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2 Abstract

3 The relationship between the strength of the intermolecular interaction in liquid and the positionspecific ¹³C fractionation observed during distillation was investigated. A range of molecules 4 5 showing different intermolecular interactions in terms of mode and intensity were incorporated in the study. Although it had previously been suggested that during evaporation the diffusive ${}^{13}C$ 6 isotope effect in the thin liquid layer interfaced with vapor is not position-specific, herein we 7 8 show that this is not the case. In particular, the position-specific effect was demonstrated for a 9 series of alcohols. Our hypothesis is that intermolecular interactions in the liquid phase are the source of position-specific ¹³C fractionation observed on the molecule. A clear trend is observed 10 between the ¹³C isotope effect of the carbon bearing the heteroatom of chemical function and the 11 12 relative permittivity, the solvent hydrogen-bond acidity and the solvent hydrogen-bond basicity, while only a weak trend was observed when using the ¹³C content of the whole molecule. 13 14 Furthermore two families of products appeared when using the hydrogen-bond acidity parameter 15 for the correlation by distinguishing H-acceptors and H-donors molecules to those H-acceptors only. This strongly reinforces the hypothesis of an important role of the ¹³C positioned close to 16 17 the interaction center.

18

19 Keywords

20 Position-specific isotope fractionation; isotope ratio monitoring ¹³C NMR spectrometry;
21 Volatilization, Distillation, Craig-Gordon model

23 Introduction

24 Stable isotopes were widely used in the past to study the nature of phase transfer processes like liquid-vapor transfer (References Jancso and van Hook, book of Wolfberg et al, etc.).¹² Past 25 26 studies used fully substituted isotopic molecules for which large isotope effects are observed 27 which could be better measured with past analytical techniques. Progress in analytical techniques 28 has led to the development of Compound-Specific Isotope Analysis (CSIA) capable of 29 monitoring stable isotope ratios at natural abundance ratios. With the help of CSIA, the 30 mechanisms of phase transfer processes were furthermore investigated and elucidated (Hunkeler 31 and Jeannottat, Kuder, Huang, etc.). However, it has been shown that CSIA based on isotope ratio monitoring by Mass Spectrometry (irm-MS) is not always sufficient to describe the ¹³C 32 33 fractionation during the whole evaporation phenomenon. Recently, we have reported the study of several liquid-vapor transition processes using isotope ratio monitoring by ¹³C Nuclear Magnetic 34 Resonance spectrometry (irm-¹³C NMR) in order to simulate position-specific fractionation 35 during evaporation.³ We have shown that Position-Specific Isotope Analysis (PSIA) by irm-¹³C 36 37 NMR can provide new insights into physical processes, including in circumstances in which CSIA may not detect any effect on the whole molecule.⁴ Furthermore, bulk ¹³C composition 38 $(\delta^{13}C_{bulk})$ analysis (CSIA), obtained by irm-MS, only indicates which isotopologue reacts 39 preferentially in the studied process, whereas PSIA shows which isotopomer is the most sensitive 40 41 (see Figure 1 for a further definition).

42 Isotope fractionation is conveniently described by the isotopic fractionation factor α or the 43 isotope effect IE and is associated with discrimination between the behavior of isotopomers.⁵ A 44 previous study showed that the Craig-Gordon isotope model, originally derived for water 45 evaporation,⁶ is also valid for organic liquids as demonstrated by Kuder and collaborators,⁷

46 especially for the description of the volatilization of nonpolar organic liquids with air-side limitation of the volatilization rate.⁴ In the Craig-Gordon model in its original form, it is assumed 47 that the diffusive effect in the stagnant liquid $\varepsilon_{diff-liq}$ (thin liquid layer interfaced with vapor, see 48 ref 4) is not position-specific, i.e. is independent of the position of the ${}^{13}C$ in the molecule. 49 50 However, among the compounds studied, ethanol and propan-1-ol both showed a position-51 specific behavior. Working with the hypothesis that intermolecular interactions in the liquid phase were the source of position-specific ¹³C fractionation observed on the molecule collected 52 from the vapor phase, we have therefore generated a modified Craig-Gordon equation to take 53 these position-specific interactions into account.⁴ 54

