Supplementary Information For:

Structure and Dynamics of Monomer-Template Complexation: An Explanation for Molecularly Imprinted Polymer Recognition Site Heterogeneity

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^{1}H NMR Spectroscopy

MAA-Bupivacaine Titration

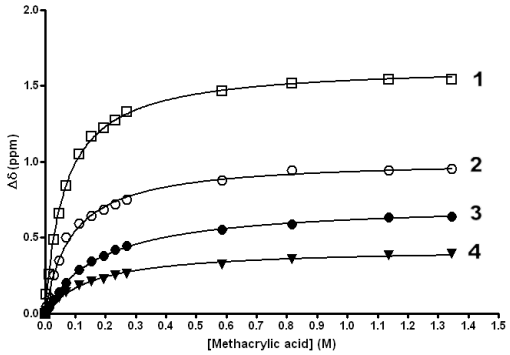


Figure S1. MAA-bupivacaine ^{1}H NMR titration experiment in $CDCl_3$ at 293 K. Analysis of the bupivacaine protons studied (see Chart 2) using a non-linear one-site binding model yielded:
R^2*>0.99* and K_D*= 0.065 ± 0.001 M* (K_A*= 15.4 ± 0.1 M^{-1}*) for **1** (□),
R^2*>0.99* and K_D*= 0.086 ± 0.005 M* (K_A*= 11.7 ± 0.4 M^{-1}*) for **2** (○),
R^2*>0.99* and K_D*= 0.154 ± 0.009 M* (K_A*= 6.5 ± 0.2 M^{-1}*) for **3** (●),
R^2*>0.99* and K_D*= 0.176 ± 0.005 M* (K_A*= 5.7 ± 0.1 M^{-1}*) for **4** (▼).

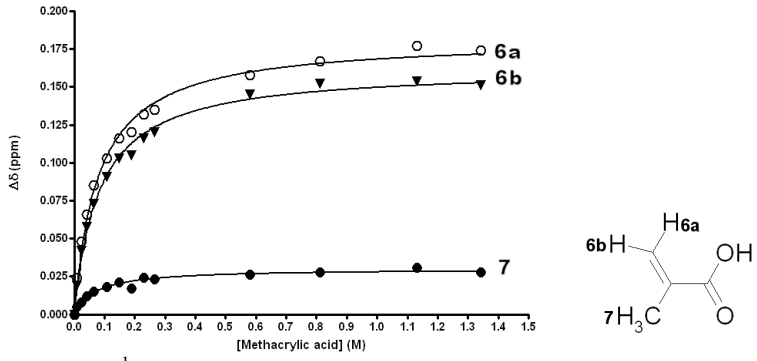


Figure S2. MAA-bupivacaine ^{1}H NMR titration experiment in $CDCl_3$ at 293 K. Analysis of the MAA protons studied using a non-linear one-site binding model yielded:
R^2*>0.99* and K_D*= 0.080 ± 0.005 M* (K_A*= 12.5 ± 0.5 M^{-1}*) for proton **6a** (○),
R^2*>0.99* and K_D*= 0.082 ± 0.005 M* (K_A*= 12.2 ± 0.4 M^{-1}*) for proton **6b** (▼),
R^2*=0.97* and K_D*= 0.071 ± 0.011* M (K_A*= 14.3 ± 1.3 M^{-1}*) for proton **7** (●).

MAA-Bupivacaine Continuous Variation Study

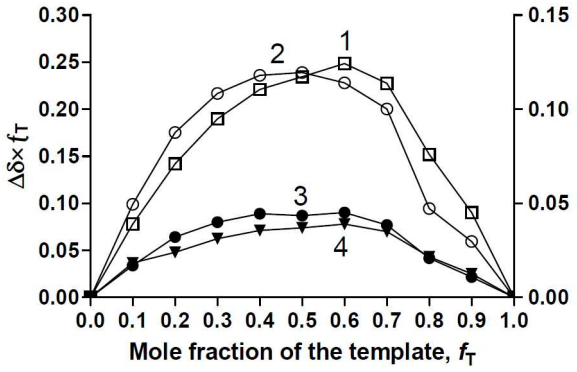


Figure S3. MAA-bupivacaine ^{1}H NMR continuous variation experiment in $CDCl_3$ at 293 K. Bupivacaine protons studied (see Chart 2) and the different optimal molar fractions of the template observed in the experiment were *0.6* for proton **1** (□), *0.4* for proton **2** (○), *0.5* for proton 3 (●) and finally *0.6* for proton 4 (▼). Protons 3 and 4 have due to smaller chemical shifts, been clarified by the addition of an extra y-axis on the right-hand side. The title on this axis is the same as on the left-hand side.

