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Glycerol Acetals and Ketals as Bio-based Solvents: Positioning in Hansen and COSMO-RS spaces, Volatility and Stability towards Hydrolysis and Autoxidation

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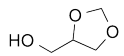
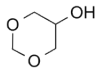
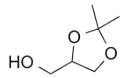
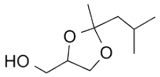
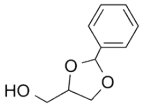
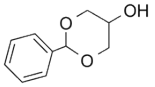
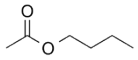
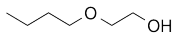
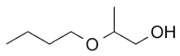
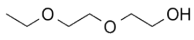
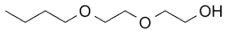
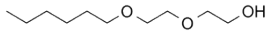
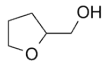
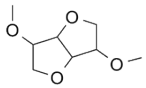
Table 1: Number, name and structure of the glycerol acetals/ketals and of the various oxygenated solvents studied in this work. The experimental boiling points (b.p.) at atmospheric pressure reported in SciFinder are given. For **4**, the value reported at reduced pressure has been extrapolated at atmospheric pressure (in italics) using the Pressure-Temperature nomograph based on the Clausius-Clapeyron equation. $T_{50\%}$ is the temperature at which half of the sample has vaporised during an ATG experiment (see text). It allows predicting a b.p. value, also indicated (see text). The Hansen solubility parameters δ_d, δ_p and δ_h are the ones provided by Hansen[50] or calculated using the Yamamoto Molecular Breaking (Y-MB) method implemented in the HSPiP software (HSPiP, version 4.0.05). The F1, F2, F3, F4 coordinates in the COSMO-RS are also provided, as described in references [51] and [7].

N°	Name	Structure	experimental b.p. (°C)	$T_{50\%}$ (°C)	estimated b.p. (°C)	δ_d (MPa$^{1/2}$)	δ_p (MPa$^{1/2}$)	δ_h (MPa$^{1/2}$)	F□	F2	F3	F4
1a	Glycerol formal (dioxolane)		194	118	208	18.0	10.6	15.9	-4.93	2.61	-0.83	-0.93
1b	Glycerol formal (dioxane)					18.2	10.9	16.3	-5.54	3.47	-0.73	-0.87
2	Solketal		189	104	188	16.6	7.7	12.0	-3.12	1.07	1.11	-0.88
3	1-2-Methylisobutylidene glycerol		n.d.	128	224	16.5	6.2	9.3	-1.49	0.71	2.63	-0.31
4a	Benzaldehyde glycerol acetal (dioxolane)		*309*	193	318	18.4	7.2	11.0	-2.50	1.66	0.43	-1.40
4b	Benzaldehyde glycerol acetal (dioxane)					18.6	7.4	11.4	-2.57	3.21	2.27	-0.80
5	1,3-Dioxolane		74.5	33	85	18.1	6.6	9.3	-1.06	-2.04	-2.98	-1.61

6	2-Methyl-1,3-dioxolane		82	28	77	17.3	4.8	5.8				
7	2,2-Dimethyl-1,3-dioxolane		92.5	36	89	16.1	5.6	5.3				
8	2,2,4-Trimethyl-1,3-dioxolane		100	33	85	15.9	4.7	4.2				
9	1,4-Dioxane		101	39	94	19.0	1.8	7.4	-3.64	-6.23	-0.75	-1.17
10	Methylal		42	23	70	15.6	6.8	6.5	-1.59	-5.60	0.29	-0.35
11	Ethylal		88	38	92	15.4	5.8	5.1	2.04	-3.99	1.12	0.62
12	*n*-Butyl acetate		125	46	104	15.8	3.7	6.3	1.69	-2.34	-0.14	-0.36
13	Ethylene glycol *n*-butyl ether (C_4E_1)		171	83	158	16.0	5.1	12.3	-4.53	-0.99	4.64	0.08
14	Propylene glycol *n*-butyl ether (C_4P_1)		172	93	172	16.0	5.7	11.6	-0.99	-1.76	2.84	0.35
15	Diethylene glycol ethyl ether (C_2E_2)		200	110	198	16.1	9.2	12.2	-1.39	-1.14	1.75	0.37

16	Diethylene glycol butyl ether (C_4E_2)		231	130	226	16.0	7.0	10.6	-0.70	-3.16	1.89	0.31
17	Diethylene glycol hexyl ether (C_6E_2)		260	154	261	16.0	6.0	10.0	-0.65	0.07	3.27	0.96
18	Tetrahydrofurfuryl alcohol		178	92	171	17.8	8.2	12.9	-4.00	1.13	1.55	-0.08
19	Dimethyl isosorbide		234	142	244	17.6	7.1	7.5	-0.98	-2.73	-2.10	-1.35

Synthesis of Benzaldehyde Glycerol Acetal (BGA) 4a + 4b

Material and methods

For syntheses of **4a** + **4b**, glycerol (Sigma-Aldrich, 98%), benzaldehyde (Sigma-Aldrich, 98%) and cyclohexane (Sigma-Aldrich, 99%) were used. The cation exchange resin catalyst, Amberlyst-15, commercially available from Fluka, had a capacity of 4.7 meq H^+/g and an average particle size of 600-850 μm. As a pre-treatment before the experiments, the resin was washed with distilled water, methanol then ether. It was dried under vacuum for 10 h at 40 °C.

