Unraveling Prothionamide Solubility Enhancement by Ionic Liquids: From Molecular Screening to Microscopic insights

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Contents

Section 1. Details of MD simulation

The MD simulations are divided in the following steps:

(1) The energy was minimized to obtain a reasonable distribution of molecules in the system, where the maximum force in systems will be less than 100 kJ/(mol·nm).

(2) Under the canonical (NVT) ensemble, the systems were equilibrated for 20 ns accompanying with the time step of 1 fs. The Berendsen thermostat and barostat were used to fix the temperature and pressure, and the coupling constants were 0.2 ps and 1.0 ps.[1,2]

(3) The systems of the balanced configuration based on the last frame mentioned above under Isobaric-Isothermal (NPT) ensemble was further simulated for 60 ns possessing the time step of 1 fs. The Nose-Hoover [2] with a coupling constant of 0.2 ps and the Parrinello-Rahman barostat [3] with a coupling constant of 4 ps are used to fix the temperature and pressure, respectively. The cutoff distances of the dispersion and Coulombic interactions both are 1.4 nm, and the particle mesh Ewald (PME) method was used to calculate the long-range electrostatic interactions.[4]

The last 5 ns of the trajectory was used for analysis.

References

1 T. Hansson, C. Oostenbrink, and W. F. van Gunsteren, Molecular dynamics simulations, *Curr. Opin. Struc. Biol*., 2002, **12**, 190–196.

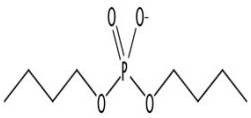
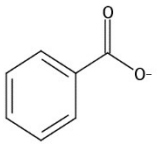
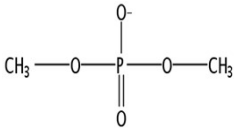
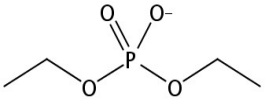
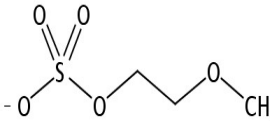
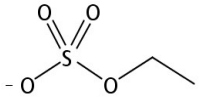
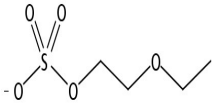
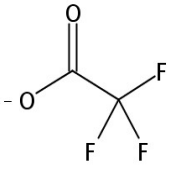
2 G. Bussi, D. Donadio and M. Parrinello, Canonical Sampling through Velocity Rescaling, *J. Chem. Phys*., 2007, **126**, 014101.

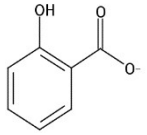
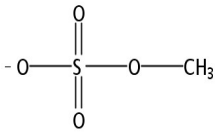
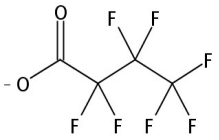
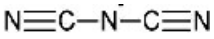
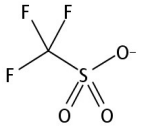
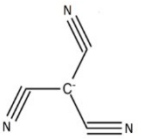
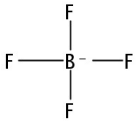
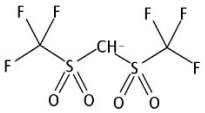
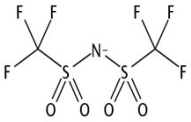
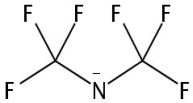
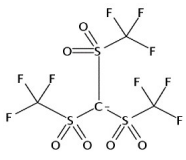
3 N. Weinberg, E. Edwards, L. Huber, Z. Sentell and J. Spooner, A Newtonian algorithm for constant pressure molecular dynamics with periodic boundary conditions, *Mol. Phys*., 2022, **120**, 2046–2060.

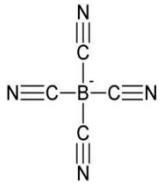
4 M. Parrinello and A. Rahman, Polymorphic Transitions in Single Crystals: A New Molecular Dynamics Method, *J. Appl. Phys*., 1981, **52**, 7182–7190.

Table S1 IL information

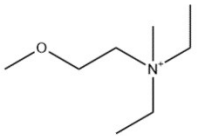
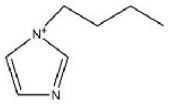
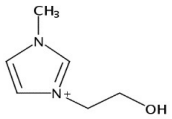
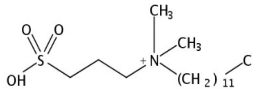
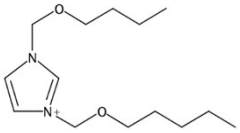
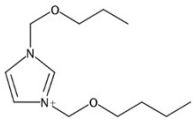
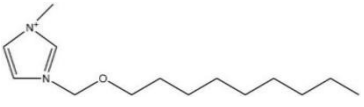
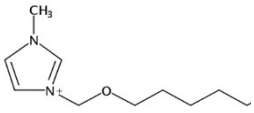
(a) Anions information

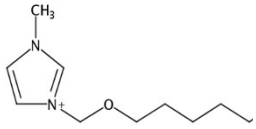
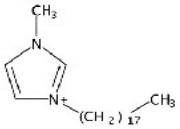
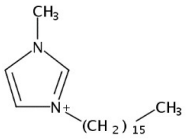
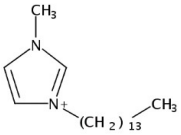
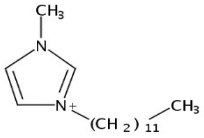
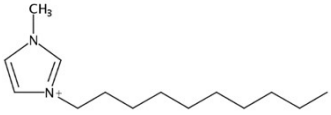
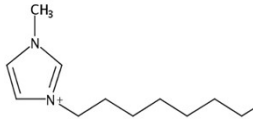
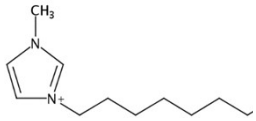
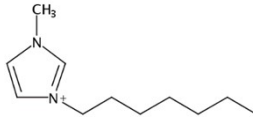
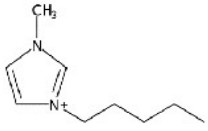
Number	Abbreviation	Anions name	Formula	Structure
1	Ac	acetate	$C_2H_3O_2$	
2	DBP	dibutylphosphate	$C_8H_{18}O_4P$	
3	Bza	benzoate	$C_7H_5O_2$	
4	DMP	dimethylphosphate	$C_2H_6O_4P$	
5	DEP	diethylphosphate	$C_4H_{10}O_4P$	
6	$MoeSO_4$	methoxyethylsulfate	$C_3H_7O_5S$	
7	$MoeoeSO_4$	2-(2-methoxyethoxy)ethylsulfate	$C_5H_{11}O_6S$	
8	ESO_4	ethylsulfate	$C_2H_5O_4S$	
9	$EoeSO_4$	ethoxyethylsulfate	$C_4H_9O_5S$	
10	TFA	trifluoroacetate	$C_2F_3O_2$	

11	Sal	salicylate	$C_7H_5O_3$	
12	MSO_4	methylsulfate	CH_3O_4S	
13	F_7Bta	heptafluorobutanoate	$C_4F_7O_2$	
14	DCA	dicyanamide	C_2N_3	
5	TfO	trifluoromethanesulfonate	CF_3O_3S	
16	TCM	tricyanomethane	C_4N_3	
17	BF_4	tetrafluoroborate	BF_4	
18	Tf_2C	bis(trifluoromethylsulfonyl)methane	$C_3HF_6O_4S_2$	
19	Tf_2N	bis(trifluoromethylsulfonyl)imide	$C_2F_6NO_4S_2$	
20	$N(CF_3)_2$	bis(trifluoromethyl)imide	C_2F_6N	
21	TMSC	tris(trifluoromethylsulfonyl)methide	$C_4F_9O_6S_3$	