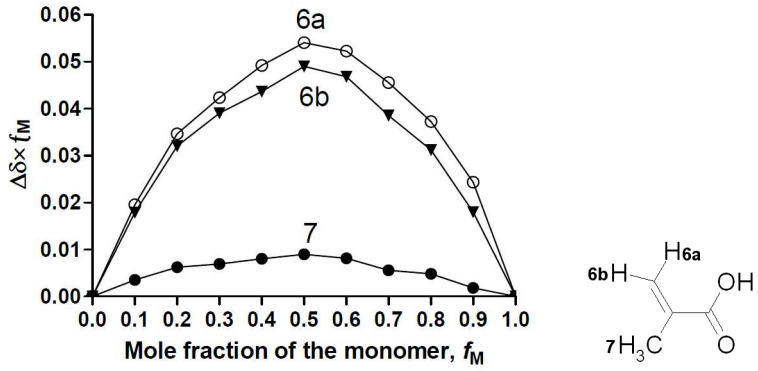


Figure S4. MAA-bupivacaine ^{1}H NMR continuous variation experiment in $CDCl_3$ at 293 K. MAA Protons studied and the different optimal molar fractions of bupivacaine observed in the experiment were *0.5* for proton **6a** (◊), *0.5* for proton **6b** (Δ) and *0.5* for proton 7 (▼).

Acetic acid-d_4-EDMA-Bupivacaine Titration

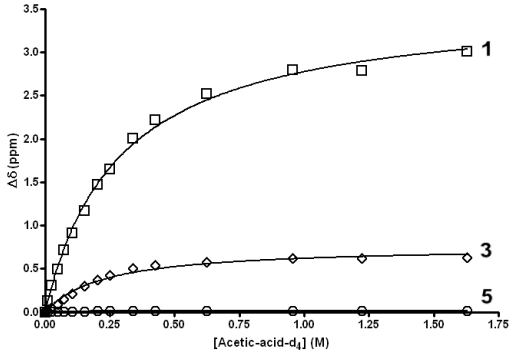


Figure S5. Acetic acid-d_4-EDMA-bupivacaine ^{1}H NMR titration experiment in $CDCl_3$ at 293 K. Analysis of the bupivacaine protons (see Chart 2) studied using a non-linear one-site binding model yielded:
R^2*>0.99* and K_D*= 0.284 ± 0.013 M* (K_A*= 3.5 ± 0.1 M*$^{-1}$) for proton **1** (□),
R^2*=0.98* and K_D*= 0.225 ± 0.026 M* (K_A*= 4.5 ± 0.3 M*$^{-1}$) for proton **3** (◇),
R^2*=0.98* and K_D*= 0.091 ± 0.012 M* (K_A*= 11.1 ± 0.9 M*$^{-1}$) for proton **5** (○).

EDMA-Bupivacaine Titration

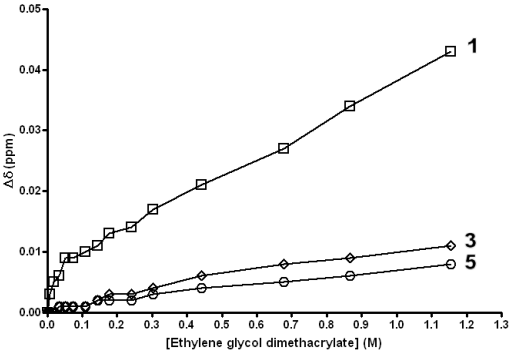


Figure S6. EDMA-bupivacaine ^{1}H NMR titration experiment in $CDCl_3$ at 293 K showing the bupivacaine protons studied (see Chart 2) **1** (□), **3** (◇) and **5** (○) upon addition of the crosslinker EDMA.