Gas Chromatography analysis

Chromatograms were obtained using Varian 3800 GC instrument coupled to a flame ionisation detector (FID). The silica capillary column (Stabilwax, 30 m) was supplied by Restek Corporation. The carrier gas was helium (Air Liquide, France) delivered at a flow rate of 1.7 mL/min. The injector and detector temperatures were set at 250 °C.
The oven temperature was held at 60°C for 1 min, ramped up to 240 °C at 20 °C/min and held for 10 min at this temperature. The retention times for the relevant compounds are 2 min, for cyclohexane, 3.8 min for dodecane, 6.3 min for benzaldehyde, 10.4 min for glycerol, 12.4 min for *cis*-**4b**, 12.8 min for *cis*-**4a**, 13.5 min for *trans*-**4a**, 16.1 min for *trans*-**4b**. **4b** as the 6-member ring is a 1,3-dioxane derivative called 2-phenyl-(1,3)dioxan-5-ol and **4a** as the 5-member ring is a 1,3-dioxolane derivative called (2-phenyl-(1,3)dioxolan-4-yl)-methanol.
Dodecane was added in samples of reaction mixture as an internal standard before analysis by gas chromatography. Benzaldehyde conversion (X_B), acetals yield (Y_{BGA}) and products selectivity (S_i) were calculated according to the following expressions:

$$X_B(\%) = \left(1 - \frac{n^{reacted}_{benzaldehyde}}{n^{initial}_{benzaldehyde}}\right) \times 100, \quad Y_{BGA}(\%) = \frac{n_{BGA}}{n^{initial}_{benzaldehyde}} \times 100, \quad S_{4a}(\%) = \frac{n_{4a}}{n_{4a} + n_{4b}} \times 100, \quad S_{4b}(\%) = \frac{n_{4b}}{n_{4a} + n_{4b}} \times 100$$

Preparation of benzaldehyde glycerol acetal (BGA)

Acetalisation reactions of glycerol with benzaldehyde were carried out in a 100 mL glass multi-reactors device equipped with a magnetic stirrer, a thermometer and a heating controller. Dean–Stark apparatus was used to remove continuously the water *via* its hetero-azeotrope with cyclohexane (69.5 °C, 91.6% wt./wt. cyclohexane). The magnetically stirring was fixed at 150 rpm for all the experiments to avoid external diffusion limitation.
In a typical experiment, an equimolar mixture of glycerol (6.3 g, 68.5 mol) and benzaldehyde (7.3 g, 68.5 mol) was stirred with pre-activated Amberlyst-15 (4% mol, 4.7 mmol H^+/g) and cyclohexane (10 mL). The reaction was conducted under reflux for 3 hours. At the end of the reaction, the medium was diluted with ethyl acetate, filtered immediately and concentrated under vacuum to remove the solvent.

Results and discussion

As described by Deutsch et al.,[43] acetalisation of glycerol and benzaldehyde yields cyclic acetals composed of 1,3-dioxolane and 1,3-dioxane derivatives. The authors have identified several factors that govern the yield and selectivity of acetal isomers among which temperature, reaction time and nature of solvent. The influence of these different parameters on the synthesis of benzaldehyde glycerol acetal (BGA) **4a** + **4b** was investigated by using Amberlyst-15. Cyclohexane has been selected as solvent because it matches the requirements of compatibility with the medium and equilibrium shift by forming an azeotropic mixture with water.

First, the effect of reaction temperature was investigated in order to control the isomers ratios (Table 2).

Table 2: Effect of reaction temperature (T) and time (t) on benzaldehyde conversion (X_B), yield (Y_{BGA}) and selectivity of benzaldehyde glycerol acetal isomers **4a** and **4b**. Conditions: molar ratio glycerol:benzaldehyde 1:1, 4% Amberlyst-15, 10 mL cyclohexane, 150 rpm.