22	TCB	tetracyanoborate	C_4BN_4	

(b) Cations information

Number	Abbreviation	ILs name	Formula	Structure
1	DEME	diethyl-methyl-(2-methoxyethy)ammonium	$C_8H_{20}NO$	
2	BIMIM	1-butylimidazolium	$C_7H_{13}N_2$	
3	HoeMIM	1-(2-hydroxyethyl)-3-methylimidazolium	$C_6H_{11}N_2O$	
4	DDAPS	dodecyl-dimethyl-3-sulfopropylammonium	$C_{17}H_{38}NO_3S$	
5	BomBomIM	1-butoxymethyl-3-pentoxymethylimidazolium	$C_{14}H_{27}N_2O_2$	
6	C_3omBomIM	1-butoxymethyl-3-propoxymethylimidazolium	$C_{12}H_{23}N_2O_2$	
7	NomMIM	1-methyl-3-nonoxymethylimidazolium	$C_{14}H_{27}N_2O$	
8	C_7omMIM	1-methyl-3-heptoxymethylimidazolium	$C_{12}H_{23}N_2O$	

9	HomMIM	1-hexyloxymethyl-3-methylimidazolium	$C_{11}H_{21}N_2O$	
10	C_{18}MIM	1-octadecyl-3-methylimidazolium	$C_{22}H_{43}N_2$	
11	C_{16}MIM	1-hexadecyl-3-methylimidazolium	$C_{20}H_{39}N_2$	
12	C_{14}MIM	1-tetradecyl-3-methylimidazolium	$C_{18}H_{35}N_2$	
13	C_{12}MIM	1-dodecyl-3-methylimidazolium	$C_{16}H_{31}N_2$	
14	DMIM	1-decyl-3-methylimidazolium	$C_{14}H_{27}N_2$	
15	NMIM	1-methyl-3-nonylimidazolium	$C_{13}H_{25}N_2$	
16	OMIM	1-octyl-3-methylimidazolium	$C_{12}H_{23}N_2$	
17	C_7MIM	1-heptyl-3-methylimidazolium	$C_{11}H_{21}N_2$	
18	C_5MIM	1-pentyl-3-methylimidazolium	$C_9H_{17}N_2$	

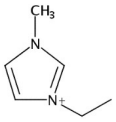
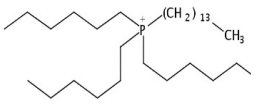
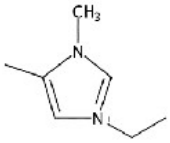
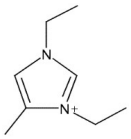
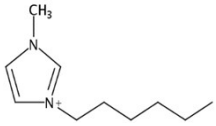
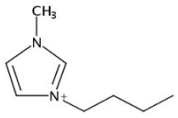
19	C_7MIM	1-heptyl-3-methylimidazolium	$C_{11}H_{21}N_2$	
20	EMIM	1-ethyl-3-methylimidazolium	$C_6H_{11}N_2$	
21	$P_{6,6,6,14}$	trihexyl-tetradecylphosphonium	$C_{32}H_{68}P$	
22	5MEMIM	1-ethyl-3,4-dimethylimidazolium	$C_7H_{13}N_2$	
23	4MEEIM	1,3-diethyl-4-methylimidazolium	$C_8H_{15}N_2$	
24	HMIM	1-hexyl-3-methylimidazolium	$C_{10}H_{19}N_2$	
25	BMIM	1-butyl-3-methylimidazolium	$C_8H_{15}N_2$	

Table S2 Restrained electrostatic potential (RESP) charge of different ions of PTO, and [BMIM][TfO] used in MD simulation.

PTO		$[BMIM]^+$		$[TfO]^-$	
atom	charge	atom	charge	atom	charge
C01	-0.6407	C01	-0.2181	C01	-0.2246
C02	0.5194	C02	-0.2301	N02	-0.0230
N03	-0.7327	N03	0.0966	C03	-0.0249
C04	0.5766	C04	0.0765	N04	0.1194
C05	-0.4563	N05	0.1601	C05	-0.1313
C06	0.4649	C06	-0.3439	C06	0.3152
C07	0.1087	C07	-0.1665	C07	-0.2936
N08	-0.4353	C08	0.0992	C08	-0.1028
S09	-0.3631	C09	-0.0328	H09	0.2236
C0A	-0.0419	C0A	-0.1264	H0A	0.2421
C0B	0.3819	H0B	0.2388	H0B	0.2103
C0C	-0.4134	H0C	0.2538	H0C	-0.0100
H0D	0.2122	H0D	0.0917	H0D	-0.0100
H0E	0.0223	H0E	0.1550	H0E	0.0878
H0F	0.1547	H0F	0.1550	H0F	0.0878
H10	0.3047	H10	0.1550	H10	0.0878
H11	0.2162	H11	0.0799	H11	0.0952
H12	-0.0007	H12	0.0799	H12	0.0952
H13	-0.0007	H13	0.0213	H13	0.0952
H14	-0.0839	H14	0.0213		
H15	-0.0839	H15	0.0276		
H16	0.0906	H16	0.0276		
H17	0.0906	H17	0.0388		
H18	0.0906	H18	0.0388		
		H19	0.0388		

Table S3 Restrained electrostatic potential (RESP) charge of different ions of [BMIM][BF_4] and [DEME][BF_4] used in MD simulation.

$[BMIM]^+$		$[BF_4]^-$		$[DEME]^+$		$[BF_4]^-$	
atom	charge	atom	charge	atom	charge	atom	charge
C01	-0.1887	B	-0.4515	O01	-0.3769	B	-0.4850
C02	-0.3405	F	1.0711	C02	0.2177	F	1.0347
N03	0.2447	F	-0.4995	C03	-0.6224	F	-0.4856
C04	-0.0430	F	-0.4697	N04	-0.0912	F	-0.4559
N05	0.1335	F	-0.4950	C05	-0.0997	F	-0.4650
C06	-0.1978			C06	-0.1650		
C07	-0.2573			C07	0.0626		
C08	0.0661			C08	-0.4843		
C09	-0.0566			C09	-0.2223		
C0A	-0.1894			C0A	0.2153		
H0B	0.2370			H0B	0.0657		
H0C	0.2760			H0C	0.0657		
H0D	0.1903			H0D	0.2460		
H0E	0.1194			H0E	0.2460		
H0F	0.1194			H0F	0.0946		
H10	0.1194			H10	0.0946		
H11	0.1528			H11	0.0946		
H12	0.1528			H12	0.1427		
H13	0.0094			H13	0.1427		
H14	0.0094			H14	0.1427		
H15	0.0621			H15	0.1756		
H16	0.0621			H16	0.1756		
H17	0.0559			H17	0.1494		
H18	0.0559			H18	0.1494		
H19	0.0559			H19	0.1494		

Table S4 Restrained electrostatic potential (RESP) charge of different ions of [EMIM][Tf_2N] and [EMIM][BF_4] used in MD simulation.