Polymer Gelation

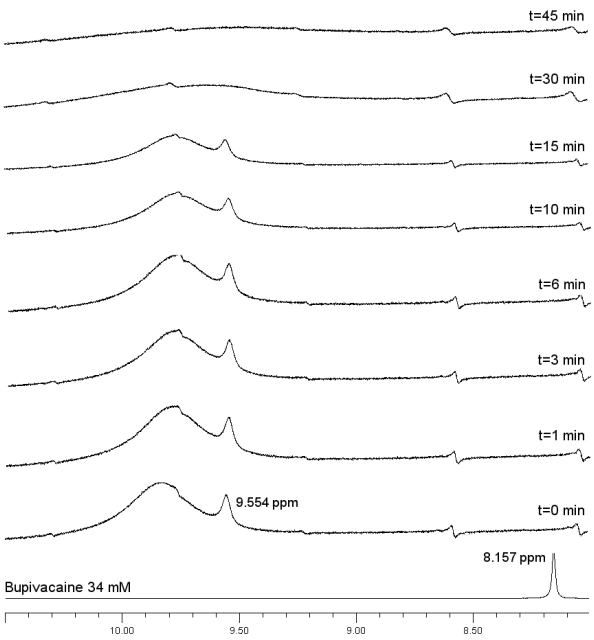


Figure S7. Fate of the bupivacaine complexation during the radical polymerization as studied by ^{1}H NMR spectroscopy following the bupivacaine amide proton (proton **1** in Chart 2) during the polymerization process in $CDCl_3$ at 293 K.

MD - Equilibration and Production Run Data

Prepolymerization Mixtures

System Design and Methodology

TABLE S1: System Design and Molecular Dynamics Methodology Applied.

System[a]	Bupivacaine	MAA	EDMA	$CHCl_3$	AIBN	Eq. (ps)[b]	Prod. (ns)
SP	7	79	-	270	-	20+200	5
P	7	75	368	741	8	200+600	5

[a]The simplified prepolymerization (**SP**) and the prepolymerization (**P**) mixtures in chloroform. [b]The equilibration phase was divided into two parts in which the first part involved a process slowly heating the system from 0 to 293 K (NVT) followed by a longer equilibration step at NPT (293 K, 1 bar) to assure a stable value in density of the system (see Table S2).

Thermodynamic Properties

TABLE S2: Thermodynamic Properties for the Different Systems Studied.

			Energies (kcal/mol)			
System[a]	Temp. (K)	ρ (g/cm^3)	E_{POT}	E_{KIN}	E_{TOT}	Volume (Å^3)
SP	293.2 ± 4.9	1.35	-3815.5 ± 37.0	2112.3 ± 35.0	-1703.3 ± 50.3	37.0×37.0×36.8
P	293.1 ± 2.0	1.25	-4905.2 ± 90.6	11775.8 ± 82.3	6870.6 ± 120.4	61.1×61.0×61.0

[a]The simplified prepolymerization (**SP**) and the prepolymerization (**P**) mixtures in chloroform.

MD - Hydrogen Bond Analysis

TABLE S3: Hydrogen Bonding Observed in the Prepolymerization Solutions Studied by MD. Values are Presented as Mean ± Standard deviation.

Atom Pair		Occupied (%)[a]		Distance (Å)		Angle (°)[b]		Average lifetime, τ (ps)	
Acc.	Don.	SP	P	SP	P	SP	P	SP	P
CO	MH	47.8	34.1	1.77 ± 0.04	1.79 ± 0.06	25.2 ± 9.2	24.0 ± 6.9	13.2 ± 7.1	11.9 ± 7.5
AN	MH	27.4	*n.d.*	1.85 ± 0.03	*n.d.*	22.1 ± 5.5	*n.d.*	5.7 ± 2.4	*n.d.*
MO	AH	17.9	0.3	1.89 ± 0.03	1.92 ± 0.02	33.9 ± 14.2	45.4 ± 5.1	1.8 ± 0.8	1.1 ± 0.1
MO1	AH	0.3	*n.d.*	1.92 ± 0.02	*n.d.*	33.9 ± 15.2	*n.d.*	1.2 ± 0.2	*n.d.*
EO	AH		0.7		1.91 ± 0.02		41.7 ± 1.9		1.2 ± 0.2
EO1	AH		*n.d.*		*n.d.*		*n.d.*		*n.d.*
EO2	AH		*n.d.*		*n.d.*		*n.d.*		*n.d.*
EO3	AH		0.7		1.92 ± 0.04		42.4 ± 2.9		1.1 ± 0.1
CO	AH	*n.d.*	6.4	*n.d.*	2.88 ± 0.02	*n.d.*	35.1 ± 9.8	*n.d.*	0.5 ± 0.1
AN	AH	0.5	0.7	2.86 ± 0.01	2.86 ± 0.00	58.1 ± 0.1	58.1 ± 0.2	0.2 ± 0.0	0.2 ± 0.0