T (°C)	t (h)	X_B (%)	Y_{BGA} (%)	**4a** (%)	**4b** (%)
Reflux	3	89	84	56	44
40	16	58	54	50	50
30	16	43	37	44	56
Reflux[(a)]	3	89	84	42	58
Reflux[(b)]	3	88	82	54	46

[(a)] + overnight at room temperature in the presence of Amberlyst-15 resin, [(b)] + overnight at room temperature after removing catalyst

The results in Table 2 show that the selectivity of acetal isomers is quite dependent on the temperature / catalyst couple. The highest proportion of 1,3-dioxolane derivative **4a** is 56% after a reaction conducted for 3 hours at reflux temperature, and decreases when lower temperatures are used. Therefore, the formation of the six-membered cyclic acetal seems to be enhanced under mild temperatures (30 °C in cyclohexane), which is compliant with the results reported by Deutsch, under refluxing dichloromethane as a low boiling point solvent.[43] We also found that the 1,3-dioxane derivative **4b** slightly predominates (58%), by keeping the reaction mixture overnight at room temperature, in the presence of Amberlyst-15 resin, while the ratio **4a**:**4b** does not change in the same conditions without catalyst. In fact, a ring-transformation process occurs according to the acid-catalysed equilibrium previously described.[43]
As expected, increased temperature improved the conversion of benzaldehyde into acetals, therefore the azeotropic reflux temperature was kept for the following experiments.

Table 3 shows the effect of varying the solvent amount and the catalyst loading on the production of glycerol acetals. The results for the three cyclohexane volumes tested presented in Table 3 show that an increase of solvent content in the reaction mixture does not significantly change the selectivity towards five/six-membered cyclic acetals. The best acetals yield of 82% was obtained for 10 mL, meaning that the maximum of water was removed by azeotropic distillation.
The increase in catalyst loading from 1 to 5 mol % has a slight effect on the reaction kinetics since acetals yields vary from 80 to 84%. From 4 mol %, the number of available active catalytic sites is enough to ensure an adsorption process of reactant on catalyst surface.
The results illustrate that the varying amounts of solvent and of resin always direct the selectivity in favor of the 5-membered ring isomer **4a**, which is the kinetic product. Finally, 10 mL of solvent and 4% of Amberlyst-15 were kept for kinetic studies.

Table 3: Effect of catalyst loading (Cat) and solvent amount (V_{cyclo}) on benzaldehyde conversion (X_B), yield (Y_{BGA}) and selectivity of benzaldehyde glycerol acetal isomers **4a** and **4b**. Catalyst loading is given in mol. % towards glycerol. Conditions: molar ratio glycerol:benzaldehyde 1:1, refluxing temperature, 3h, 150 rpm.

Cat (%)	V_{cyclo} (mL)	X_B (%)	Y_{BGA} (%)	**4a**	**4b**
1	10	85	80	55	45
3	10	89	83	56	44
4	10	89	84	56	44
5	10	86	82	56	44
5	5	83	73	57	43
5	20	88	82	53	47

While keeping these experimental conditions, acetalisation reaction was monitored over time. The results are given in Figure 1.

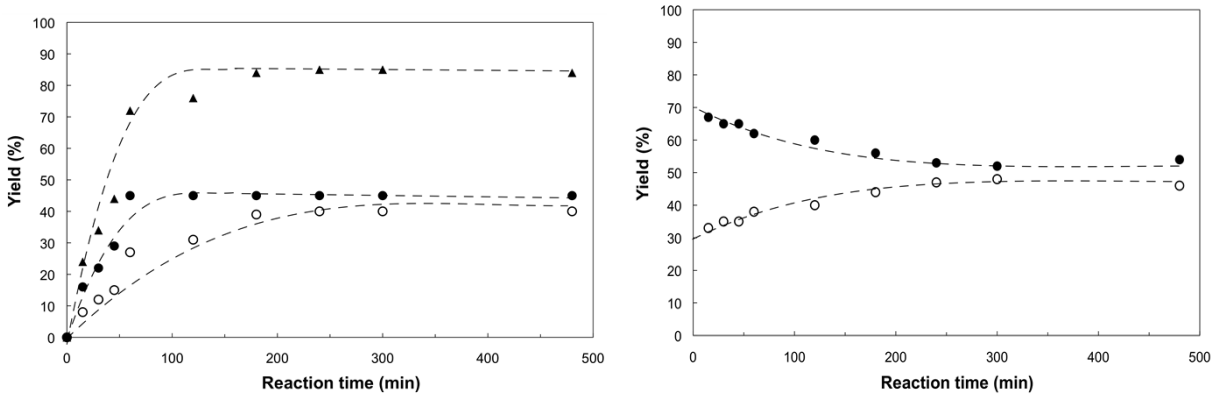


Figure 1: Kinetics of the Amberlyst-15-catalysed condensation of glycerol with benzaldehyde. Left: evolution of the total benzaldehyde glycerol acetal **4** (triangles), isomers **4a** (black dots) and **4b** (empty dots); right: evolution of the ratio of isomers **4a** (black dots) and **4b** (empty dots) in the product formed. Conditions: molar ratio glycerol:benzaldehyde 1:1, 4 mol.% Amberlyst-15, 10 mL refluxing cyclohexane, 150 rpm