$[EMIM]^+$		$[Tf_2N]^-$		$[EMIM]^+$		$[BF_4]^-$	
atom	charge	atom	charge	atom	charge	atom	charge
C01	-0.2246	F01	-0.1728	C01	-0.2513	B	-0.4498
N02	-0.0230	C02	0.5374	N02	0.0421	F	0.9436
C03	-0.0249	F03	-0.1716	C03	0.0496	F	-0.4428
N04	0.1194	F04	-0.1772	N04	0.1827	F	-0.4178
C05	-0.1313	S05	0.9639	C05	-0.1679	F	-0.4587
C06	0.3152	O06	-0.5536	C06	0.2867		
C07	-0.2936	O07	-0.5815	C07	-0.1740		
C08	-0.1028	N08	-0.5672	C08	-0.4094		
H09	0.2236	S09	0.6765	H09	0.2291		
H0A	0.2421	O0A	-0.4538	H0A	0.1413		
H0B	0.2103	O0B	-0.3853	H0B	0.2083		
H0C	-0.0100	C0C	0.4946	H0C	-0.0224		
H0D	-0.0100	F0D	-0.1693	H0D	-0.0224		
H0E	0.0878	F0E	-0.1511	H0E	0.0607		
H0F	0.0878	F0F	-0.1612	H0F	0.0607		
H10	0.0878			H10	0.0607		
H11	0.0952			H11	0.1820		
H12	0.0952			H12	0.1820		
H13	0.0952			H13	0.1820		

Table S5 Box size and composition of the systems in MD simulation.

Systems	Size/nm	PTO	$[DEME]^+$	$[BMIM]^+$	$[EMIM]^+$	$[BF_4]^-$	$[TfO]^-$	$[Tf_2N]^-$
$[DEME][BF_4]$	7.5×7.5×7.5	15	750				750	
$[BMIM][BF_4]$	6.5×6.5×6.5	100			500		500	
[BMIM][TfO]	7.5×7.5×7.5	100			750			
$[EMIM][Tf_2N]$	7.5×7.5×7.5	40				640		640
$[EMIM][BF_4]$	7.0×7.0×7.0	20				460	460	

Table S6 Summary of $\ln\gamma^{\infty}$ values for screened ionic liquids classified by anion and cation.

anion	cation	$\ln\gamma^{\infty}$	anion	cation	$\ln\gamma^{\infty}$
TCB	BIM	0.52	Sal	BIM	-0.62
TCB	HoeMIM	1.17	Sal	HoeMIM	-0.72
TCB	DDAPS	-0.86	Sal	DDAPS	-0.68
TCB	BomBomIM	-0.02	Sal	BomBomIM	-1.77
TCB	C_3omBomIM	0.07	Sal	C_3omBomIM	-1.74
TCB	NomMIM	-0.02	Sal	NomMIM	-2.01
TCB	C_7omMIM	0.06	Sal	C_7omMIM	-1.98
TCB	HomMIM	0.13	Sal	HomMIM	-1.94
TCB	C_{18}MIM	0.09	Sal	C_{18}MIM	-2.33
TCB	C_{16}MIM	0.02	Sal	C_{16}MIM	-2.37
TCB	C_{14}MIM	-0.03	Sal	C_{14}MIM	-2.41
TCB	C_{12}MIM	-0.07	Sal	C_{12}MIM	-2.47
TCB	DMIM	-0.09	Sal	DMIM	-2.50
TCB	NMIM	-0.08	Sal	NMIM	-2.50
TCB	OMIM	-0.05	Sal	OMIM	-2.50
TCB	C_7MIM	-0.02	Sal	C_7MIM	-2.50
TCB	C_5MIM	0.12	Sal	C_5MIM	-2.50
TCB	C_7MIM_2	0.63	Sal	C_7MIM_2	-2.28
TCB	EMIM	0.75	Sal	EMIM	-2.42
TCB	$P_{6,6,6,14}$	0.59	Sal	$P_{6,6,6,14}$	-3.56
TCB	5MEMIM	0.18	Sal	5MEMIM	-3.35
TCB	4MEEIM	-0.09	Sal	4MEEIM	-3.60
TCB	HMIM	0.04	Sal	HMIM	-2.51
TCB	BMIM	0.25	Sal	BMIM	-2.49
TCB	IsbMIM	0.26	Sal	IsbMIM	-2.50
TCB	C_3MIM	0.44	Sal	C_3MIM	-2.47
TCB	BEIM	0.02	Sal	BEIM	-2.72

TCB	C_3EIM	0.13	Sal	C_3EIM	-2.73
TCB	EEIM	0.33	Sal	EEIM	-2.68
TCB	BISQU	-0.04	Sal	BISQU	-3.05
TMSC	DEME	0.52	TFA	DEME	-3.28
TMSC	BIM	-0.16	TFA	BIM	-0.31
TMSC	HoeMIM	-0.13	TFA	HoeMIM	-0.42
TMSC	DDAPS	-1.87	TFA	DDAPS	-0.54
TMSC	BomBomIM	0.06	TFA	BomBomIM	-1.56
TMSC	C_3omBomIM	0.05	TFA	C_3omBomIM	-1.50
TMSC	NomMIM	0.12	TFA	NomMIM	-1.80
TMSC	C_7omMIM	0.10	TFA	C_7omMIM	-1.75
TMSC	HomMIM	0.12	TFA	HomMIM	-1.71
TMSC	C_{18}MIM	0.51	TFA	C_{18}MIM	-2.09
TMSC	C_{16}MIM	0.43	TFA	C_{16}MIM	-2.14
TMSC	C_{14}MIM	0.35	TFA	C_{14}MIM	-2.18
TMSC	C_{12}MIM	0.29	TFA	C_{12}MIM	-2.24
TMSC	DMIM	0.22	TFA	DMIM	-2.27
TMSC	NMIM	0.20	TFA	NMIM	-2.28
TMSC	OMIM	0.18	TFA	OMIM	-2.27
TMSC	C_7MIM	0.18	TFA	C_7MIM	-2.27
TMSC	C_5MIM	0.19	TFA	C_5MIM	-2.27
TMSC	C_7MIM_2	0.32	TFA	C_7MIM_2	-2.05
TMSC	EMIM	0.36	TFA	EMIM	-2.28
TMSC	$P_{6,6,6,14}$	0.74	TFA	$P_{6,6,6,14}$	-2.99
TMSC	5MEMIM	0.29	TFA	5MEMIM	-3.22
TMSC	4MEEIM	0.22	TFA	4MEEIM	-3.44
TMSC	HMIM	0.06	TFA	HMIM	-2.28
TMSC	BMIM	0.22	TFA	BMIM	-2.28
TMSC	IsbMIM	0.25	TFA	IsbMIM	-2.27