[a]The hydrogen-bonded state with respect to the total simulation time in average per template molecule present in the mixture. [b]Defines as the angle between three atoms whereas the hydrogen donating group includes two atoms such as *e.g. MO1-MH* and the hydrogen bond accepting atom includes a single atom such as e.g. atom *CO*. n.d. means not detected.

MD- Potentials of Mean Force (PMFs) Calculations

Thermodynamics

TABLE S4: Thermodynamic Data Obtained From the Umbrella Sampling Simulations in Chloroform at 293 K Using Different Starting Coordinates.

Series 1: ***CO-MH***

		Energies (kcal/mol)			
d_0	d_{mean}	E_{pot}	E_{kin}	E_{tot}	Temp.
1.9	1.8	-991.8 ± 21.7	846.1 ± 21.9	-145.7 ± 30.2	293.0 ± 7.6
2.3	1.9	-990.0 ± 22.4	847.7 ± 22.2	-142.3 ± 31.7	293.6 ± 7.7
2.7	2.1	-986.5 ± 21.7	849.2 ± 22.3	-137.4 ± 31.0	294.1 ± 7.7
3.1	2.4	-989.4 ± 21.7	845.7 ± 21.5	-143.7 ± 29.8	292.9 ± 7.5
3.5	4.6	-988.4 ± 21.4	847.4 ± 21.6	-141.0 ± 29.5	293.5 ± 7.5
3.9	4.8	-991.0 ± 21.8	847.0 ± 21.8	-144.0 ± 30.5	293.3 ± 7.5
4.3	4.9	-991.7 ± 21.3	846.6 ± 21.8	-145.1 ± 30.0	293.2 ± 7.5
4.7	4.9	-992.8 ± 21.2	845.8 ± 21.9	-147.0 ± 30.0	292.9 ± 7.6
5.1	5.1	-993.4 ± 21.9	846.2 ± 22.7	-147.2 ± 30.4	293.1 ± 7.6
5.5	5.1	-991.5 ± 21.8	846.9 ± 22.7	-144.5 ± 31.4	293.3 ± 7.9
5.9	6.1	-984.1 ± 22.3	847.7 ± 22.2	-136.4 ± 31.7	293.6 ± 7.7
6.3	5.8	-989.2 ± 21.5	846.8 ± 22.0	-142.4 ± 30.1	293.3 ± 7.6
7.1	6.9	-987.6 ± 22.1	845.7 ± 21.9	-141.9 ± 31.2	292.9 ± 7.6
7.9	7.9	-985.3 ± 22.1	845.9 ± 22.5	-139.4 ± 31.8	293.0 ± 7.8
8.7	8.8	-989.2 ± 21.8	844.6 ± 21.9	-144.6 ± 30.6	292.5 ± 7.6
9.5	9.5	-986.8 ± 21.8	846.8 ± 22.0	-140.1 ± 30.9	293.3 ± 7.6
10.3	10.3	-986.9 ± 22.5	847.3 ± 22.1	-139.6 ± 31.7	293.4 ± 7.7

