Isohexide-based solvents: Conformationally induced differences in solvent properties

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Background

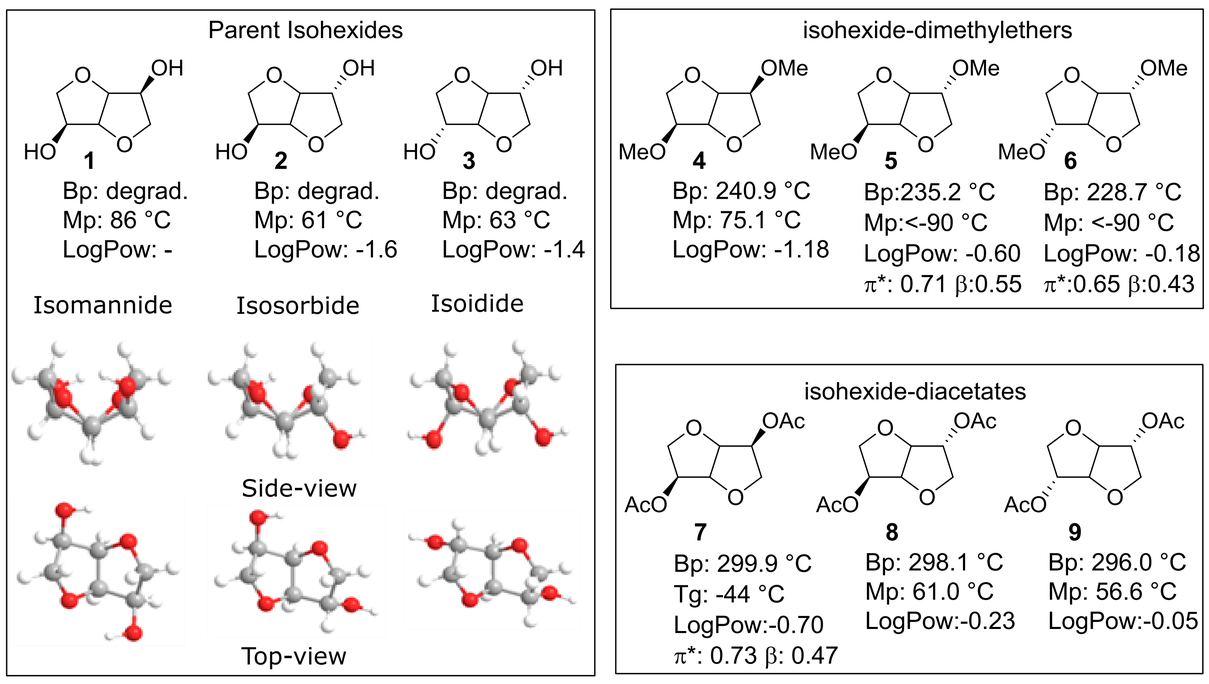
The quest for safe bio-based alternatives to reprotoxic dipolar aprotic solvents such as N-methyl-2-pyrrolidone (NMP) is receiving increasing attention.[1] Isosorbide dimethyl ether (DMIs) has been succesfully used in reactions normally employing dipolar aprotic solvents, showing the potential of an isohexide as bio-based polar aprotic solvent.[2,3] From a structural point of view, the isohexide scaffold is a *V*-shaped molecule consisting of two *cis*-fused tetrahydrofuran rings having two hydroxyl groups at C2 and C5, either in the *endo*- or *exo*-orientation.[4,5] Sterically and electronically the *endo*- and *exo*-positions are non-equivalent thus providing possibilities to steer the physico-chemical properties.

Modelling

Table 1. Predictive property calculation (Cosmotherm[a];HSPiP[b];ACD/i-lab[c])

	Mp[b] (°C)	Bp[c] (°C)	ρ[a]	μ[a] (cP)	δd[b] ($MPa_{1/2}$)	δp[b] ($MPa_{1/2}$)	δh[b] ($MPa_{1/2}$)	Log P_{ow}[c]
1	123.8	372.1	1.39	10.57	18.0	10.1	16.5	-1.75
2	123.8	372.1	1.43	79.75	18.0	10.1	16.5	-1.75
3	123.8	372.1	1.46	362.54	18.0	10.1	16.5	-1.75
4	-129.8	236.4	1.25	5.27	16.8	6.4	5.1	-0.65
5	-129.8	236.4	1.25	5.35	16.8	6.4	5.1	-0.65
6	-129.8	236.4	1.25	5.34	16.8	6.4	5.1	-0.65
7	35.1	309.8	1.29	20.75	17.5	6.4	7.3	-0.13
8	35.1	309.8	1.40	24.54	17.5	6.4	7.3	-0.13
9	35.1	309.8	1.32	22.96	17.5	6.4	7.3	-0.13

Physico-chemical properties



Toxicity

Table 2. In vitro toxicity data from a panel of human cell based CALUX reporter gene assays (lowest effect concentrations in log(M)