Figure 1 (left) confirms that a maximum yield in BGA (84%) is reached after 3 h of reaction. On the other hand, the percentage of isomers presented in Figure 2 (right) indicates that the five-membered cyclic acetal **4a** is the major product during the whole reaction; the initial ratio 65/35 **4a**/**4b** tends towards an equilibrium corresponding to about 50% of each isomer, reached after 4 h reaction time. This result confirms that 1,3-dioxolane **4a** is the kinetic product. We have checked that the maximal yield was obtained after 3 h, corresponding to a 56/44 ratio for 1,3-dioxolane **4a** / 1,3-dioxane **4b**. After a distillation under vacuum of this mixture, the distribution switched towards 66/34, due to an enrichment in 1,3-dioxolane derivative **4a**, of lower boiling point. This fraction enriched in 1,3-dioxolane compound **4a** has been selected for hydrolysis studies.

Finally, the experimental conditions proposed allow a quick acetalisation reaction with a high yield. Moreover, factors acting on the selectivity have been identified. It is thus possible to design a specific composition by tuning parameters during the reaction (reaction time or temperature), as well as during the post-reaction treatments (contact with acid catalyst or distillation).

Table 4: Name, CAS number, Hansen solubility parameters and coordinates in COSMO-RS space of the 88 traditional solvents of Hansen's work[50].

Name	CAS	δ_d	δ_p	δ_h	F1	F2	F3	F4
1-Bromonaphthalene	90-11-9	20.6	3.1	4.1	6.33	3.05	-0.79	3.31
1-Butanol	71-36-3	16	5.7	15.8	-5.42	2.51	5.67	1.50
1-Chlorobutane	109-69-3	16.2	5.5	2	6.14	0.27	0.75	1.89
1-Pentanol	71-41-0	15.9	5.9	13.9	-4.80	2.15	6.17	2.11
1-Propanol	71-23-8	16	6.8	17.4	-6.34	2.87	5.29	1.53
1,1,1-Trichloroethane	71-55-6	16.8	4.3	2	7.56	2.03	0.19	1.72
1,3-Butanediol	107-88-0	16.5	8.1	20.9	-6.98	-0.69	4.40	1.80
1,4-Dioxane	123-91-1	17.5	1.8	9	-3.64	-6.23	-0.75	-1.17
2-Ethyl-1-Butanol	97-95-0	15.8	4.3	13.5	-4.66	3.44	6.16	1.87
2-Ethyl-Hexanol	104-76-7	15.9	3.3	11.8	-3.79	2.78	6.57	2.60
2-Nitropropane	79-46-9	16.2	12.1	4.1	0.84	-0.15	-1.45	2.64
Acetic Acid	64-19-7	14.5	8	13.5	-10.23	8.59	3.51	0.58
Acetic Anhydride	108-24-7	16	11.7	10.2	-2.02	-1.37	-3.33	0.86
Acetone	67-64-1	15.5	10.4	7	-3.75	-5.34	-1.87	-0.25
Acetonitrile	75-05-8	15.3	18	6.1	-5.26	1.58	-8.86	2.56
Acetophenone	98-86-2	18.8	9	4	-1.66	-4.16	0.53	1.85
Aniline	62-53-3	20.1	5.8	11.2	-3.56	4.74	1.17	-0.57
Benzaldehyde	100-52-7	19.4	7.4	5.3	-1.16	-2.96	0.01	1.98
Benzene	71-43-2	18.4	0	2	6.20	2.30	-0.78	2.44
Butyl Lactate	138-22-7	15.8	6.5	10.2	-3.70	-0.01	3.65	0.11
Butyric Acid	107-92-6	15.7	4.8	12	-7.86	8.18	5.64	-0.83
Butyronitrile	109-74-0	15.3	12.4	5.1	-0.57	-1.02	-2.74	1.95
Carbon Disulfide	75-15-0	20.2	0	0.6	8.57	3.73	0.44	9.82
Carbon Tetrachloride	56-23-5	17.8	0	0.6	9.26	1.64	0.59	3.53
Chlorobenzene	108-90-7	19	4.3	2	6.60	2.52	-0.26	2.19
Chlorocyclohexane	542-18-7	17.3	5.5	2	6.20	-0.24	1.07	2.25
Chloroform	67-66-3	17.8	3.1	5.7	4.26	4.90	0.29	-1.91
Cyclohexane	110-82-7	16.8	0	0.2	9.58	2.06	0.83	6.04
Cyclohexanol	108-93-0	17.4	4.1	13.5	-6.05	2.85	6.06	0.31