Series 2: ***AN-MH***

		Energies (kcal/mol)			
d_0	d_{mean}	E_{pot}	E_{kin}	E_{tot}	Temp.
1.9	3.3	-984.0 ± 21.8	846.7 ± 22.4	-137.3 ± 30.9	293.3 ± 7.8
2.3	3.5	-984.9 ± 21.7	847.5 ± 21.6	-137.3 ± 30.1	293.5 ± 7.5
2.7	3.5	-989.9 ± 21.1	845.7 ± 21.9	-144.2 ± 29.7	292.9 ± 7.6
3.1	3.8	-988.5 ± 21.9	847.4 ± 22.1	-141.2 ± 30.9	293.5 ± 7.7
3.5	3.8	-989.3 ± 21.8	846.0 ± 22.1	-143.4 ± 30.9	293.0 ± 7.7
3.9	4.1	-990.4 ± 21.9	847.3 ± 22.4	-143.1 ± 31.3	293.5 ± 7.8
4.3	4.5	-988.9 ± 22.1	846.4 ± 22.1	-142.1 ± 31.4	293.1 ± 7.7
4.7	4.8	-992.8 ± 21.1	846.2 ± 21.6	-146.6 ± 29.4	293.1 ± 7.5
5.1	5.0	-992.2 ± 21.4	846.1 ± 21.7	-143.1 ± 29.4	293.0 ± 7.5
5.5	5.2	-993.4 ± 21.5	845.6 ± 21.9	-147.9 ± 30.2	292.9 ± 7.6
5.9	5.7	-987.7 ± 22.5	847.0 ± 22.5	-140.7 ± 32.5	293.3 ± 7.8
6.3	6.3	-984.4 ± 22.2	847.0 ± 22.1	-137.4 ± 31.5	293.3 ± 7.7
7.1	7.2	-985.6 ± 21.6	847.0 ± 21.9	-138.6 ± 30.5	293.3 ± 7.6
7.9	8.0	-986.3 ± 21.5	846.9 ± 21.8	-139.4 ± 29.7	293.3 ± 7.6
8.7	8.7	-985.5 ± 21.9	846.9 ± 21.8	-138.1 ± 31.4	293.5 ± 7.8
9.5	9.5	-986.2 ± 23.2	846.7 ± 22.8	-139.5 ± 33.7	293.3 ± 7.9
10.3	10.3	-987.0 ± 22.0	846.9 ± 22.1	-140.1 ± 31.7	293.3 ± 7.7

Series 3: *AH-MH*

		Energies (kcal/mol)			
d_0	d_{mean}	E_{pot}	E_{kin}	E_{tot}	Temp.
1.9	3.4	-985.9 ± 21.3	845.4 ± 22.1	-140.5 ± 30.5	292.8 ± 7.7
2.3	3.6	-987.2 ± 21.9	846.7 ± 22.2	-140.5 ± 31.2	293.2 ± 7.7
2.7	3.7	-988.1 ± 22.4	846.6 ± 23.2	-141.5 ± 32.9	293.2 ± 8.0
3.1	3.9	-991.0 ± 21.4	846.2 ± 21.4	-144.8 ± 29.3	293.1 ± 7.4
3.5	4.0	-991.9 ± 22.4	845.3 ± 22.2	-146.6 ± 32.1	292.8 ± 7.7
3.9	4.3	-992.2 ± 21.1	845.0 ± 22.8	-147.2 ± 32.1	292.6 ± 7.9
4.3	4.5	-990.9 ± 22.1	846.8 ± 22.3	-144.1 ± 31.7	293.3 ± 7.7
4.7	4.7	-992.9 ± 21.5	846.5 ± 22.3	-146.4 ± 30.7	293.2 ± 7.7
5.1	4.9	-990.7 ± 22.2	846.3 ± 22.3	-144.4 ± 31.8	293.1 ± 7.7
5.5	5.0	-988.7 ± 21.0	848.8 ± 21.5	-139.9 ± 28.5	294.0 ± 7.5
5.9	5.6	-989.2 ± 22.5	846.0 ± 22.5	-143.2 ± 32.5	293.0 ± 7.8
6.3	5.6	-988.8 ± 21.5	845.2 ± 21.7	-143.6 ± 29.8	292.7 ± 7.5
7.1	7.1	-984.8 ± 20.9	847.9 ± 21.1	-136.9 ± 28.2	293.7 ± 7.3
7.9	7.9	-984.3 ± 21.5	848.6 ± 22.0	-135.7 ± 30.5	293.9 ± 7.6
8.7	8.7	-989.8 ± 22.4	844.7 ± 22.4	-145.1 ± 31.9	293.6 ± 7.8
9.5	9.5	-987.2 ± 22.1	848.0 ± 22.0	-139.1 ± 31.1	293.7 ± 7.6
10.3	10.3	-988.6 ± 21.1	847.1 ± 21.7	-141.5 ± 29.2	293.4 ± 7.5