55 The most widespread non-covalent molecular interaction is hydrogen bonding. The strength of the hydrogen bond depends on the properties of both the hydrogen-bond acceptor (HBA) and the 56 hydrogen-bond donor (HBD).⁸ Recently, a specific methodology has been proposed by which 57 58 both solvent hydrogen-bond basicity and solvent hydrogen-bond acidity can be quantified, leading to the parameters β_1^{9} and ET(30),¹⁰ respectively. β_1 is linked to the original scale of 59 Kamlet and Taft¹¹ but is specific for the solvent scales. Thus, the scale of solvent hydrogen-bond 60 basicity was established by the method that compares the ¹⁹F NMR chemical shift of 4-61 62 fluorophenol and 4-fluoroanisole in hydrogen-bond acceptor solvent. In addition to the empirical 63 parameter describing the hydrogen-bond acidity α_1 (from Kamlet-Taft), the quantitative solvent 64 polarity parameter ET(30) was introduced. This is based on the negative solvachromism of 2,6diphenyl-4-(2,4,6-triphenylpyridinium-1-yl)phenolate (known as betaine 30).¹² Weaker 65 interactions are encompassed under van der Waals, π -bonding¹³ or halogen-bond¹⁴ interactions 66 67 that explain intermolecular associations between apolar molecules, molecules possessing an

aromatic-ring, or halogen-containing compounds. The unit accounting for these interactions is the
 relative permittivity,¹⁵ previously known as the dielectric constant diE.¹¹

The goal of the present work was to investigate the relationship between the strength of the 70 intermolecular interaction in liquid and the position-specific ¹³C fractionation observed during 71 vaporization. We asked three fundamental questions: "Does the presence of ¹³C in the molecule 72 increase (or decrease) the interaction?", "Is this interaction stabilized in a specific ¹³C 73 isotopomer?", and "What is the influence of the proximity of ¹³C to the interaction site?" To 74 75 answer these questions conditions are required in which the isotope fractionation measured 76 should reflect the transition liquid-vapor only with the influence on the liquid phase, but with no 77 further isotope effect in the vapor phase. These conditions are essentially met in distillation in 78 which no diffusive boundary layer is occurring when the compounds are boiling. Furthermore, this process is quick, simple, and known to induce significant isotope effects in ²H and ¹³C.¹⁶ 79 80 Hence, this allows insight into isotope effects occurring on the liquid side. To express the isotope effect during the liquid-vapor transition we used the nomenclature already proposed for such 81 transformation.^{16a} In the case of a small transformation of the substrate, such as the collection of a 82 83 very small distillate volume ($\leq 3\%$), any associated isotope effects can readily be detected in the distillate, but impact negligibly on the isotopomer composition of the remaining liquid. The 84 85 corresponding fractionation factor α was defined in the classical literature as separation factor α 86 (Jancso and Van Hook, 1974):

87
$$\alpha = (N'/N)_{vap}/(N'/N)_{liq}$$
(1)

where N' and N are the mole fractions of light and heavy isotopomers respectively in the system at equilibrium. The specific-isotope fractionation of site i (the isotopomer with ¹³C at position isotopomer i) is then defined as the experimental fractionation factor α_{exp} :

91
$$\alpha_{\exp, i} = ({}^{13}C/{}^{12}C)_{i, vap}/({}^{13}C/{}^{12}C)_{i, liq}$$
 (2)

92

93 Equation 2 is adapted to more recent work on stable isotopes where ratios are measured and 94 expressed as abundance of heavy isotopes divided by abundance of light isotopes (Aelion et al, 95 2010). Thus, a normal isotope effect leads to $\alpha_{exp} < 1$: i.e. the liquid (distillate) is impoverished in 96 heavy isotopes with respect to the vapor (starting product), while an inverse isotope effect 97 favoring the heavy atom in the vapor gives $\alpha_{exp}>1$. This is the convention that is used in the 98 present work. Several compounds were selected with respect to their physicochemical properties 99 in terms of hydrogen-bond capabilities, or more generally their intermolecular interactions. The 100 code of the samples used and the carbon numbering are shown in Table 1. The alcohols are 101 clearly hydrogen-bond acceptors and donors (amphiprotic solvents). Other chemical functions, 102 such as those which involve heteroatoms, could be polar and/or hydrogen-bond acceptors. 103 Furthermore, Br and Cl atoms may generate a halogen-bond. Two apolar compounds, toluene and 104 *n*-heptane were also distilled for comparison. All the experiments were conducted at natural 105 abundance isotope composition.

106

107 **Experimental**

108 Chemicals

Methyl *tert*-butyl ether (99.8%), *n*-heptane (99%), toluene (99.9%), bromoethane (98%), trichloroethylene (99.5%), propan-1-ol (99.7%), propan-2-ol (99%), butan-1-ol (99.7%), *tert*butanol (99.5%), 2-methyl-2-butanol (99%), pentan-1-ol (99%), cyclohexanol (99%), ethyl acetate (99.9%), acetonitrile (99.9%), and 4-heptanone (98%), were obtained from Sigma-Aldrich. Ethanol (99.8%), methanol (98%) and chloroform (98%) were purchased from VWR

114 Prolabo and acetone (99.5%) from Alfa Aesar. DMSO-d₆, dioxane-d₈ and CD₃CN were obtained

115 from Eurisotop. Tris(2,4-pentadionato)chromium(III) [Cr(Acac)₃] was from Merck.

