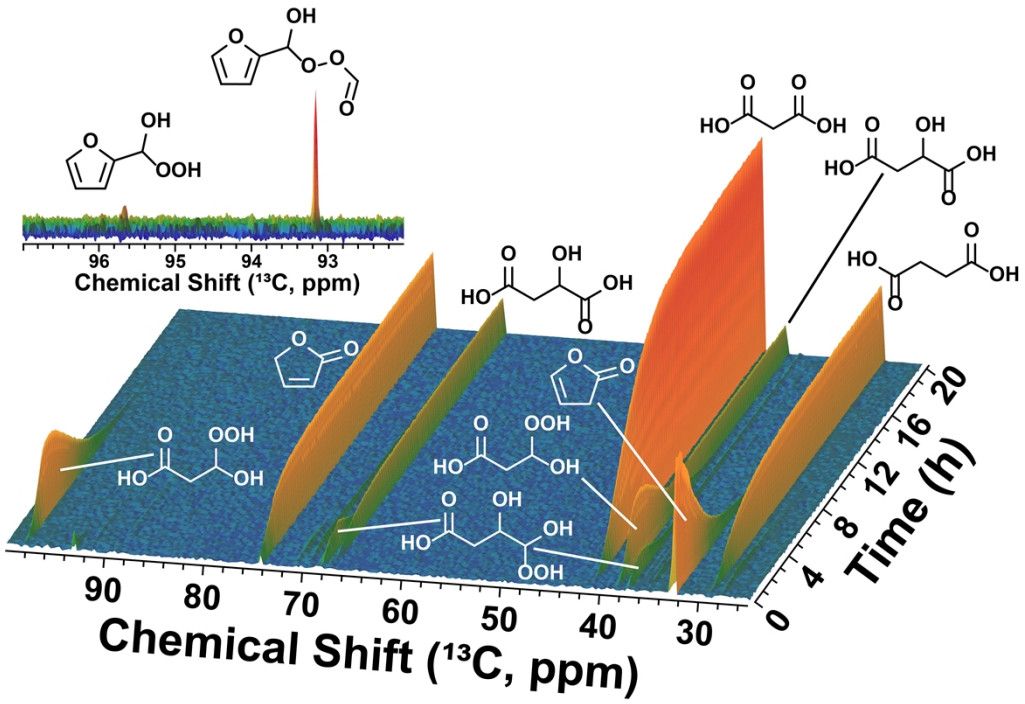

Figure S2. Time series of conventional *in situ* ^{13}C-NMR spectra in an ongoing oxidation of furfural. The main product malonic acid has received surprisingly little attention, despite being a prospective substrate for 1,3-propanediol synthesis, which in turn is a precursor in the formation of polytrimethylene terephthalate (PTT). Reaction conditions: furfural (16.7 µL, 201.0 µmol, 1 equiv.), hydrogen peroxide (>30%, 100 µL, 979.0 µmol, 4.9 equiv.), and formic acid (50% in H_2O, 400 µL, 5.30 mmol, 26.5 equiv.), 201 MHz, 313 K.