TMSC	C_3MIM	0.27	TFA	C_3MIM	-2.27
TMSC	BEIM	0.18	TFA	BEIM	-2.50
TMSC	C_3EIM	0.21	TFA	C_3EIM	-2.53
TMSC	EEIM	0.25	TFA	EEIM	-2.52
TMSC	BISQU	0.14	TFA	BISQU	-2.81
$N(CF_3)_2$	DEME	0.37	$EoeSO_4$	DEME	-2.75
$N(CF_3)_2$	BIM	0.52	$EoeSO_4$	BIM	-0.94
$N(CF_3)_2$	HoeMIM	1.87	$EoeSO_4$	HoeMIM	-1.23
$N(CF_3)_2$	DDAPS	-0.34	$EoeSO_4$	DDAPS	-0.83
$N(CF_3)_2$	BomBomIM	-0.01	$EoeSO_4$	BomBomIM	-1.48
$N(CF_3)_2$	C_3omBomIM	0.08	$EoeSO_4$	C_3omBomIM	-1.48
$N(CF_3)_2$	NomMIM	-0.04	$EoeSO_4$	NomMIM	-1.59
$N(CF_3)_2$	C_7omMIM	0.05	$EoeSO_4$	C_7omMIM	-1.59
$N(CF_3)_2$	HomMIM	0.12	$EoeSO_4$	HomMIM	-1.59
$N(CF_3)_2$	C_{18}MIM	0.10	$EoeSO_4$	C_{18}MIM	-1.73
$N(CF_3)_2$	C_{16}MIM	0.03	$EoeSO_4$	C_{16}MIM	-1.79
$N(CF_3)_2$	C_{14}MIM	-0.04	$EoeSO_4$	C_{14}MIM	-1.84
$N(CF_3)_2$	C_{12}MIM	-0.08	$EoeSO_4$	C_{12}MIM	-1.90
$N(CF_3)_2$	DMIM	-0.10	$EoeSO_4$	DMIM	-1.95
$N(CF_3)_2$	NMIM	-0.09	$EoeSO_4$	NMIM	-1.97
$N(CF_3)_2$	OMIM	-0.06	$EoeSO_4$	OMIM	-1.99
$N(CF_3)_2$	C_7MIM	-0.02	$EoeSO_4$	C_7MIM	-2.02
$N(CF_3)_2$	C_5MIM	0.17	$EoeSO_4$	C_5MIM	-2.10
$N(CF_3)_2$	C_7MIM_2	0.88	$EoeSO_4$	C_7MIM_2	-2.07
$N(CF_3)_2$	EMIM	1.04	$EoeSO_4$	EMIM	-2.29
$N(CF_3)_2$	$P_{6,6,6,14}$	0.51	$EoeSO_4$	$P_{6,6,6,14}$	-1.96
$N(CF_3)_2$	5MEMIM	0.38	$EoeSO_4$	5MEMIM	-2.87
$N(CF_3)_2$	4MEEIM	0.03	$EoeSO_4$	4MEEIM	-3.00
$N(CF_3)_2$	HMIM	0.06	$EoeSO_4$	HMIM	-2.06

$N(CF_3)_2$	BMIM	0.35	$EoeSO_4$	BMIM	-2.16
$N(CF_3)_2$	IsbMIM	0.40	$EoeSO_4$	IsbMIM	-2.17
$N(CF_3)_2$	C_3MIM	0.61	$EoeSO_4$	C_3MIM	-2.22
$N(CF_3)_2$	BEIM	0.09	$EoeSO_4$	BEIM	-2.32
$N(CF_3)_2$	C_3EIM	0.26	$EoeSO_4$	C_3EIM	-2.38
$N(CF_3)_2$	EEIM	0.50	$EoeSO_4$	EEIM	-2.42
$N(CF_3)_2$	BISQU	-0.19	$EoeSO_4$	BISQU	-2.46
Tf_2N	DEME	0.12	ESO_4	DEME	-3.10
Tf_2N	BIM	0.07	ESO_4	BIM	-0.69
Tf_2N	HoeMIM	0.26	ESO_4	HoeMIM	-1.26
Tf_2N	DDAPS	-1.42	ESO_4	DDAPS	-0.75
Tf_2N	BomBomIM	-0.10	ESO_4	BomBomIM	-1.45
Tf_2N	C_3omBomIM	-0.08	ESO_4	C_3omBomIM	-1.43
Tf_2N	NomMIM	-0.09	ESO_4	NomMIM	-1.58
Tf_2N	C_7omMIM	-0.07	ESO_4	C_7omMIM	-1.58
Tf_2N	HomMIM	-0.04	ESO_4	HomMIM	-1.56
Tf_2N	C_{18}MIM	0.19	ESO_4	C_{18}MIM	-1.80
Tf_2N	C_{16}MIM	0.11	ESO_4	C_{16}MIM	-1.85
Tf_2N	C_{14}MIM	0.03	ESO_4	C_{14}MIM	-1.90
Tf_2N	C_{12}MIM	-0.03	ESO_4	C_{12}MIM	-1.96
Tf_2N	DMIM	-0.08	ESO_4	DMIM	-2.01
Tf_2N	NMIM	-0.09	ESO_4	NMIM	-2.02
Tf_2N	OMIM	-0.10	ESO_4	OMIM	-2.05
Tf_2N	C_7MIM	-0.09	ESO_4	C_7MIM	-2.07
Tf_2N	C_5MIM	-0.04	ESO_4	C_5MIM	-2.18
Tf_2N	C_7MIM_2	0.23	ESO_4	C_7MIM_2	-2.24
Tf_2N	EMIM	0.27	ESO_4	EMIM	-2.57
Tf_2N	$P_{6,6,6,14}$	0.99	ESO_4	$P_{6,6,6,14}$	-2.13
Tf_2N	5MEMIM	0.00	ESO_4	5MEMIM	-3.23

Tf_2N	4MEEIM	-0.15	ESO_4	4MEEIM	-3.32
Tf_2N	HMIM	-0.07	ESO_4	HMIM	-2.12
Tf_2N	BMIM	0.02	ESO_4	BMIM	-2.27
Tf_2N	IsbMIM	0.05	ESO_4	IsbMIM	-2.29
Tf_2N	C_3MIM	0.12	ESO_4	C_3MIM	-2.39
Tf_2N	BEIM	-0.09	ESO_4	BEIM	-2.44
Tf_2N	C_3EIM	-0.04	ESO_4	C_3EIM	-2.54
Tf_2N	EEIM	0.05	ESO_4	EEIM	-2.64
Tf_2N	BISQU	-0.20	ESO_4	BISQU	-2.57
Tf_2C	DEME	-0.01	$MoeoeSO_4$	DEME	-2.96
Tf_2C	BIM	0.10	$MoeoeSO_4$	BIM	-1.27
Tf_2C	HoeMIM	0.28	$MoeoeSO_4$	HoeMIM	-1.61
Tf_2C	DDAPS	-1.19	$MoeoeSO_4$	DDAPS	-1.01
Tf_2C	BomBomIM	-0.17	$MoeoeSO_4$	BomBomIM	-1.67
Tf_2C	C_3omBomIM	-0.15	$MoeoeSO_4$	C_3omBomIM	-1.69
Tf_2C	NomMIM	-0.17	$MoeoeSO_4$	NomMIM	-1.77
Tf_2C	C_7omMIM	-0.15	$MoeoeSO_4$	C_7omMIM	-1.79
Tf_2C	HomMIM	-0.13	$MoeoeSO_4$	HomMIM	-1.80
Tf_2C	C_{18}MIM	0.06	$MoeoeSO_4$	C_{18}MIM	-1.90
Tf_2C	C_{16}MIM	-0.02	$MoeoeSO_4$	C_{16}MIM	-1.95
Tf_2C	C_{14}MIM	-0.09	$MoeoeSO_4$	C_{14}MIM	-2.01
Tf_2C	C_{12}MIM	-0.14	$MoeoeSO_4$	C_{12}MIM	-2.07
Tf_2C	DMIM	-0.19	$MoeoeSO_4$	DMIM	-2.13
Tf_2C	NMIM	-0.20	$MoeoeSO_4$	NMIM	-2.15
Tf_2C	OMIM	-0.21	$MoeoeSO_4$	OMIM	-2.18
Tf_2C	C_7MIM	-0.20	$MoeoeSO_4$	C_7MIM	-2.22
Tf_2C	C_5MIM	-0.15	$MoeoeSO_4$	C_5MIM	-2.33
Tf_2C	C_7MIM_2	0.12	$MoeoeSO_4$	C_7MIM_2	-2.34
Tf_2C	EMIM	0.15	$MoeoeSO_4$	EMIM	-2.57