Histograms

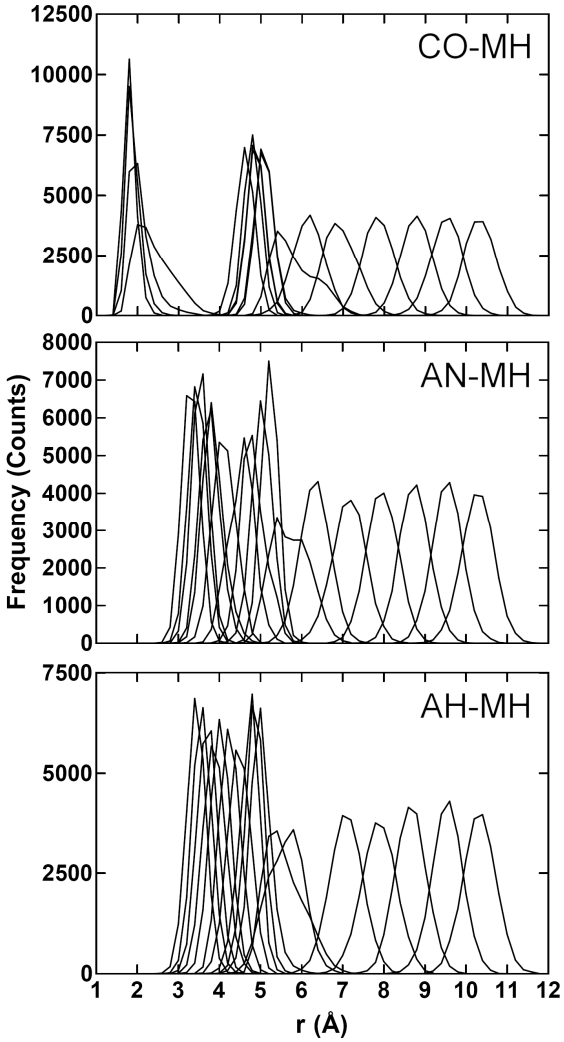


Figure S8. Histograms used for the generation of bupivacaine-MAA potentials of mean force in chloroform at 293 K.