116

117 *Distillation experiments*

For each experiment, 100 mL of pure compound was introduced into a 1 L round bottom flask and distillation was carried out using a Cadiot distillation column equipped with a Teflon spinning band (see Murray and reference therein for its characteristics¹⁷). This distillation equipment allows the reflux to be rigorously controlled. Once reflux conditions were reached, the distillate was collected up to approximately 3% maximum of the mass of the starting substrate. The distillate was then submitted to ¹³C-irm-EA/MS and irm-¹³C NMR.

124 In the present study, distillation has been chosen in order to study liquid-vapor equilibrium 125 effects, because this method is quick and easy to perform which is perfect to study a large panel 126 of chemical compounds in very controlled conditions. The inconvenient of this protocol is that 127 the resulting isotope effects are magnified, especially using a spinning band distillation column 128 which displays many theoretical plates and the capability of maintaining the system at 129 equilibrium. Nevertheless, these overexpressed isotopic fractionations have the same direction 130 (normal or inverse) as those observed in static phase equilibrium (Refs. Jeannottat+Hunkeler) or 131 vapor pressure measurements (Jancso+Van Hook, 1974).

In the case of isotopic studies, the concept of "pure compound" needs to be further defined. The term "pure" means that there is only one chemical species present. However, it is in fact a mixture of all potential isotopologues and isotopomers of the considered compound. As an example, a sample of pure ethanol contains four types of molecules isotopically different in ¹³C (see Figure 1).

138 ^{13}C -irm-EA/MS

Bulk ¹³C abundance ($\delta^{13}C_{bulk}$) was determined by irm-MS using an Integra2 spectrometer (Sercon 139 140 Instruments, Crewe, UK) linked to a Sercon elemental analyser (EA) (Sercon Instruments, 141 Crewe, UK). A precise amount of each compound was weighted into tin capsules (2x5 mm, Thermo Fisher scientific) using a 10^{-6} g precision balance (Ohaus Discovery DV215CD) to give 142 143 approx. 0.4 mg of carbon for each compound. Great care was taken to ensure that there was no 144 leakage from the capsule. First, during the weighing of the Volatile Organic Compound (VOC) 145 introduced into the tin-capsule, the sealed capsule was left on the balance for a short delay to 146 verify the stability of the mass. No change in mass indicated that the capsule was effectively 147 sealed. Secondly, the percentage of carbon was checked by the operator by comparing this value 148 with that usually obtained on the solid working reference. This gives a check in relation to the 149 intensity of the signal of the ions obtained from the CO₂ generated from the different isotopologues (m/z = 44, 45, 46). Moreover, each sample is analyzed three times to ensure 150 measuring true δ^{13} C values and a repeatability study has also been performed in a previous study 151 (see ref 3) which demonstrates the capability of these experimental conditions to measure the 152 bulk isotopic composition of VOCs such as MTBE. The δ^{13} C (‰) values were expressed relative 153 154 to the international reference (Vienna-Pee Dee Belemnite, V-PDB) using the relationship: $\delta^{13}C_{VPDB}(\%_0) = \left(\frac{R_{sample}}{R_{standard}} - 1\right) \times 1000.^{18}$ The instrument was calibrated for $\delta^{13}C$ using the 155 international reference materials NBS-22 ($\delta^{13}C_{PDB} = -30.03$ %), SUCROSE-C6 ($\delta^{13}C_{PDB} = -$ 156 10.80 ‰), and IAEA-CH-7 PEF-1 ($\delta^{13}C_{PDB}$ = -32.15 ‰) (IAEA, Vienna, Austria) and 157 158 instrumental deviation followed via a laboratory working standard of glutamic acid. 159