Tf_2C	$P_{6,6,6,14}$	0.74	$MoeoeSO_4$	$P_{6,6,6,14}$	-2.13
Tf_2C	5MEMIM	-0.14	$MoeoeSO_4$	5MEMIM	-3.10
Tf_2C	4MEEIM	-0.30	$MoeoeSO_4$	4MEEIM	-3.20
Tf_2C	HMIM	-0.18	$MoeoeSO_4$	HMIM	-2.27
Tf_2C	BMIM	-0.09	$MoeoeSO_4$	BMIM	-2.40
Tf_2C	IsbMIM	-0.06	$MoeoeSO_4$	IsbMIM	-2.42
Tf_2C	C_3MIM	0.01	$MoeoeSO_4$	C_3MIM	-2.48
Tf_2C	BEIM	-0.20	$MoeoeSO_4$	BEIM	-2.53
Tf_2C	C_3EIM	-0.15	$MoeoeSO_4$	C_3EIM	-2.62
Tf_2C	EEIM	-0.06	$MoeoeSO_4$	EEIM	-2.68
Tf_2C	BISQU	-0.34	$MoeoeSO_4$	BISQU	-2.65
BF_4	DEME	-1.19	$MoeSO_4$	DEME	-2.95
BF_4	BIM	1.08	$MoeSO_4$	BIM	-0.87
BF_4	HoeMIM	0.74	$MoeSO_4$	HoeMIM	-1.35
BF_4	DDAPS	-0.52	$MoeSO_4$	DDAPS	-0.83
BF_4	BomBomIM	-0.26	$MoeSO_4$	BomBomIM	-1.47
BF_4	$C_3omBomIM$	-0.12	$MoeSO_4$	$C_3omBomIM$	-1.47
BF_4	NomMIM	-0.33	$MoeSO_4$	NomMIM	-1.59
BF_4	C_7omMIM	-0.19	$MoeSO_4$	C_7omMIM	-1.59
BF_4	HomMIM	-0.09	$MoeSO_4$	HomMIM	-1.58
BF_4	$C_{18}MIM$	-0.49	$MoeSO_4$	$C_{18}MIM$	-1.76
BF_4	$C_{16}MIM$	-0.54	$MoeSO_4$	$C_{16}MIM$	-1.81
BF_4	$C_{14}MIM$	-0.58	$MoeSO_4$	$C_{14}MIM$	-1.86
BF_4	$C_{12}MIM$	-0.60	$MoeSO_4$	$C_{12}MIM$	-1.92
BF_4	DMIM	-0.60	$MoeSO_4$	DMIM	-1.97
BF_4	NMIM	-0.57	$MoeSO_4$	NMIM	-1.99
BF_4	OMIM	-0.55	$MoeSO_4$	OMIM	-2.01
BF_4	C_7MIM	-0.51	$MoeSO_4$	C_7MIM	-2.04
BF_4	C_5MIM	-0.45	$MoeSO_4$	C_5MIM	-2.16

BF_4	C_7MIM_2	-0.31	$MoeSO_4$	C_7MIM_2	-2.20
BF_4	EMIM	-0.67	$MoeSO_4$	EMIM	-2.49
BF_4	$P_{6,6,6,14}$	-0.11	$MoeSO_4$	$P_{6,6,6,14}$	-2.01
BF_4	5MEMIM	-1.38	$MoeSO_4$	5MEMIM	-3.09
BF_4	4MEEIM	-1.47	$MoeSO_4$	4MEEIM	-3.18
BF_4	HMIM	-0.47	$MoeSO_4$	HMIM	-2.10
BF_4	BMIM	-0.43	$MoeSO_4$	BMIM	-2.24
BF_4	IsbMIM	-0.42	$MoeSO_4$	IsbMIM	-2.26
BF_4	C_3MIM	-0.46	$MoeSO_4$	C_3MIM	-2.35
BF_4	BEIM	-0.69	$MoeSO_4$	BEIM	-2.39
BF_4	C_3EIM	-0.72	$MoeSO_4$	C_3EIM	-2.49
BF_4	EEIM	-0.77	$MoeSO_4$	EEIM	-2.58
BF_4	BISQU	-0.85	$MoeSO_4$	BISQU	-2.52
TCM	DEME	-0.75	DEP	DEME	-5.35
TCM	BIM	0.69	DEP	BIM	-2.51
TCM	HoeMIM	1.28	DEP	HoeMIM	-3.00
TCM	DDAPS	-0.41	DEP	DDAPS	-1.72
TCM	BomBomIM	-0.32	DEP	BomBomIM	-3.05
TCM	C_3omBomIM	-0.22	DEP	C_3omBomIM	-3.09
TCM	NomMIM	-0.38	DEP	NomMIM	-3.34
TCM	C_7omMIM	-0.28	DEP	C_7omMIM	-3.38
TCM	HomMIM	-0.20	DEP	HomMIM	-3.41
TCM	$C_{18}MIM$	-0.46	DEP	$C_{18}MIM$	-3.72
TCM	$C_{16}MIM$	-0.51	DEP	$C_{16}MIM$	-3.77
TCM	$C_{14}MIM$	-0.56	DEP	$C_{14}MIM$	-3.83
TCM	$C_{12}MIM$	-0.59	DEP	$C_{12}MIM$	-3.91
TCM	DMIM	-0.59	DEP	DMIM	-3.98
TCM	NMIM	-0.57	DEP	NMIM	-4.01
TCM	OMIM	-0.54	DEP	OMIM	-4.05