Cyclohexanone	108-94-1	17.8	8.4	5.1	-1.84	-6.39	0.88	0.50
Cyclohexylamine	108-91-8	17.2	3.1	6.5	-5.15	-8.18	4.62	1.37
Di-(2-Chloroethyl) Ether	111-44-4	18.8	9	5.7	2.52	-0.91	0.75	1.03
Di-Isobutyl Ketone	108-83-8	16	3.7	4.1	1.48	-4.57	2.40	2.94
Diacetone Alcohol	123-42-2	15.8	8.2	10.8	-4.96	-4.44	1.92	-0.14
Diethyl Amine	109-89-7	14.9	2.3	6.1	-6.89	-11.72	6.55	-0.49
Diethyl Ether	60-29-7	14.5	2.9	4.6	-0.46	-7.43	3.45	1.50
Diethyl Sulfide	352-93-2	16.8	3.1	2	3.30	-2.19	0.95	2.41
Diethylene Glycol	111-46-6	16.6	12	19	-8.23	1.64	0.87	0.04
Diethylene Glycol Monobutyl Ether	112-34-5	16	7	10.6	-4.58	-1.37	4.23	-0.37
Diethylene Glycol Monomethyl Ether	111-77-3	16.2	7.8	12.6	-6.42	-1.70	1.89	-1.69
Dimethyl Formamide	68-12-2	17.4	13.7	11.3	-5.88	-7.01	-2.86	-1.31
Dimethyl Sulfoxide	67-68-5	18.4	16.4	10.2	-10.03	-7.40	-7.14	-2.40
Dipropyl Amine	142-84-7	15.3	1.4	4.1	-5.92	-11.26	6.72	0.51
Dipropylene Glycol	2396-61-4	16.5	10.6	17.7	-7.78	-0.07	3.98	-1.03
Ethanol	64-17-5	15.8	8.8	19.4	-7.49	2.74	4.29	1.52
Ethanolamine	141-43-5	17	15.5	21	-9.54	-0.90	-0.55	2.56
Ethyl Acetate	141-78-6	15.8	5.3	7.2	-1.47	-4.53	-0.19	0.95
Ethyl Benzene	100-41-4	17.8	0.6	1.4	7.15	1.94	-0.23	3.02
Ethyl Lactate	97-64-3	16	7.6	12.5	-8.09	4.34	3.12	-2.28
Ethylene Dichloride	107-06-2	18	7.4	4.1	4.89	1.87	0.35	0.15
Ethylene Glycol	107-21-1	17	11	26	-10.61	4.82	1.06	2.84
Ethylene Glycol Monobutyl Ether	111-76-2	16	5.1	12.3	-4.53	-0.99	4.64	0.08
Ethylene Glycol Monoethyl Ether	110-80-5	15.9	7.2	14	-1.93	-6.22	1.41	0.49
Ethylene Glycol Monoethyl Ether Acetate	111-15-9	15.9	4.7	10.6	-1.12	-4.89	0.59	0.92
Ethylene Glycol Monomethyl Ether	109-86-4	16	8.2	15	-7.12	0.26	2.17	-1.30
Formic Acid	64-18-6	14.6	10	14	-10.66	11.47	7.30	2.43
Furan	110-00-9	17	1.8	5.3	3.30	1.38	0.11	2.09
Glycerol	56-81-5	17.4	11.3	27.2	-11.31	5.78	1.74	2.50
Hexane	110-54-3	14.9	0	0	9.46	2.08	0.73	5.90
Isoamyl Acetate	123-92-2	15.3	3.1	7	0.36	-4.43	1.35	2.16
Isobutyl Isobutyrate	97-85-8	15.1	2.8	5.8	1.31	-4.55	2.12	2.89