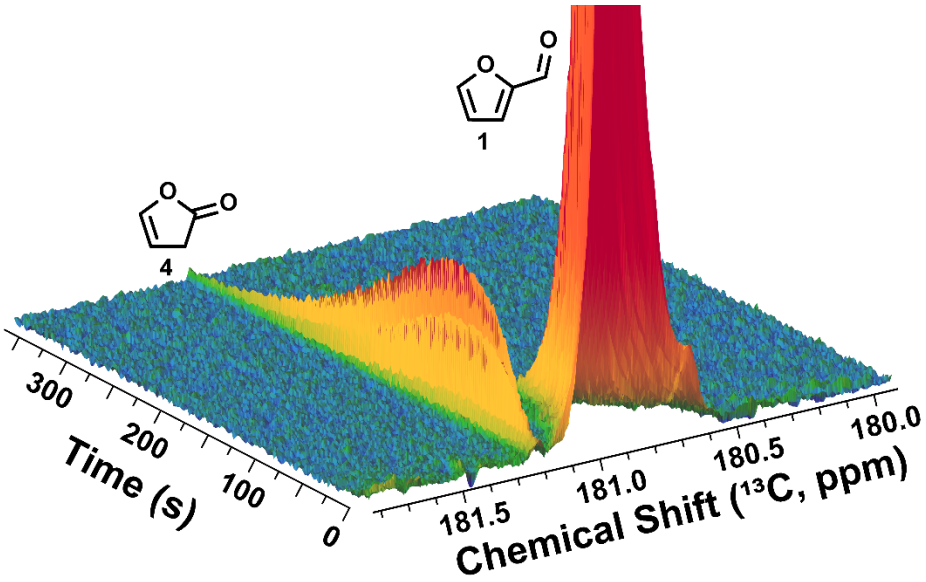

Figure S3. Time series of ^{13}C NMR spectra after injection of hyperpolarized furfural solution into 40% formic acid and 3% (v/v) H_2O_2 at 310 K, showing the formation of 2(3*H*)-furanone by influx of hyperpolarized signal from the quaternary site of furfural into the C1 carbon of 2(3*H*)-furanone. Integrals were included in the fits of reaction kinetics in main text Figure 5B.

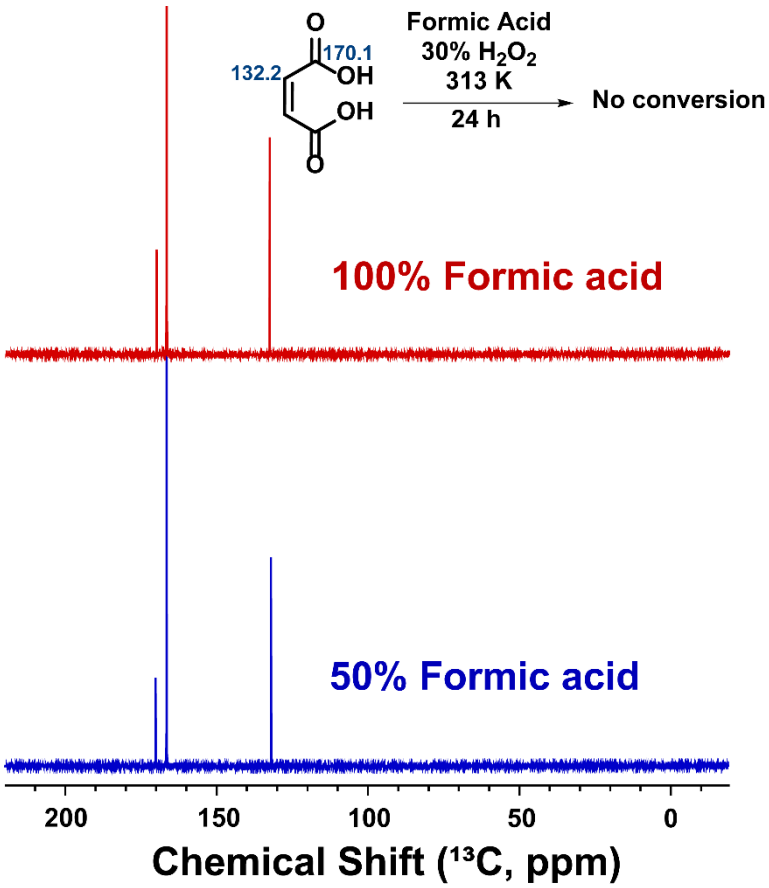

Figure S4. ^{13}C spectra of a mixture of maleic acid (23 mg, 198.1 µmol), formic acid (400 µL, 100% or 50% in water (v/v)), and hydrogen peroxide (200 µL, >30%) after 24 hours at 313 K, showing no hydration to malic acid.