Domain	xenobiotic		endocrine			obesogens		acute toxicity				
Essay	PXR	AhR	ERα	AR-anti	PR-anti	PPARδ	PPARγ	Cytotox (20%)	AP1	ESRE	Nrf2	p53GENTOX
NMP		-2.0				-2.2		-1.4	-1.5			
DMAc		-2.2				-2.2			-1.7			
1												
2												
3												
4	-2.0											
5	-2.2											-1.2
6	-2.5			-2.2				-1.2				
7	-2.2											

Figure 1. Structure and physical-properties of the isohexides and their di-ether & di-acetate derivatives

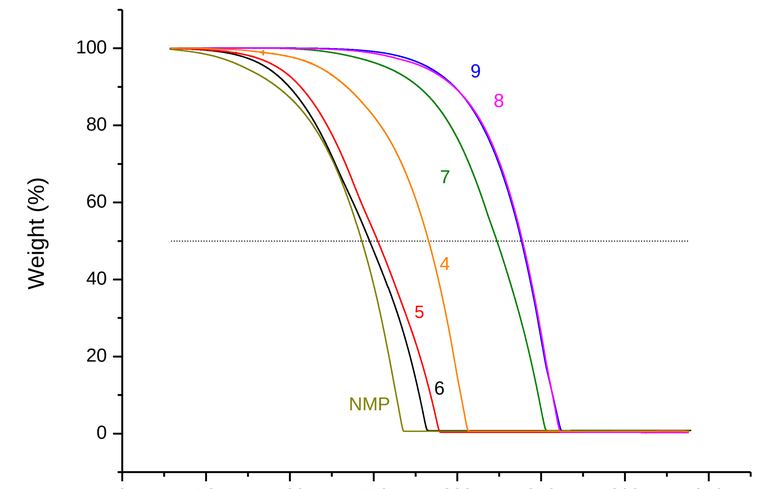


Figure 2. TGA: Volatility measurement

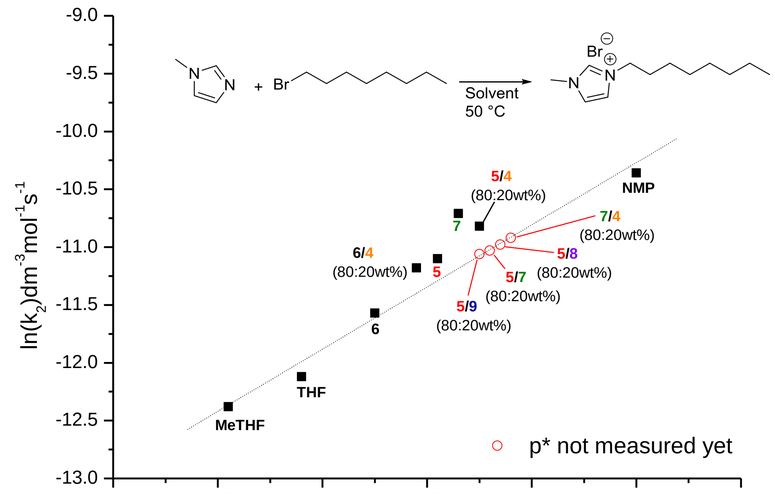


Figure 3. Menschutkin and Kamlet-Taft LSER

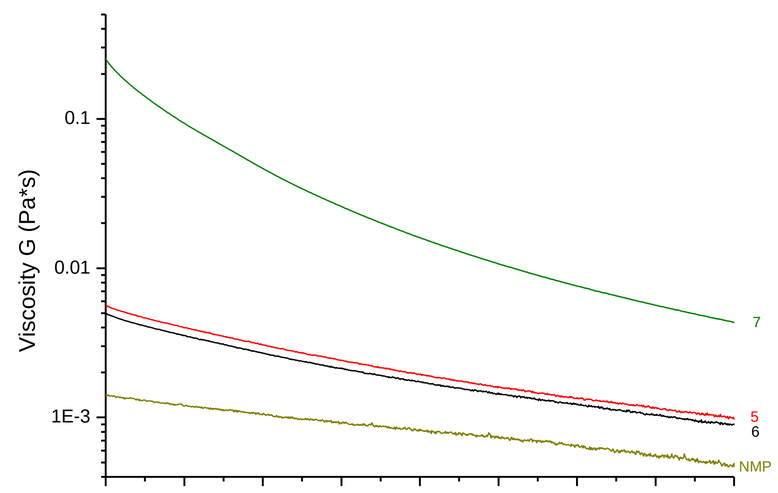


Figure 4. Viscosity of isohexide solvents

Conclusions & outlook

- Predictive property calculation (Cosmotherm;HSPiP;ACD/i-lab) does not correctly account for effects of stereochemistry in rigid cyclic structures
- Based on in vitro bioassay testing, the isohexide derivatives show a more favourable toxicity profile than commonly used polar aprotic solvents NMP and DMAc
- Physico-chemical properties of isohexides highly depend on the *endo*- or *exo*- configurations on the scaffold and type of functional groups
- Currently the reported solvents are under investigation to replace polair reprotoxic solvents in various applications

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