Isophorone	78-59-1	17	8	5	-2.37	-7.20	1.45	0.61
m-Cresol	108-39-4	18.5	6.5	13.7	-9.70	14.02	4.87	-6.34
Mesityl Oxide	141-79-7	16.4	7.2	5	-2.64	-7.52	1.96	0.97
Methanol	67-56-1	14.7	12.3	22.3	-8.81	2.65	2.26	2.62
Methyl Ethyl Ketone	78-93-3	16	9	5.1	-2.34	-5.61	0.01	0.43
Methyl Isoamyl Ketone	110-12-3	16	5.7	4.1	-0.56	-5.53	1.80	1.73
Methyl Isobutyl Carbinol	108-11-2	15.4	3.3	12.3	-6.35	3.21	6.04	-0.73
Methyl Isobutyl Ketone	108-10-1	15.3	6.1	4.1	-1.05	-5.87	1.75	1.56
Methylal	109-87-5	15	1.8	8.6	-1.59	-5.60	0.29	-0.35
Methylene Dichloride	75-09-2	17	7.3	7.1	5.10	2.98	0.67	-0.29
Morpholine	110-91-8	18	4.9	11	-8.16	-8.89	2.32	-0.81
n-Butyl Acetate	123-86-4	15.8	3.7	6.3	-0.14	-4.71	1.32	1.87
Nitrobenzene	98-95-3	20	10.6	3.1	1.53	0.00	-0.02	2.89
Nitroethane	79-24-3	16	15.5	4.5	-0.66	0.84	-2.32	2.85
Nitromethane	75-52-5	15.8	18.8	6.1	-3.08	2.89	-1.61	5.63
o-Dichlorobenzene	95-50-1	19.2	6.3	3.3	7.01	2.50	-0.02	2.12
o-Xylene	95-47-6	17.8	1	3.1	6.74	1.36	0.03	2.74
p-Xylene	106-42-3	17.8	1	3.1	7.22	1.89	-0.23	3.18
Propylene Carbonate	108-32-7	20	18	4.1	-4.02	-0.37	-5.03	1.71
Propylene Glycol	57-55-6	16.8	10.4	21.3	-8.51	2.73	3.42	1.15
Pyridine	110-86-1	19	8.8	5.9	-4.75	-6.51	0.49	1.35
Styrene	100-42-5	18.6	1	4.1	6.04	2.20	-0.57	2.30
Tetrahydrofuran	109-99-9	16.8	5.7	8	-2.41	-8.68	2.75	-0.31
Tetrahydronaphthalene	119-64-2	19.6	2	2.9	7.24	1.25	0.39	3.10
Toluene	108-88-3	18	1.4	2	6.85	2.00	-0.37	2.73
Trichloroethylene	79-01-6	18	3.1	5.3	7.46	2.62	0.24	1.85
γ-Butyrolactone	96-48-0	18	16.6	7.4	-4.68	-2.83	-5.74	-0.32

Table 5: Ranking of the 88 traditional solvents of Hansen's work[50] as regards to their proximity to acetals **1** to **4** according to the Hansen approach.

Classical solvents	**Ranking from acetal/ketal**				
	1a	**1b**	**2**	**3**	**4a**
1-Bromonaphthalene	71	70	76	68	50
1-Butanol	12	13	16	44	32
1-Chlorobutane	72	73	61	48	68
1-Pentanol	14	15	8	19	17
1-Propanol	7	8	25	59	41
1,1,1-Trichloroethane	76	76	65	53	61
1,3-Butanediol	13	11	52	79	70
1,4-Dioxane	42	43	29	22	19
2-Ethyl-1-Butanol	25	26	12	21	24
2-Ethyl-Hexanol	31	31	20	13	23
2-Nitropropane	52	52	55	55	58
Acetic Acid	23	25	17	39	42
Acetic Anhydride	16	17	19	32	26
Acetone	35	38	26	26	37
Acetonitrile	61	60	77	80	83
Acetophenone	48	48	56	52	35
Aniline	24	21	36	49	3
Benzaldehyde	45	44	50	47	20
Benzene	83	83	81	69	75
Butyl Lactate	27	27	6	2	11
Butyric Acid	28	28	10	9	18
Butyronitrile	50	51	51	54	64
Carbon Disulfide	87	86	87	82	79
Carbon Tetrachloride	85	85	82	75	78
Chlorobenzene	75	74	72	63	57
Chlorocyclohexane	70	71	62	51	55
Chloroform	54	53	42	30	29
Cyclohexane	86	87	83	76	82
Cyclohexanol	15	16	14	24	4
Cyclohexanone	40	41	37	29	21
Cyclohexylamine	49	49	34	15	25
Di-(2-Chloroethyl) Ether	39	39	40	42	15
Di-Isobutyl Ketone	67	68	53	34	49
Diacetone Alcohol	18	19	4	7	10

Diethyl Amine	68	69	49	37	59
Diethyl Ether	74	75	59	45	73
Diethyl Sulfide	79	81	67	56	69
Diethylene Glycol	2	2	43	77	62
Diethylene Glycol Monobutyl Ether	21	22	3	3	8
Diethylene Glycol Monomethyl Ether	5	9	1	12	6
Dimethyl Formamide	6	6	27	57	30
Dimethyl Sulfoxide	26	23	57	73	52
Dipropyl Amine	77	78	64	50	72
Dipropylene Glycol	1	1	28	65	44
Ethanol	9	7	39	72	63
Ethanolamine	19	14	74	86	81
Ethyl Acetate	41	42	24	6	28
Ethyl Benzene	84	84	80	67	77
Ethyl Lactate	11	12	2	10	9
Ethylene Dichloride	51	50	45	40	31
Ethylene Glycol	36	32	84	87	87
Ethylene Glycol Monobutyl Ether	22	24	7	8	12
Ethylene Glycol Monoethyl Ether	8	10	5	23	16
Ethylene Glycol Monoethyl Ether Acetate	29	30	11	4	14
Ethylene Glycol Monomethyl Ether	3	4	9	41	22
Formic Acid	17	18	23	46	47
Furan	65	65	54	38	43
Glycerol	44	40	88	88	88
Hexane	88	88	86	78	86
Isoamyl Acetate	55	56	35	17	45
Isobutyl Isobutyrate	66	67	46	31	56
Isophorone	43	45	31	20	27
m-Cresol	4	3	15	36	2
Mesityl Oxide	47	47	30	16	34
Methanol	30	29	73	85	85
Methyl Ethyl Ketone	46	46	32	25	38
Methyl Isoamyl Ketone	59	63	44	27	46
Methyl Isobutyl Carbinol	34	35	22	18	36
Methyl Isobutyl Ketone	64	64	47	33	54
Methylal	56	58	38	28	48
Methylene Dichloride	33	33	21	5	7
Morpholine	20	20	13	11	1
n-Butyl Acetate	53	54	33	14	39
Nitrobenzene	60	59	71	70	51