160 Isotope ratio monitoring
$${}^{13}C$$
 NMR spectrometry (irm- ${}^{13}C$ NMR)

161	The sample preparation consisted of the successive addition in a 4 mL vial of the compound, the
162	lock substance and the relaxation agent Cr(Acac) ₃ (which acts to decrease the longitudinal
163	relaxation time T1). ¹⁹ The respective amount of each was adapted according to (i) the T_1 values
164	of the analyte, (ii) the reciprocal solubility with the deuterated solvents and/or the relaxation
165	agent and (iii) the ¹³ C NMR spectrum: no peak overlapping. The exact preparation procedures
166	were described previously. ³ Quantitative ¹³ C NMR spectra were recorded using an AVANCE I
167	400 spectrometer (Bruker Biospin, Wissembourg, France), fitted with a 5 mm i.d. ${}^{1}\text{H}/{}^{13}\text{C}$ dual ⁺
168	probe, carefully tuned at the recording frequency of 100.61 MHz, or a Bruker AVANCE III 400
169	spectrometer fitted with a 5 mm i.d. BBFO probe tuned at the recording frequency of 100.62
170	MHz. The temperature of the probe was set to 303 K. Spectra were acquired without tube
171	rotation. Isotope ${}^{13}C/{}^{12}C$ ratios were calculated from processed spectra as described previously. ³ ,
172	20

173

- 174 *Calculation of* \mathcal{E}_{bulk} *and* \mathcal{E}_i
- 175 The isotope effect IE (‰) was obtained from the equation:
- 176 IE = $(\alpha_{=} -1) \ge 1000$
- 177 where the isotope isotope effect (IE) is calculated as explained in detail in the work of Julien et

(3)

- 178 $al.^4$ where IE is equivalent to ε .
- 179 Here IE<0 is a normal isotope effect is observed while IE>0 indicates an inverse isotope effect.

- 181 **Results and discussion**
- 182 Position-specific ¹³C analysis by NMR

183 PSIA may be performed by fragmenting the molecule in such a way that, after subsequent analysis of the resulting fragments by irm-MS.²¹ information on the isotopomer composition is 184 retrieved. This fragmentation can conveniently be achieved on-line by pyrolysis prior to mass 185 spectrometry analysis.²² However, this approach is not easily applicable to molecules containing 186 187 more than 4 carbon atoms. In contrast, quantitative NMR gives access to all spectrally-resolved sites in the compound, i.e. relative titration of the ¹³C isotopomers constituting the molecule 188 when irm-¹³C NMR conditions are used.²³ It offers the advantage of directly analyzing the target 189 190 molecule, hence avoiding the risk of technique-associated fractionation. The precision in irm-191 NMR depends primarily on the signal-to-noise ratio (SNR) and it is described in the present work by a standard deviation of 0.3% on the δ^{13} C scale (%). We have shown in a previous study that, 192 under these conditions, the uncertainty on IE_i is $\pm 0.2\%$ (95% confidence level)²⁴ for the 193 evaporation processes and the molecules used.³ This value is the threshold of significance that 194 195 will be used for the interpretation of the results presented.

196

197 Bulk ¹³C and position-specific fractionation upon distillation

Zhang et al. showed that distillation can be a useful tool to determine isotopic fractionation 198 factors at equilibrium during liquid-vapor transitions.^{16a} For a given compound heated at reflux, 199 200 an equilibrium between the liquid and the vapor is established. When a very small amount of 201 distillate is collected (\leq 3%) it can be assumed that the isotope profile of the distillate represents the isotopic composition of the vapor at equilibrium with the liquid. These authors measured ²H 202 the position-specific isotope effect (by irm-²H NMR) as well as isotope bulk effect (by irm-MS) 203 on heteroatoms (¹³C, ¹⁵N and ¹⁸O) in a series of organic molecules containing typical functional 204 205 groups. They observed that the isotopic fractionation enrichments varied with (i) the element, (ii)

the type of chemical function and (iii) the ²H isotopomers (²H position in the molecule). We 206 207 previously confirmed that distillation under similar conditions also led to position-specific ${}^{13}C$ fractionation in ethanol: the distillate is enriched in ¹³C mainly on the CH₂ moiety.^{3, 16b} In the 208 209 present work we have extended this protocol to other organic compounds that have several 210 specific chemical characteristics in terms of substituent, heteroatoms and chemical functions. The isotopomer profiles expressed as $\delta^{13}C_{bulk}$, $\delta^{13}C_i$ and $\Delta\delta^{13}C$ (difference between the $\delta^{13}C$ in 211 distillate and δ^{13} C in starting material) are summarized in Table 2. Two key observations can be 212 made. First, in the majority of cases the distillate is enriched in ¹³C. Second, a large variability of 213 $\Delta \delta^{13}C_i$ within and between molecules is seen. In a previous study (ref 4), ^{13}C isotopic 214 215 fractionation associated with distillation has been determined analyzing the remaining substrate 216 after distillation of 93 to 98% of pure compound. Under these conditions, it can be assumed that 217 the detected isotopic fractionation corresponds to the isotope effect associated with the liquid-218 vapor transformation without contribution of the diffusion. In the present case, the distillate has 219 been analyzed in order to study the isotopic fractionation associated with distillation. The low 220 distillation yields (around 3%) along with the presence of multiple theoretical plates both induce 221 the detection of larger isotope effects than the analysis of the remaining substrate. However, this 222 overestimation of the isotopic fractionation associated with distillation is not misleading for the 223 interpretation because the intramolecular distribution of the fractionation is conserved. As an 224 example, the analysis of the distillation tail of TCE showed an isotope effect of +0.8% mostly 225 located on the carbon bearing two chlorine atoms (see ref 4) and this isotope effects is about 226 +5.1% in the present study but still mostly located on the same carbon position (see Table 3). 227 The distillation protocol employed in this study doesn't allow obtaining true values of liquid-228 vapor equilibrium isotope effect but it is still available to study its mechanism. Table 1 shows the