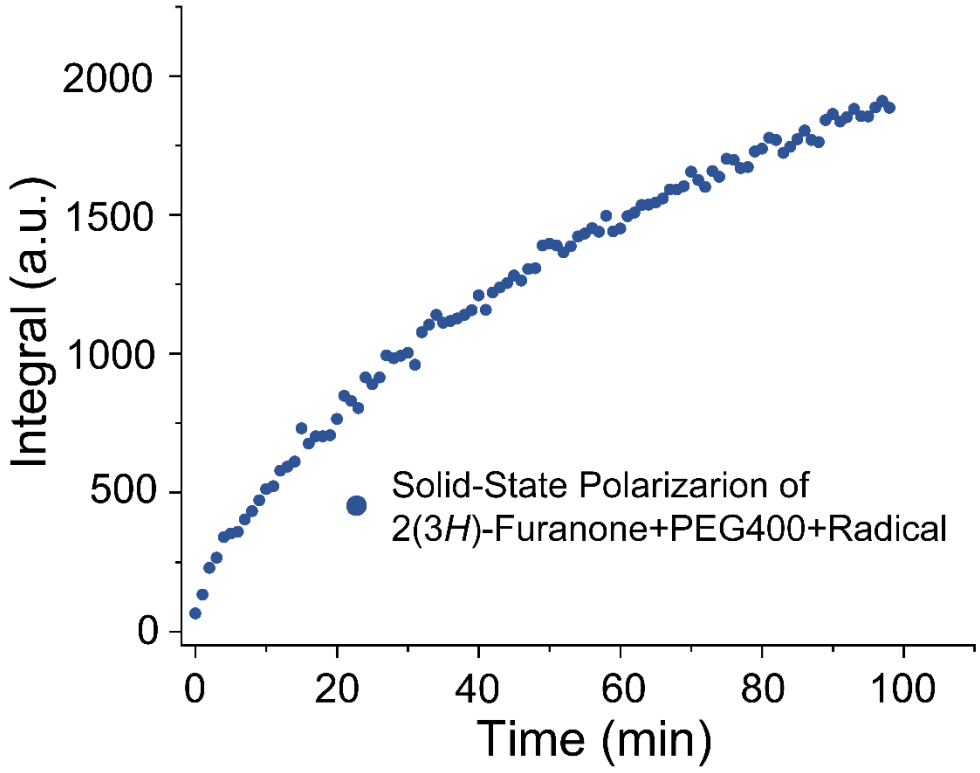

Figure S5. Solid-state polarization buildup (DNP with 188.0 GHz microwave frequency, 6.7 T magnetic field) for a mixture of 2(3*H*)-furanone (50 µL), PEG-400 (50 µL), and trityl radical AH111501 (35 mM).