Nitroethane	58	55	66	71	76
Nitromethane	62	61	79	83	84
o-Dichlorobenzene	63	62	60	58	40
o-Xylene	80	79	69	61	66
p-Xylene	81	80	70	62	67
Propylene Carbonate	69	66	85	84	80
Propylene Glycol	10	5	58	81	74
Pyridine	37	37	41	43	13
Styrene	73	72	68	60	53
Tetrahydrofuran	32	34	18	1	5
Tetrahydronaphthalene	78	77	78	66	60
Toluene	82	82	75	64	71
Trichloroethylene	57	57	48	35	33
γ-Butyrolactone	38	36	63	74	65

Table 6: Ranking of the 88 traditional solvents of Hansen's work[50] as regards to their proximity to acetals **1** to **4** according to the COSMO-RS approach.

Classical solvents	**Ranking from acetal/ketal**			
	1a	**1b**	**2**	**3**
1-Bromonaphthalene	71	71	68	64
1-Butanol	6	6	8	16
1-Chlorobutane	70	70	63	56
1-Pentanol	12	12	7	11
1-Propanol	7	7	17	26
1,1,1-Trichloroethane	82	82	79	74
1,3-Butanediol	22	22	21	30
1,4-Dioxane	43	43	43	47
2-Ethyl-1-Butanol	13	13	14	15
2-Ethyl-Hexanol	20	20	9	10
2-Nitropropane	30	30	20	4
Acetic Acid	40	40	71	80
Acetic Anhydride	24	24	5	9
Acetone	37	37	36	42
Acetonitrile	23	23	35	52
Acetophenone	35	35	26	17
Aniline	1	1	4	12
Benzaldehyde	31	31	18	8
Benzene	68	68	67	60
Butyl Lactate	4	4	1	1
Butyric Acid	33	33	59	75
Butyronitrile	27	27	13	5
Carbon Disulfide	86	86	86	83
Carbon Tetrachloride	85	85	82	78
Chlorobenzene	73	73	69	62
Chlorocyclohexane	72	72	66	58
Chloroform	54	54	55	48
Cyclohexane	88	88	87	82
Cyclohexanol	10	10	16	22
Cyclohexanone	52	52	47	44
Cyclohexylamine	62	62	61	72
Di-(2-Chloroethyl) Ether	42	42	33	13
Di-Isobutyl Ketone	58	58	49	33
Diacetone Alcohol	32	32	27	32
Diethyl Amine	84	84	84	86
Diethyl Ether	63	63	60	55

Diethyl Sulfide	56	56	50	29
Diethylene Glycol	3	3	24	45
Diethylene Glycol Monobutyl Ether	21	21	3	6
Diethylene Glycol Monomethyl Ether	16	16	15	25
Dimethyl Formamide	53	53	56	68
Dimethyl Sulfoxide	67	67	80	85
Dipropyl Amine	83	83	81	84
Dipropylene Glycol	19	19	22	38
Ethanol	9	9	23	39
Ethanolamine	28	28	46	61
Ethyl Acetate	38	38	29	20
Ethyl Benzene	77	77	74	70
Ethyl Lactate	14	14	31	51
Ethylene Dichloride	59	59	53	43
Ethylene Glycol	29	29	58	76
Ethylene Glycol Monobutyl Ether	17	17	2	3
Ethylene Glycol Monoethyl Ether	49	49	45	40
Ethylene Glycol Monoethyl Ether Acetate	39	39	32	23
Ethylene Glycol Monomethyl Ether	2	2	12	27
Formic Acid	66	66	83	87
Furan	45	45	41	19
Glycerol	36	36	65	77
Hexane	87	87	85	81
Isoamyl Acetate	48	48	39	21
Isobutyl Isobutyrate	55	55	48	31
Isophorone	57	57	52	50
m-Cresol	79	79	88	88
Mesityl Oxide	60	60	54	57
Methanol	18	18	34	54
Methyl Ethyl Ketone	41	41	38	36
Methyl Isoamyl Ketone	50	50	42	34
Methyl Isobutyl Carbinol	11	11	19	28
Methyl Isobutyl Ketone	51	51	44	37
Methylal	44	44	40	35
Methylene Dichloride	61	61	57	46
Morpholine	69	69	77	79
n-Butyl Acetate	46	46	37	24
Nitrobenzene	34	34	25	7
Nitroethane	25	25	6	2
Nitromethane	5	5	11	14
o-Dichlorobenzene	76	76	73	67