numbering of the carbon positions, according to the shielding order of the peak in the ¹³C NMR 229 230 spectrum. This shielding (or deshielding) is associated with the electron density surrounding the given carbon atom and depends to some degree on the polarity of the neighboring heteroatoms 231 (or chemical functions). The isotopomer 'C-1' which contains the ¹³C directly linked to this 232 233 heteroatom is clearly identified in alcohols. It is, however, less straightforward for other chemical 234 species, such as ester, ketone, nitrile, etc. (see Table 1 for the attribution of C-1 in each molecule). In general, the ¹³C ratio at the C-1 is seen to be the most effected by the liquid-vapor 235 236 transition, i.e. it is the isotopomer containing ¹³C at that position which distils first. Exceptions are notable for acetonitrile (acni), for which $\delta^{13}C_{C-1}$ is depleted, and for *n*-heptane (hept) and 237 238 toluene (tol) for which there is a homogeneous enrichment effect for each carbon. In the series of alcohols, a further effect is observed: the preference of the ¹³C isotopomer for the vapor phase is 239 240 diminished, stabilized or even increased according to the distance from the OH function along the carbon chain. Thus, in butan-1-ol (al-5) and pentan-1-ol (al-8) $\Delta \delta^{13}$ C upon distillation is large for 241 242 the carbon-bearing OH (C-1): +5% and +4.1%, lower for the inner carbon(s) of the chain: 243 +3.0/+2.6‰ and +2.7/+2.0‰ and slightly larger for the terminal carbon positions: +2.9 and +2.7% respectively (Table 2). This is clear evidence that the presence of ${}^{13}C$ close to the OH 244 245 function influences strongly the facility for the molecule to be transformed into vapor. 246 Interestingly, a remote effect is associated with the terminal carbon.

247

248 *Position-specific*¹³C fractionation versus intermolecular interactions

The above discussion of the alcohol series addresses the issue of interactions within the liquid. As a first deduction, it appears that the proximity of ¹³C to the OH function favors the distillation of the corresponding isotopomer. Therefore the question is: does ε_{C-1} (the amplitude of the ¹³C

252 fractionation or the discrimination between the isotopomer C-1 and the other isotopomers) 253 represent the strength of the interaction between alcohol molecules in the liquid state? Among 254 several parameters used for describing the potential level of intermolecular associations, the 255 relative permittivity (diE) is the most commonly used. Table 3 reports the isotope effects (IE_{bulk} and IE_{C-1}), diE, ET(30) and β 1 (see Introduction for a definition of these terms). Unfortunately, 256 257 these parameters are not available in the literature for all the molecules studied, but sufficient 258 values are available to establish trend lines. These lines have been drawn according to the visual 259 distribution of data points, which means that Figures 2 and 3 do not present real correlations 260 between isotope effects and the physical properties of compounds but, rather, lines drawn without 261 a priori to make the discussion easier. Trend lines have been drawn using Microsoft Excel so 262 they have an equation and a root mean square (R²) which also are detailed in Figures captions in 263 order to help the discussion the results. Figures 2 and 3 illustrate the potential trends between the 264 isotope effects and diE, ET(30) and β 1, respectively. A clear trend is observed between IE_{C-1} and 265 diE, ET(30) and a weaker for β 1 (Figures 2), while a loose trend can even be discerned between 266 IE_{bulk} and diE, ET(30) and β 1 (Figures 3). This strongly reinforces the deduction of an important role of the ¹³C isotopomer C-1 in the interaction between molecules. 267