TCM	C_7MIM	-0.50	DEP	C_7MIM	-4.10
TCM	C_5MIM	-0.36	DEP	C_5MIM	-4.25
TCM	C_7MIM_2	0.15	DEP	C_7MIM_2	-4.27
TCM	EMIM	0.20	DEP	EMIM	-4.57
TCM	$P_{6,6,6,14}$	-0.41	DEP	$P_{6,6,6,14}$	-5.01
TCM	5MEMIM	-0.62	DEP	5MEMIM	-5.44
TCM	4MEEIM	-0.92	DEP	4MEEIM	-5.63
TCM	HMIM	-0.44	DEP	HMIM	-4.18
TCM	BMIM	-0.25	DEP	BMIM	-4.35
TCM	IsbMIM	-0.24	DEP	IsbMIM	-4.37
TCM	C_3MIM	-0.07	DEP	C_3MIM	-4.45
TCM	BEIM	-0.54	DEP	BEIM	-4.53
TCM	C_3EIM	-0.44	DEP	C_3EIM	-4.63
TCM	EEIM	-0.26	DEP	EEIM	-4.68
TCM	BISQU	-0.69	DEP	BISQU	-4.72
TFO	DEME	-1.38	DMP	DEME	-5.70
TFO	BIM	0.24	DMP	BIM	-2.40
TFO	HoeMIM	0.47	DMP	HoeMIM	-3.36
TFO	DDAPS	-0.60	DMP	DDAPS	-1.58
TFO	BomBomIM	-0.71	DMP	BomBomIM	-2.97
TFO	$C_3omBomIM$	-0.65	DMP	$C_3omBomIM$	-3.02
TFO	NomMIM	-0.81	DMP	NomMIM	-3.27
TFO	C_7omMIM	-0.75	DMP	C_7omMIM	-3.33
TFO	HomMIM	-0.70	DMP	HomMIM	-3.36
TFO	$C_{18}MIM$	-0.86	DMP	$C_{18}MIM$	-3.64
TFO	$C_{16}MIM$	-0.92	DMP	$C_{16}MIM$	-3.70
TFO	$C_{14}MIM$	-0.98	DMP	$C_{14}MIM$	-3.75
TFO	$C_{12}MIM$	-1.03	DMP	$C_{12}MIM$	-3.84
TFO	DMIM	-1.06	DMP	DMIM	-3.92

TFO	NMIM	-1.06	DMP	NMIM	-3.97
TFO	OMIM	-1.07	DMP	OMIM	-4.02
TFO	C_7MIM	-1.05	DMP	C_7MIM	-4.09
TFO	C_5MIM	-1.00	DMP	C_5MIM	-4.33
TFO	C_7MIM_2	-0.63	DMP	C_7MIM_2	-4.56
TFO	EMIM	-0.73	DMP	EMIM	-5.01
TFO	$P_{6,6,6,14}$	-0.76	DMP	$P_{6,6,6,14}$	-4.89
TFO	5MEMIM	-1.44	DMP	5MEMIM	-5.82
TFO	4MEEIM	-1.47	DMP	4MEEIM	-5.90
TFO	HMIM	-1.03	DMP	HMIM	-4.21
TFO	BMIM	-0.94	DMP	BMIM	-4.50
TFO	IsbMIM	-0.91	DMP	IsbMIM	-4.54
TFO	C_3MIM	-0.84	DMP	C_3MIM	-4.72
TFO	BEIM	-1.16	DMP	BEIM	-4.62
TFO	C_3EIM	-1.12	DMP	C_3EIM	-4.80
TFO	EEIM	-1.04	DMP	EEIM	-4.97
TFO	BISQU	-1.37	DMP	BISQU	-4.77
DCA	DEME	-2.38	Bza	DEME	-5.94
DCA	BIM	0.53	Bza	BIM	-2.01
DCA	HoeMIM	0.36	Bza	HoeMIM	-2.65
DCA	DDAPS	-0.20	Bza	DDAPS	-1.56
DCA	BomBomIM	-0.87	Bza	BomBomIM	-3.04
DCA	C_3omBomIM	-0.76	Bza	C_3omBomIM	-3.05
DCA	NomMIM	-1.02	Bza	NomMIM	-3.41
DCA	C_7omMIM	-0.92	Bza	C_7omMIM	-3.43
DCA	HomMIM	-0.84	Bza	HomMIM	-3.44
DCA	C_{18}MIM	-1.33	Bza	C_{18}MIM	-3.91
DCA	C_{16}MIM	-1.37	Bza	C_{16}MIM	-3.96
DCA	C_{14}MIM	-1.40	Bza	C_{14}MIM	-4.00

DCA	$C_{12}MIM$	-1.42	Bza	$C_{12}MIM$	-4.08
DCA	DMIM	-1.42	Bza	DMIM	-4.13
DCA	NMIM	-1.41	Bza	NMIM	-4.16
DCA	OMIM	-1.38	Bza	OMIM	-4.18
DCA	C_7MIM	-1.35	Bza	C_7MIM	-4.21
DCA	C_5MIM	-1.30	Bza	C_5MIM	-4.34
DCA	C_7MIM_2	-1.10	Bza	C_7MIM_2	-4.34
DCA	EMIM	-1.33	Bza	EMIM	-4.64
DCA	$P_{6,6,6,14}$	-1.94	Bza	$P_{6,6,6,14}$	-5.98
DCA	5MEMIM	-2.27	Bza	5MEMIM	-5.73
DCA	4MEEIM	-2.46	Bza	4MEEIM	-5.93
DCA	HMIM	-1.33	Bza	HMIM	-4.29
DCA	BMIM	-1.29	Bza	BMIM	-4.43
DCA	IsbMIM	-1.31	Bza	IsbMIM	-4.46
DCA	C_3MIM	-1.29	Bza	C_3MIM	-4.53
DCA	BEIM	-1.57	Bza	BEIM	-4.62
DCA	C_3EIM	-1.59	Bza	C_3EIM	-4.71
DCA	EEIM	-1.58	Bza	EEIM	-4.76
DCA	BISQU	-1.80	Bza	BISQU	-4.94
F_7Bta	DEME	-2.70	DBP	DEME	-4.84
F_7Bta	BIM	-0.43	DBP	BIM	-2.47
F_7Bta	HoeMIM	-0.46	DBP	HoeMIM	-2.71
F_7Bta	DDAPS	-0.57	DBP	DDAPS	-1.75
F_7Bta	BomBomIM	-1.41	DBP	BomBomIM	-2.95
F_7Bta	$C_3omBomIM$	-1.39	DBP	$C_3omBomIM$	-2.98
F_7Bta	NomMIM	-1.63	DBP	NomMIM	-3.22
F_7Bta	C_7omMIM	-1.61	DBP	C_7omMIM	-3.25
F_7Bta	HomMIM	-1.59	DBP	HomMIM	-3.27
F_7Bta	$C_{18}MIM$	-1.81	DBP	$C_{18}MIM$	-3.58

F_7Bta	C_{16}MIM	-1.86	DBP	C_{16}MIM	-3.63
F_7Bta	C_{14}MIM	-1.91	DBP	C_{14}MIM	-3.68
F_7Bta	C_{12}MIM	-1.98	DBP	C_{12}MIM	-3.75
F_7Bta	DMIM	-2.02	DBP	DMIM	-3.81
F_7Bta	NMIM	-2.02	DBP	NMIM	-3.84
F_7Bta	OMIM	-2.03	DBP	OMIM	-3.86
F_7Bta	C_7MIM	-2.02	DBP	C_7MIM	-3.89
F_7Bta	C_5MIM	-2.01	DBP	C_5MIM	-3.98
F_7Bta	C_7MIM_2	-1.76	DBP	C_7MIM_2	-3.89
F_7Bta	EMIM	-1.83	DBP	EMIM	-4.07
F_7Bta	$P_{6,6,6,14}$	-2.63	DBP	$P_{6,6,6,14}$	-4.87
F_7Bta	5MEMIM	-2.60	DBP	5MEMIM	-4.89
F_7Bta	4MEEIM	-2.85	DBP	4MEEIM	-5.13
F_7Bta	HMIM	-2.03	DBP	HMIM	-3.94
F_7Bta	BMIM	-1.98	DBP	BMIM	-4.02
F_7Bta	IsbMIM	-1.96	DBP	IsbMIM	-4.03
F_7Bta	C_3MIM	-1.92	DBP	C_3MIM	-4.06
F_7Bta	BEIM	-2.16	DBP	BEIM	-4.22
F_7Bta	C_3EIM	-2.14	DBP	C_3EIM	-4.26
F_7Bta	EEIM	-2.08	DBP	EEIM	-4.25
F_7Bta	BISQU	-2.50	DBP	BISQU	-4.45
MSO_4	DEME	-3.28	Ac	DEME	-8.01
MSO_4	BIM	-0.46	Ac	BIM	-3.14
MSO_4	HoeMIM	-1.44	Ac	HoeMIM	-5.24
MSO_4	DDAPS	-0.65	Ac	DDAPS	-2.05
MSO_4	BomBomIM	-1.35	Ac	BomBomIM	-3.79
MSO_4	C_3omBomIM	-1.32	Ac	C_3omBomIM	-3.89
MSO_4	NomMIM	-1.49	Ac	NomMIM	-4.26
MSO_4	C_7omMIM	-1.47	Ac	C_7omMIM	-4.39