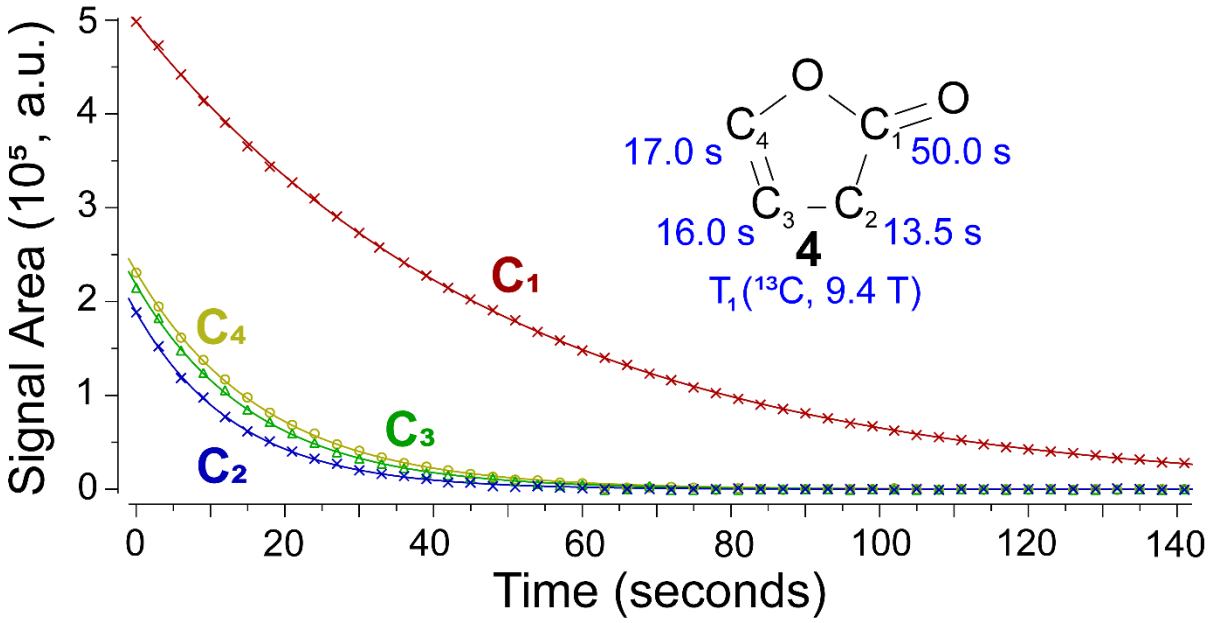

Figure S6. Relaxation of signals to thermal equilibrium over time for a mixture of hyperpolarized 2(3*H*)-furanone (50 µL), PEG-400 (50 µL), and trityl radical AH111501 (35 mM) that was rapidly dissolved in 5 mL milli-Q water. Resultant T_1 values at 9.4 T are given for the individual ^{13}C sites in 2(3*H*)-furanone (**4**) at natural abundance.

Supplementary methods

Chemicals.

Furfural (99%) was purchased from ThermoScientific (Waltham, MA, USA). Hydrogen peroxide (>30%) and sodium bisulfite were purchased from Fischer Scientific. Formic acid (99-100%) was purchased from Avantor (Radnor, PA, USA). Trityl radical AH111501 was purchased from GE Healthcare (Amersham, UK). PEG400 was purchased from Sigma Aldrich (St. Louis, MI, USA).

Purification of 2(3H)-furanone.

To a 250 mL round-bottom flask with a magnetic stirrer, furfural (5.0 mL, 60.36 mmol, 1.0 equiv.) and formic acid (10% in H_2O, 120 mL, 318.19 mmol, 5.3 equiv.) were added. Hydrogen peroxide (>30% in H_2O, 30 mL, 293.70 mmol, 4.9 equiv.) was added, and the mixture was stirred at 40 °C for 45 minutes. After cooling, the solution was extracted with dichloromethane (3 × 40 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*, yielding 5.4 g of a mixture of furfural (approximately 75%) and 2(3*H*)-furanone (approximately 25%). Acetone (10 mL) was then added, and the mixture was transferred to a separatory funnel. Saturated sodium bisulfite solution (20 mL), dichloromethane (20 mL), and water (20 mL) were added, and the layers were separated. The organic layer was rewashed with sodium bisulfite solution and water, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield 2(3*H*)-furanone, whose purity was confirmed by ^{1}H NMR.

dDNP NMR Spectroscopy.

A stock solution of furfural at natural isotopic abundance was prepared by mixing non-labelled furfural (150 µL, 174 mg, 1.82 mmol) with PEG 400 (150 µL, 169.5 mg) and doping the mixture with trityl radical AH111501 (16.8 mg). Similarly, a substrate sample stock solution of 2(3H)-furanone at natural isotopic abundance was prepared by mixing non-labelled 2(3*H*)-furanone (100 µL, 116 mg, 1.82 mmol) with PEG 400 (100 µL, 113 mg) and doping the mixture with trityl radical AH111501 (11.2 mg).

An aliquot of 100 µL (115-120 mg) from this substrate/PEG400/radical mixture was then hyperpolarized using a Spin-Aligner 6.7 T polarizer (Polarize ApS, Frederiksberg, DK) operating at a microwave frequency of 188.0 GHz. The hyperpolarization process required 1.0–1.5 hours for near-complete build-up, followed by dissolution of the sample in 5 mL of MilliQ water. Following dissolution, the substrate concentration was 121 mM. The hyperpolarized substrate solution was gathered in a receiver (50 mL container) at the polarizer, and a 1.0 mL aliquot was rapidly extracted into a syringe. The dissolved substrate was then rapidly transferred to the NMR magnet and manually injected into the NMR tube via a line with a void volume of 700 µL. Thus, in the dDNP experiment 300 µL of the hyperpolarized solution was injected into a mixture residing in the NMR instrument at 37 °C. For typical reactions, the reaction mixture residing in the NMR instrument consisted of 240 µL formic acid (50% in water, v/v) and 60 µL H_2O_2 (>30% in water, v/v). Upon injection of the furfural dissolved in the heated MilliQ water, the final temperature was approximately 40 °C. NMR spectra were recorded as a time series of ^{13}C spectra using a pseudo-2D experiment on a Bruker 500 MHz AVANCE NEO spectrometer, which was equipped with a 5 mm DCH cryoprobe for optimized sensitivity of the detection system. Following the injection of the hyperpolarized furfural, the time series of ^{13}C NMR spectra was started (nominal pulse angle 10°, time resolution 1.5 seconds) using Bruker Topspin 4.1.4.