Nevertheless, there are some exceptions which deserve comment. In all cases, toluene (tol) and even more so *n*-heptane (hept) do not follow these trends: this is readily explained by the lack of polarity (no diE) and an inability to form H-bonds or, more generally, interactions involving a specific position in the molecule. Both *n*-heptane and toluene are only able to form van der Waals and π bonding interactions, respectively, that do not induce any significant position-specific isotope effect during distillation. Interestingly, the data for bromoethane (brom) do not fit with the β 1 values either (Figure 2c) when it appears to have a behavior similar to alcohols concerning

ET(30) trends (Figure 2b). Since the parameters β 1 and ET(30) describe the potential interaction of the molecule as a solvent,⁹ it can be seen here that the molecule acts both as solute and solvent, i.e. in a self-association. Therefore, a molecule may be in a state to give or to receive H (or another interaction) but not to do both at the same time. Thus bromoethane shows a weak baseproperty, with a halogen-type association likely to be occurring.

280 As can be seen from Figure 2b, a clear double trend is observed. One encompasses the alcohols 281 (al-x), but also chloroform (chlo), which are both H-acceptors and H-donors (a proton can readily be exchanged with deuterium²⁵), and to some extent bromoethane (brom). The case of 282 283 chloroform, with the isotope effect associated with its distillation correlating very well with those 284 for alcohols (See Figure 2b), is interesting. This could be explained by (i) the high electron 285 density in this molecule and (ii) the resulting presence of the acidic hydrogen. These two features 286 of chloroform can interact forming a halogen bond and its strength seems to be dependent of the presence of a ¹³C on the central carbon position. Trichloroethene (TCE) presents an isotope effect 287 288 mostly located on the carbon bearing the acidic hydrogen that can form hydrogen bonds, but this 289 compound better correlates with H-acceptors (Figure 2b). Of the remaining products studied, that 290 are H-acceptors only, acetonitrile (acni), acetone (acet) and ethyl acetate (etac) all show good 291 correlation with amphiprotic molecules (alcohols) (Figures 2 and 3).

A change in the solvation shell of ethanol modifies the ¹³C position-specific fractionation. As an illustration, the distillation of a dilute acidic aqueous ethanol solution (10% v/v with 1 M H₂SO₄), using the same device, leads to the following isotope effect IE, measured on the distillate: bulk, +3.4‰, C-1, +6.3‰, C-2, +0.5‰. By increasing the H-bond network around the ethanol molecule, the ε_{C-1} is accentuated, thus confirming that the isotopomer containing a ¹²C at the C-1 position reinforces the intermolecular interaction. Interestingly, the reverse is found for the

position C-2 for which it is the isotopomer with a 12 C on the CH₃ that distils first. The significance of such behaviors is beyond the scope of this paper, but it is clear that the 13 C position-specific fractionation is sensitive to the types of interaction and to the models of association: most probably a large network (complex) for alcohols and chloroform versus a binary association (simple) for the other compounds investigated.

303

304 Conclusion

305 The main outcomes of this study are two-fold. First, it is shown that position-specific 306 fractionation in liquid-vapor transitions can occur in a range of molecules. When the molecular architecture within the liquid enables interactions, then the isotope effect of diffusion $\varepsilon_{diff-liq}$ (ref 307 4) is position-specific. This is a novel finding, since up to now it has been considered that ${}^{13}C$ 308 309 fractionation during diffusion shows a mass effect only, i.e. is not position-specific. These new 310 data now need to be included in the model of fractionation during the process of volatilization according to the Craig-Gordon isotope model for organic liquids.^{4, 7} Second, ¹³C position-specific 311 312 fractionation appears to be exploitable as a marker of the strength of interactions in the liquid phase within the self-association framework. Fundamentally, the presence of a ¹³C atom in a 313 molecule according to its position decreases the interaction strength. How the presence of a 13 C 314 315 acts to (de)stabilize the H-bond in alcohols now needs to be further investigated by theoretical 316 modelling. Other intermolecular interactions such as the dimerization of carboxylic acids could 317 also be studied using the same approach. Moreover, more complex systems such as VOCs 318 diffusive transport in soil could be studied in the same way where the presence of heavy carbon 319 isotopes should also have an influence on isotopic fractionation associated with diffusion.

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433 Figure Captions

- **Figure 1.** Definition of isotopologues and isotopomers: example of ethanol.
- **Figure 2.** Relationship between the isotope effect located on position C-1 (IE_{C-1}) and (a) the
- 438 relative permittivity (diE), (b) the hydrogen bond acidity (ET(30)), y=-0.31x+19.89, $R^2=0.853$ for
- both H-acceptors and H-donors, y=-0.80x+34.69, $R^2=0.938$ for H-acceptors only and (c) the
- 440 hydrogen bond basicity (β_1), y=16.1x-6.37, R²=0.619.
- **Figure 3.** Relationship between the bulk isotope effect (IE_{Bulk}) and (a) the relative permittivity 443 (diE), (b) the hydrogen bond acidity (ET(30)) y=-0.20x+13.39, R²=0.359 for both H-acceptors 444 and H-donors, y=-0.36x+15.65, R²=0.643 for H-acceptors only and (c) the hydrogen bond 445 basicity (β_1).