Potentials of Mean Force and Complexes

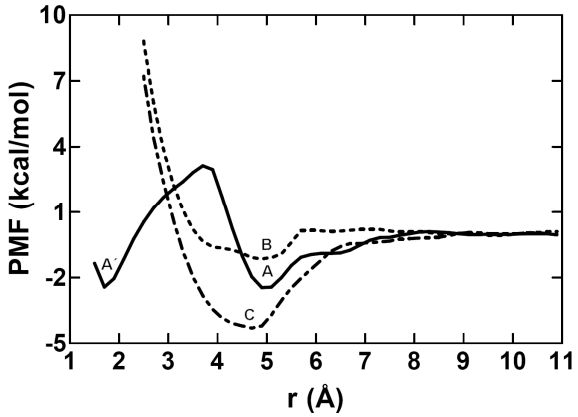
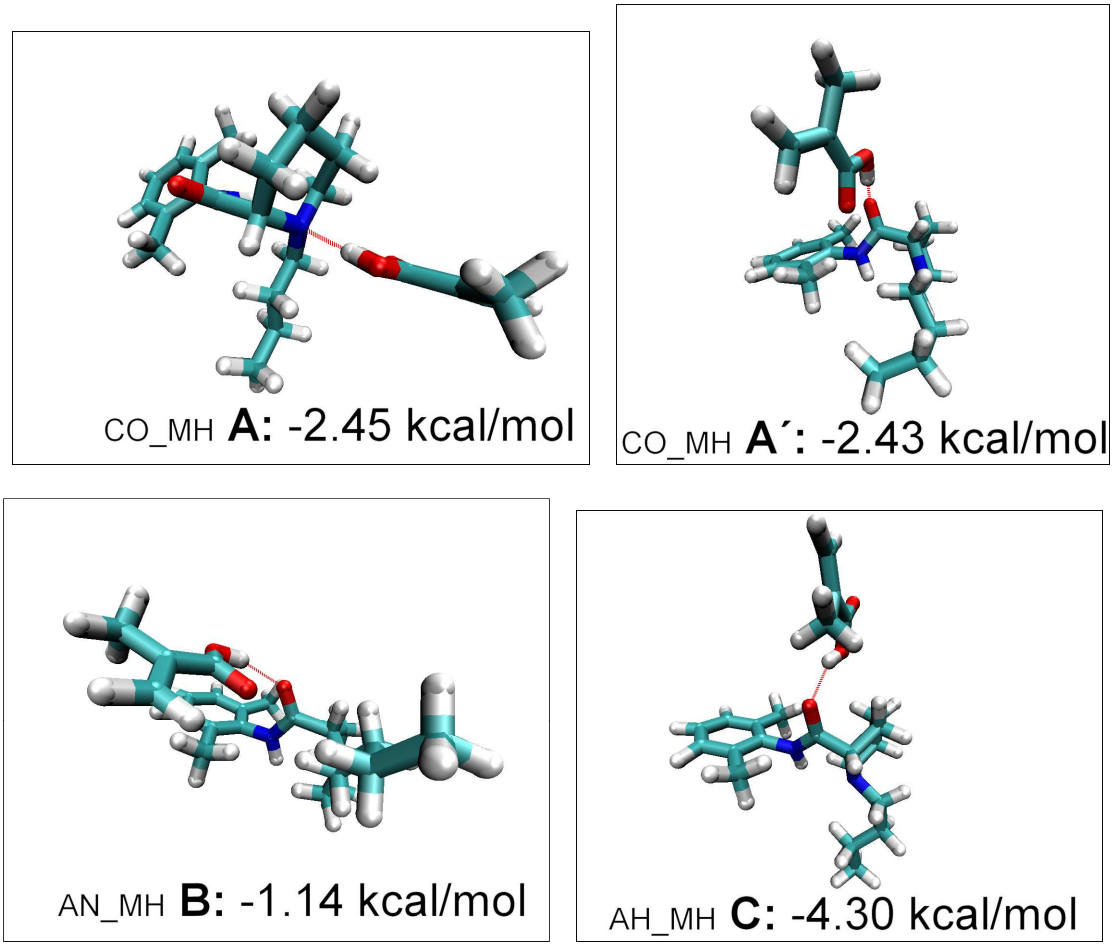


Figure S9. Bupivacaine-MAA potentials of mean force in chloroform at 293 K: starting coordinates 1 (*CO-MH*, ——), 2 (*AN-MH*, ▪▪▪▪▪▪) and 3 (*AH-MH*, ▪▪ — ▪▪).



