NMR characterisation of dynamics in solvates and desolvates of formoterol fumarate –
Supplementary Information

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1. $^1$H Spin-lattice relaxation

Proton spin-lattice relaxation times were determined at 299.8 MHz using a static sample of form C packed into a glass tube, and a saturation recovery sequence using recovery times from 0.1 to 10 s (40 increments) and a temperature range 193 to 353 K. The 90° pulses were of 3 μs duration. Since heteronuclear cross-relaxation effects are negligible due to the low natural abundance of $^{13}$C, the decays were fitted to a mono-exponential function. As shown in Figure S1, the relaxation rate passes through a maximum at 1000 K/$T_\text{~} \sim 4.1$ ($T_\text{~} \sim 244$ K). Modelling of the data is not straightforward due to the presence of multiple relaxation mechanisms and efficient spin-diffusion between the $^1$H spins. Instead arrows mark the predicted positions of the $R_1$ maxima (at $3.9 \times 10^{-3}$ and $4.2 \times 10^{-3}$ $\text{K}^{-1}$) associated with the motion of the h and O methyl group respectively derived using the dynamics parameters from fitting of the $^{13}$C data. The results are clearly consistent with proton spin-lattice relaxation being largely driven by methyl group motion in this temperature range.

2. Effects of temperature calibration on fitted activation parameters

The uncertainties on the fitted activation parameters given in the main text are based on the finite signal-to-noise ratio of the experimentally measured signal intensities and ignore any uncertainties in the temperature scale due to the effects of sample spinning. These uncertainties can, however, have a significant effect, especially on fitted activation barriers. Particularly at low temperatures, where flow rates often need to be adjusted to achieve both stable spinning and a set temperature, establishing a robust temperature calibration is not straightforward. Given that the quantitative measurement of the activation parameters is of
secondary interest (in comparison to the qualitative identification of the motions present), we here explore the effects of sample spinning on the fitted parameters using a simplified model.

In the probe design used, the spinning rotor is surrounded by a gas flow regulated to the set temperature, but the sample, particularly at its edges, is also exposed to gas flows from the sample spinning gas. The incoming spinning gas is at ambient temperature but will be warmed by frictional heating due to the sample spinning. This means that the sample temperature (at ambient temperature) is higher than the set temperature, with the deviation increasing (approximately quadratically) as the spinning rate is increased towards the maximum for probe. The correction between set and actual sample temperatures is, however, also dependent on the relative temperatures of the two gas flows and their flow rates. At high set temperatures, the spinning gas is much cooler than the “variable temperature” (VT) gas and so the correction will be reduced. Conversely, when the set temperature is below ambient, the spinning gas will tend to warm the sample, increasing the effective sample temperature.

In order to evaluate the effects of the sample spinning gas flows on the fitted parameters, we used here a simple model in which the temperature correction decreases linearly from +15 °C at the lowest (set) temperature used (−90 °C) passing through zero at +90 °C. These parameters were estimated for 4 mm MAS rotors spinning at 6.8 kHz, and correspond to a temperature rise of about 5 °C at ambient temperature. Table S1 shows the result of fitting with this modified temperature scale. Comparing the results with those of Table 1, it is apparent that the uncertainties in the temperature calibration have a significant impact on the estimated activation barrier. This can be expected since the difference in temperature between VT and spinning gas flows tends to “compress” the actual temperature range and hence increase the fitted activation barrier.

Using the same adjusted temperature scale, the fitted parameters for the rotation diffusion of the fumarate from the 2H relaxation data are \( E_a = 36.4 \pm 1.7 \text{ kJ mol}^{-1} \), \( \log_{10} D_0 = 14.4 \pm 0.3 \). Again the activation barrier is significantly affected (increased by about 15%) by the effects of sample spinning on the temperature scale, while the cone half-angle is unchanged at 10.6 ± 0.6°.

The EXSY experiments used to measure the phenylene ring dynamics covered a narrower temperature range and calibration experiments using lead nitrate as an “NMR thermometer” suggested that the temperature corrections on the 5 mm probe used were less temperature dependent. Hence a uniform correction (+3.4 K) was used, noting that the systematic error associated with the temperature scale means that the activation barriers obtained are also likely to be slightly underestimated.

Table S1 Parameters from fitting methyl 13C \( T_1 \) relaxation rates of Figure 4 to a three-site jump model of methyl group rotational diffusion using a temperature scale approximately corrected for the effects of sample spinning.

<table>
<thead>
<tr>
<th></th>
<th>h methyl</th>
<th>O-methyl</th>
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<tbody>
<tr>
<td>( E_a / \text{kJ mol}^{-1} )</td>
<td>19.1 ± 0.6</td>
<td>19.2 ± 1.2</td>
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<tr>
<td>( \log_{10} (T_0 / \text{s}) )</td>
<td>−12.9 ± 0.1</td>
<td>−13.4 ± 0.2</td>
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<tr>
<td>( D_{CH} / \text{kHz} )</td>
<td>18.6 ± 0.2</td>
<td>11.3 ± 0.2</td>
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