NMR data were processes using MestReNova software (Mestrelab Research S.L.) or Bruker Topspin 4.1.4.

Determination of polarization.

The enhancement factor (ε) was determined by comparison of signal areas from a dDNP experiment in comparison to a conventional NMR experiment regenerating equilibrium polarization between scans. The enhancement factor for a system employing different pulse angles and number of scans was determined with eq (i):

$$\varepsilon = \frac{A_{DNP}}{\left(\frac{A_{Therm}}{NS_{Therm}}\right)}\left(\frac{sin(\theta_{DNP})}{sin(\theta_{Therm})}\right) \quad \text{(i)}$$

where A_{DNP} and A_{therm} are the integrals of the signals in the dDNP-experiment and in the conventional (thermal) experiment, respectively, *NS* is the number of scans, and θ is the pulse angle in the respective experiment (5° and 20° for DNP and thermal experiment, respectively). The degree of polarization (in %) was calculated using the thermal polarization in eq (ii):

$$Polarization\ (\%) = \varepsilon \cdot \frac{\hbar\gamma B_0}{2k_B T} \cdot 100 \quad \text{(ii)}$$

where $\hbar$ is the reduced Plancks constant, γ is the magnetogyric ratio of the nucleus, B_0 is the instrument magnetic field, k_B is the Boltzmann constant, and T is the temperature. For a 9.4 T magnetic field and 310 K, the thermal polarization for ^{13}C is 7.8 ppm.

Kinetic fitting of dDNP data.

Integrals from the same molecular position in the reactant furfural and the consecutive products were extracted using the MestReNova software (Mestrelab Research S.L.). The data were extrapolated back one time unit (1.5 s) due to a delay between injection of the hyperpolarized reactant into the reaction mixture and start of the NMR acquisition. Kinetic models of the reaction as shown in Figure 5 and S1 were programmed in Python 3.9.18 using the SciPy 1.11.4 pack. The differential equations were solved numerically by use of the SciPY ODE integrator, and the model was fitted to the data using the least squares method. While fitting yielded plausible values for the rate constants and T_1 values, kinetic models were primarily used in a qualitative manner to validate the succession of initial steps as detailed in Figures 5 and S1.

Determination of T_1 times.

The polarization of furfural at the aldehydic position, and the T_1 values for all ^{13}C positions in furfural at natural isotope abundance were measured on dissolved hyperpolarized furfural solution. A volume of 600 µl of the solution was transferred to a 5 mm NMR tube that was inserted into a Bruker 400 MHz Avance Neo spectrometer equipped with a P1-HR-BBO400S1 probe with the temperature set to 310 K. The total time from dissolution to measurement was approximately 10 s. Immediately after insertion, a time series of 48 one-dimensional ^{13}C spectra was recorded by applying 5° pulses separated by a 3 s delay. Upon the recording of the time series, the sample was doped with 12 µl of the gadolinium based Omniscan clinical relaxation agent to increase the relaxation rate of the furfural ^{13}C positions. An NMR spectrum at thermal polarization was then recorded by applying 20° pulses with rapid averaging over 1024 scans. From the ratio between the integrals of the first spectrum in the time series and the thermal spectra corrected for pulse angle and number of averages (see above) an enhancement factor and a polarization value was calculated for the furfural aldehydic position according to equations (i) and (ii).

The relaxation time constants of all ^{13}C positions in furfural were calculated from the integrals of the decaying signals in the time series by fitting equation (iii) to the data. The effect of the pulse on the decay rate of the signals was considered negligible due to the small angle of the excitation pulses (nominally 5°) and the long delay (3 s) between them.

$$S(t) = S(0) \cdot e^{\left(-\frac{t}{T_{1,\,obs}}\right)} \qquad \text{(iii)}$$

The accurate value can be derived using equation (iv), where T_1 is the accurate value, while $T_{1,obs}$ is obtained from fitting the decay of hyperpolarized magnetization towards thermal equilibrium with equation (iii).

$$\frac{1}{T_1} = \frac{1}{T_{1,obs}} + \frac{ln(cos\theta)}{\Delta t} \qquad \text{(iv)}$$