MSO_4	HomMIM	-1.45	Ac	HomMIM	-4.48
MSO_4	$C_{18}MIM$	-1.74	Ac	$C_{18}MIM$	-4.77
MSO_4	$C_{16}MIM$	-1.79	Ac	$C_{16}MIM$	-4.83
MSO_4	$C_{14}MIM$	-1.83	Ac	$C_{14}MIM$	-4.90
MSO_4	$C_{12}MIM$	-1.88	Ac	$C_{12}MIM$	-5.01
MSO_4	DMIM	-1.92	Ac	DMIM	-5.14
MSO_4	NMIM	-1.94	Ac	NMIM	-5.21
MSO_4	OMIM	-1.96	Ac	OMIM	-5.29
MSO_4	C_7MIM	-1.99	Ac	C_7MIM	-5.41
MSO_4	C_5MIM	-2.14	Ac	C_5MIM	-5.83
MSO_4	C_7MIM_2	-2.35	Ac	C_7MIM_2	-6.46
MSO_4	EMIM	-2.81	Ac	EMIM	-7.24
MSO_4	$P_{6,6,6,14}$	-2.06	Ac	$P_{6,6,6,14}$	-7.05
MSO_4	5MEMIM	-3.43	Ac	5MEMIM	-8.11
MSO_4	4MEEIM	-3.44	Ac	4MEEIM	-8.02
MSO_4	HMIM	-2.06	Ac	HMIM	-5.62
MSO_4	BMIM	-2.27	Ac	BMIM	-6.16
MSO_4	IsbMIM	-2.31	Ac	IsbMIM	-6.23
MSO_4	C_3MIM	-2.48	Ac	C_3MIM	-6.60
MSO_4	BEIM	-2.41	Ac	BEIM	-6.14
MSO_4	C_3EIM	-2.58	Ac	C_3EIM	-6.47
MSO_4	EEIM	-2.75	Ac	EEIM	-6.83
MSO_4	BISQU	-2.53	Ac	BISQU	-6.33
Sal	DEME	-3.56			

Table S7 Ratio of IC_{50} to effective IL concentration in BHK 21 cells.

ILs	IL_{eff} (μM)	IC_{50} (μM)	IC_{50}/IL_{eff}
[DEME][BF_4]	213	1010	5
[EMIM][BF_4]	606	780	1
[BMIM][TfO]	86	680	8
[BMIM][BF_4]	156	370	2
[EMIM][Tf_2N]	293	260	1

IL_{eff}: Effective concentration of ILs at the MIC of PTO.

Table S8 Ratio of IC_{50} to effective concentration of IL in HepG2 cells

ILs	$IL_{eff.}$ (μM)	IC_{50} (μM)	IC_{50}/IL_{eff}
[DEME][BF_4]	213	400	2
[EMIM][BF_4]	606	2200	4
[BMIM][TfO]	86	870	10
[BMIM][BF_4]	156	2000	13
[EMIM][Tf_2N]	293	360	1

IL_{eff}: Effective concentration of ILs at the MIC of PTO.

Table S9 Comparison of Simulated and Experimental Densities for Pure ILs at 338.15 K

ILs	ρ_{sim}/(kg/m^3)	ρ_{ref}/(kg/m^3)	ARD (%)
[DEME][BF_4]	1153	1106	4.25
[BMIM][BF_4]	1176	1145	2.71
[BMIM][TfO]	1269	1282	1.01
[EMIM][Tf_2N]	1474	1439	2.43
[EMIM][BF_4]	1256	1248	0.64

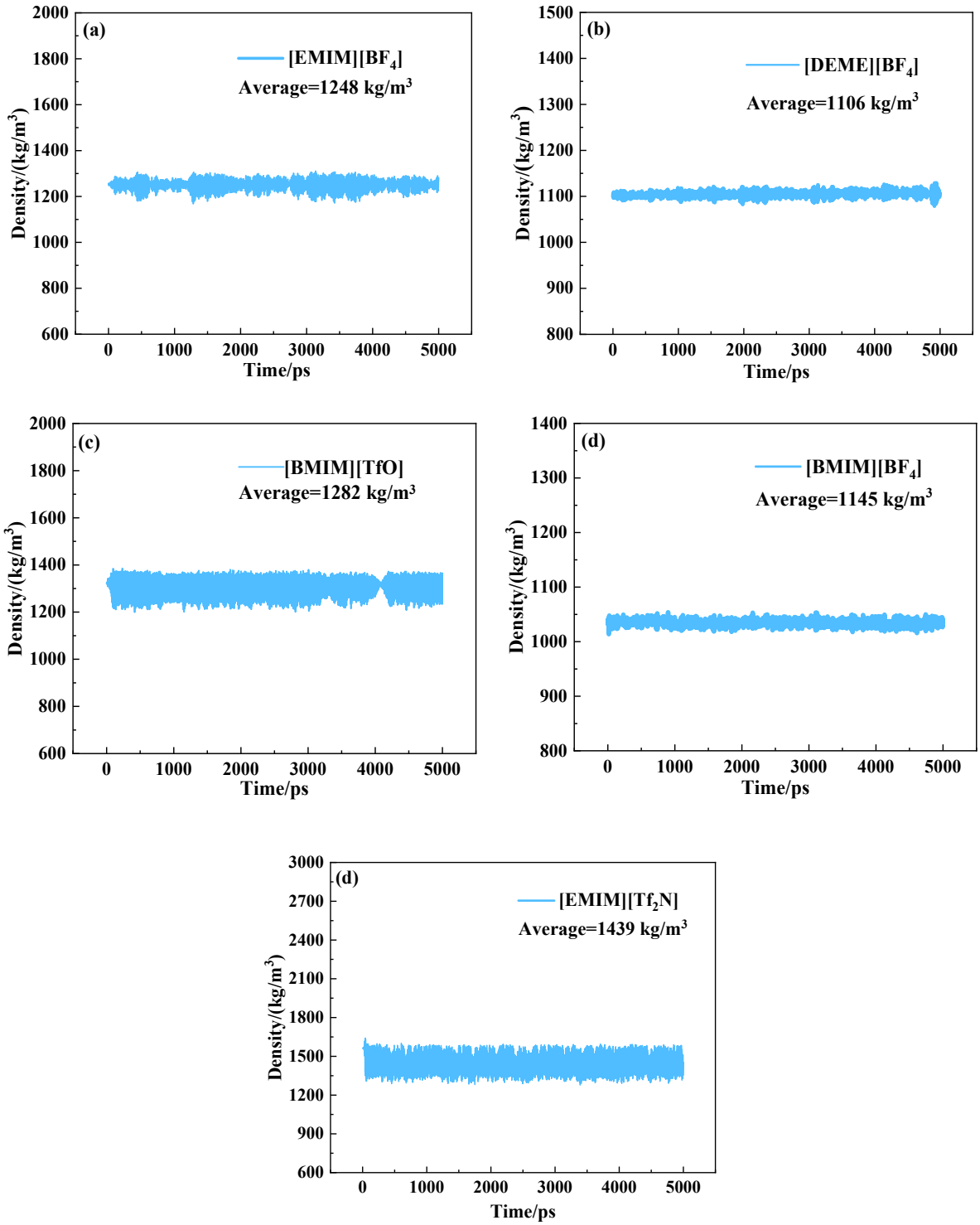


Fig. S1 The density of five IL-PTO systems calculated from the last 5 ns of the MD simulation trajectory.