-

457	Figures
458	
459	Figure 1.







487 **Figure 2.**

488



491 **Figure 3.**

492



494	Table 1. Molecular structure of each compound investigated with the carbon atoms numbered in
495	decreasing chemical shift in the ¹³ C NMR spectrum. The code of each sample used in Fig. 3 and
496	4 and in the Tables is also defined.

497

code	compound	structure	code	compound	structure	
al-1	methanol	1 ^{_OH}	brom	bromoethane	2 ⁻¹ -Br	
al-2	ethanol	2 ^{_1} _0H			ÇI	
al-3	propan-1-ol	3 ⁻² 1-OH	TCE	trichloroethylene	H_2 ^{/1} _Cl Cl	
al-4	propan-2-ol	HO_1_2 1 2	acet	acetone	0 2 ⁻¹ -2	
al-5	butan-1-ol	4 ⁻³ 2 ⁻¹ OH	4hep	4-heptanone	4-3-2-1-2-3-4 0	
al-6	<i>tert-</i> butanol (TBA)	2 2-1-OH 2	acni	acetonitrile	2−1≡N	
al-7	2-methyl-2-butanol	4 ⁻² -1<3 3OH	etac	ethyl acetate	0 1 3 ⁻¹ -0 ⁻² -4	
al-8	pentan-1-ol	5 ⁻⁴ -3 ⁻² 1-OH	MTBE	МТВЕ	3_1-0_2	
al-9	cyclohexanol	4 ⁴⁻² 3 4-2 1-ОН 4-2	tol	toluene	4 ³⁻² 3=2 ¹⁻⁵	
chlo	chloroform	CI−1−H CI	hept	<i>n</i> -heptane	4_3_1_2_1_3_4	

498

Table 2. ¹³C isotope composition δ in ‰ and the difference between ¹³C content of the starting material and of the distillate $\delta\Delta$ in ‰ for bulk isotopologue and each isotopomer of the studied samples (see Table 1 for denomination and carbon numbering).

503

Sample		Bulk	C-1	C-2	C-3	C-4	C-5
	δ ¹³ C initial	-30.7	-30.7				
al-1	δ ¹³ C distillate	-28.5	-28.5				
	Δδ ¹³ C	+2.2	+2.2				
	δ ¹³ C initial	-28.9	-32.2	-25.5			
al-2	δ ¹³ C distillate	-24.8	-27.5	-22.0			
	Δδ ¹³ C	+4.2	+4.7	+3.6			
	δ ¹³ C initial	-32.6	-35.5	-28.1	-34.1		
al-3	δ ¹³ C distillate	-29.2	-31.1	-25.1	-31.5		
	Δδ ¹³ C	+3.4	+4.5	+3.1	+2.6		
	δ ¹³ C initial	-26.9	-22.6	-29.1			
al-4	δ ¹³ C distillate	-24.4	-17.6	-27.7			
	Δδ ¹³ C	+2.6	+5.0	+1.3			
	δ ¹³ C initial	-31.0	-42.7	-29.1	-24.9	-28.5	
al-5	δ ¹³ C distillate	-28.3	-37.7	-26.1	-22.4	-25.6	
	Δδ ¹³ C	+2.8	+5.0	+3.0	+2.6	+2.9	
	δ ¹³ C initial	-25.4	-17.1	-28.2			
al-6	δ ¹³ C distillate	-23.9	-15.0	-26.9			
	Δδ ¹³ C	+1.5	+2.1	+1.3			
	δ ¹³ C initial	-31.2	-20.6	-28.0	-28.5	-50.5	
al-7	δ ¹³ C distillate	-28.8	-15.1	-26.3	-27.1	-48.3	
	Δδ ¹³ C	+2.4	+5.5	+1.7	+1.4	+2.1	
	δ ¹³ C initial	-28.3	-36.5	-23.9	-27.8	-26.2	-27.1
al-8	δ ¹³ C distillate	-25.5	-32.4	-21.3	-25.3	-24.2	-24.4
	Δδ ¹³ C	+2.8	+4.1	+2.6	+2.5	+2.0	+2.7
	δ ¹³ C initial	-24.4	-39.0	-17.2	-18.9	-26.9	
al-9	δ ¹³ C distillate	-22.2	-33.9	-17.8	-17.4	-23.0	
	$\Delta \delta^{13} C$	+2.2	+5.1	-0.5	+1.5	+3.9	
	δ ¹³ C initial	-41.7					
chlo	δ^{13} C distillate	-33.4					
	Δδ ¹³ C	+8.4					