o-Xylene	74	74	70	63
p-Xylene	78	78	76	71
Propylene Carbonate	8	8	10	18
Propylene Glycol	15	15	30	49
Pyridine	47	47	51	53
Styrene	65	65	64	59
Tetrahydrofuran	64	64	62	66
Tetrahydronaphthalene	80	80	75	69
Toluene	75	75	72	65
Trichloroethylene	81	81	78	73
γ-Butyrolactone	26	26	28	41

Possible intramolecular hydrogen bonding in solketal

In the manuscript, the surprising high stability towards hydrolysis of solketal is justified by the plausible stabilization of the molecule via an intramolecular hydrogen bonding. These results and conclusion are in agreement with the results of Bruice and Piszkiwicz[1].

We had a closer look at the molecular conformers of solketal with COSMO-RS (BP-TZVP, C30_1301). The profiles of the 2 most stable conformers (A and B) are shown in Figure 2. The σ-profile of the first conformer (A) exhibits a characteristic region for σ values below -0.01 e.Å^{-2} showing its ability to interact as a hydrogen-bond donor. This feature is absent from conformer B because it performs intramolecular hydrogen bond (Figure 2, red dotted line).

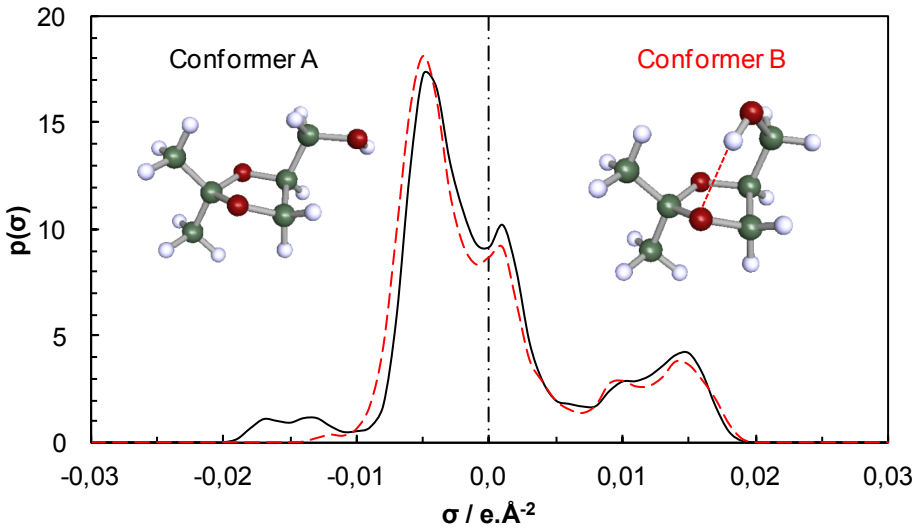


Figure 2. σ-profiles of the 2 mains conformers of solketal according to COSMO-RS, including one (B) with an intramolecular hydrogen bonding.

The predominance of conformers A or B depends on the environment of the molecule (Table 7). For instance, the low chemical potential of conformer B in n-hexane (μ^B(hexane) = -2.59 kJ.mol^{-1}) indicates that the intramolecular hydrogen-bonding is favored against interactions with the solvent. Conversely, the "open form" (conformer A) is favored in water (μ^A(water) = -5.94 kJ.mol^{-1}). This conclusion seems to be contradictory with our experimental observations which are in perfect agreement with those of Bruice and Pszkiwics for the hydrolysis of solketal. A more solid hypothesis for the experimental deviation observed would probably require a deeper computational study, including kinetic aspects and explicit solvation, but for sure this falls out of the scope of the paper.

Table 7. Chemical potential of 2 conformers of solketal in water and n-hexane.

Conformer	Chemical potential of solketal (kJ.mol^{-1})	
	Water	n-Hexane
A	-5.94	-0.94
B	0.19	-2.59

This kind of arguments can be used for the fast estimation of the potential intramolecular hydrogen bonding in molecules, even in complex cases such as pharmaceutical molecules[2], and to discuss the effect of the solvent.

[1] *J. Am. Chem. Soc.*, **1967**, *89* (14), pp 3568-3576
[2] *J. Med. Chem.*, **2013**, *56* (12), pp 4780-4879