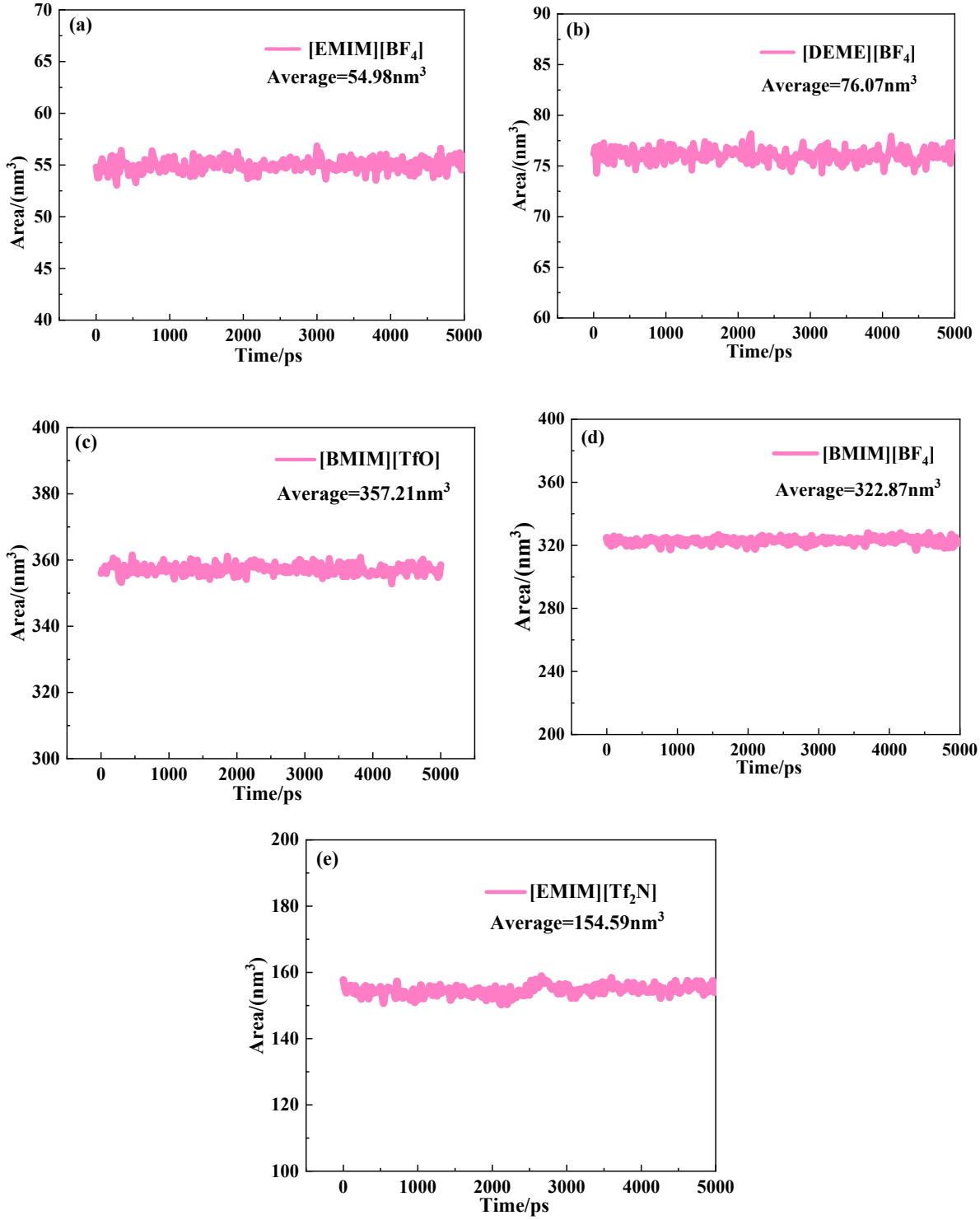


Fig. S2 The solvent-accessible surface area (SASA) of PTO in five IL-PTO systems, calculated from the last 5 ns of the MD simulation trajectory.

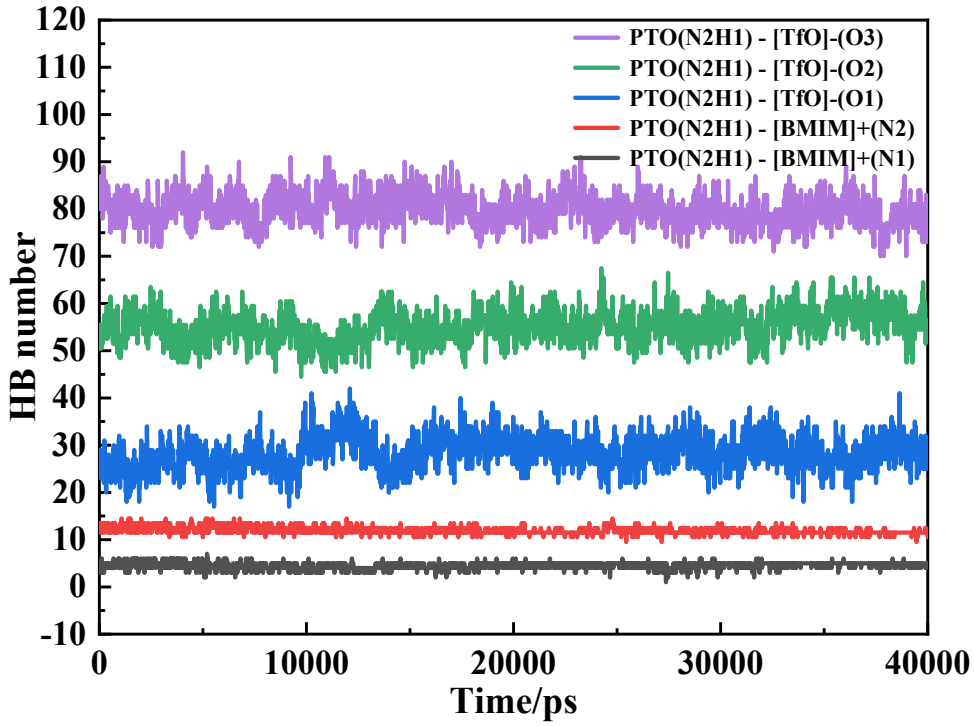


Fig. S3 Time evolution of the number of HBs during the 40 ns MD simulation.