508

507 **Table 2.** (continued)

Sample		Bulk	C-1	C-2	C-3	C-4	C-5
	δ^{13} C initial	-11.6	-12.7	-10.4			
brom	δ^{13} C distillate	-6.6	-4.2	-9.0			
	Δδ ¹³ C	+5.0	+8.6	+1.5			
	δ ¹³ C initial	-29.6	-30.9	-28.3			
TCE	δ ¹³ C distillate	-24.6	-24.5	-24.8			
	$\Delta \delta^{13} C$	+4.9	+6.4	+3.5			
	δ ¹³ C initial	-22.3	+8.8	-37.9			
acet	δ^{13} C distillate	-22.6	+10.6	-39.1			
	Δδ ¹³ C	-0.2	+1.8	-1.2			
	$\delta^{13}C$ initial	-28.2	-23.5	-26.7	-29.0	-31.4	
4hep	δ^{13} C distillate	-26.4	-16.5	-26.4	-27.5	-30.2	
	Δδ ¹³ C	+1.8	+7.0	+0.3	+1.4	+1.2	
	δ ¹³ C initial	-24.5	-2.7	-46.3			
acni	δ^{13} C distillate	-25.2	-5.2	-45.3			
	Δδ ¹³ C	-0.7	-2.5	+1.0			
	δ ¹³ C initial	-30.6	-19.5	-48.1	-30.7	-29.6	
etac	δ^{13} C distillate	-27.5	-15.5	-42.5	-31.0	-29.0	
	Δδ ¹³ C	+3.1	+4.0	+5.6	-0.3	+0.5	
	δ ¹³ C initial	-28.6	-22.1	-39.3	-27.3		
MTBE	δ^{13} C distillate	-26.1	-15.1	-37.4	-25.9		
	Δδ ¹³ C	+2.6	+7.0	+1.8	+1.4		
	δ ¹³ C initial	-22.8	-10.4	-23.3	-26.4	-26.1	-23.5
tol	δ^{13} C distillate	-19.6	-6.5	-21.1	-22.9	-22.6	-20.3
	Δδ ¹³ C	+3.2	+3.9	+2.2	+3.6	+3.6	+3.2
	δ ¹³ C initial	-27.5	-25.3	-34.3	-26.3	-27.6	
hept	δ^{13} C distillate	-25.1	-23.2	-31.2	-24.0	-25.0	
	Δδ ¹³ C	+2.4	+2.0	+3.1	+2.3	+2.6	

- 509 **Table 3.** Isotope effect IE in ‰ for bulk and isotopomer C-1, relative permittivity (dielectric 510 constant) diE, solvent hydrogen-bond acidity ET(30) and hydrogen-bond basicity β_1 of the
- 511 studied samples (see Table 1 for denomination).
- 512

code	IE _{bulk}	IE _{C-1}	ET(30)	β1	dielectric constant
al-1	+2.3	+2.3	55.4	0.54	33.0
al-2	+4.3	+4.8	51.8	0.62	24.5
al-3	+3.5	+4.6	50.5	0.65	20.3
al-4	+2.6	+5.1	48.4	0.68	20.3
al-5	+2.9	+5.2	49.7	0.67	17.5
al-6	+1.5	+2.2	nd	0.73	12.5
al-7	+2.5	+5.6	41.5	0.71	nd
al-8	+2.9	+4.3	49.3	0.70	nd
al-9	+2.3	+5.2	47.2	0.73	nd
chlo	+8.7	+8.7	39.1	nd	4.8
brom	+5.1	+8.6	37.8	0.12	9.4
TCE	+5.1	+6.6	35.9	nd	nd
acet	-0.2	+1.8	42.3	0.49	21.1
2hep	+1.3	-0.2	nd	nd	nd
3hep	+1.8	+1.1	nd	nd	nd
4hep	+1.9	+7.1	36.0	nd	nd
acni	-0.7	-2.5	45.6	0.37	36.6
etac	+3.2	+4.1	nd	0.52	6.1
MTBE	+2.6	+7.1	33.0	nd	nd
TAME	+3.5	+6.7	nd	nd	nd
tol	+3.2	+3.9	33.9	0.15	nd
hept	+2.5	+2.1	30.9	0.00	nd

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515

517 Table of Contents (TOC) graphic

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