MD – RDF Analysis
Template-Crosslinker

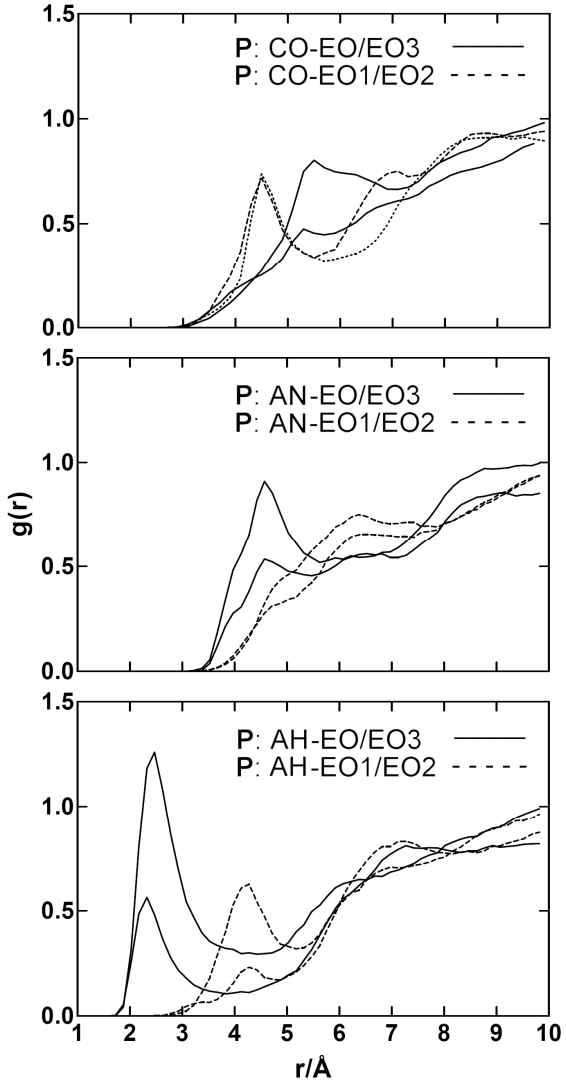


Figure S10. RDFs for the distribution of the EDMA oxygen atoms at the bupivacaine functional groups studied in the full-scale prepolymerization mixture, **P** (see Chart 1 for a description of the atoms analyzed).

Template-Initiator

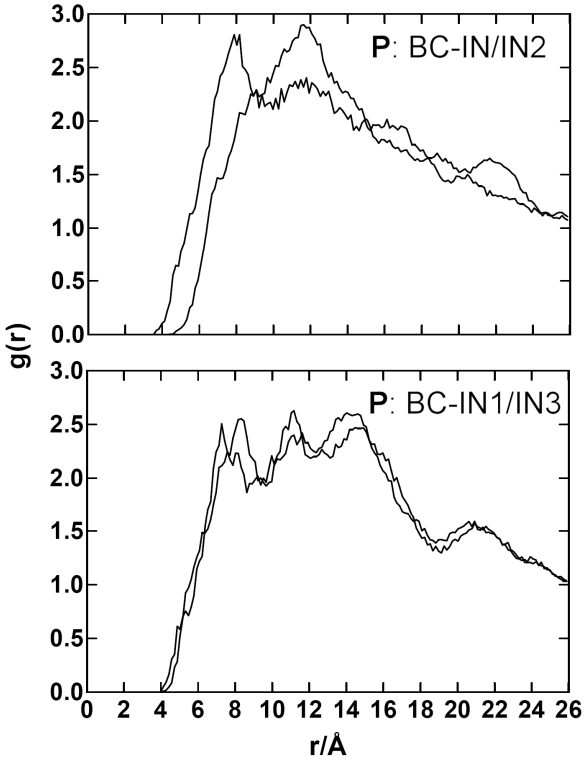


Figure S11. Atomic Distributions of AIBN at the *BC* atom of bupivacaine in the **P** mixture (see Chart 1 for a description of the atoms analyzed).

Template-Template

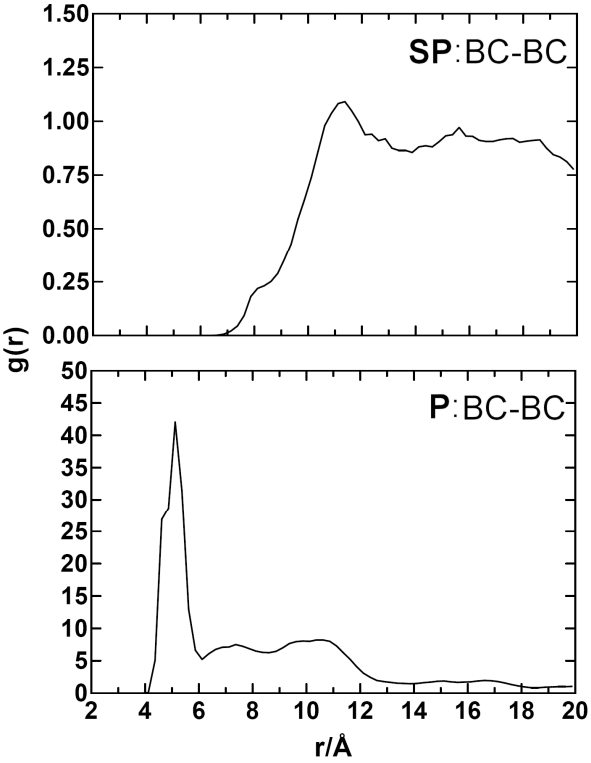


Figure S12. Template-Template distributions for the different prepolymerization mixtures studied (see Chart 1 for a description of the atoms analyzed).

Monomer-Monomer

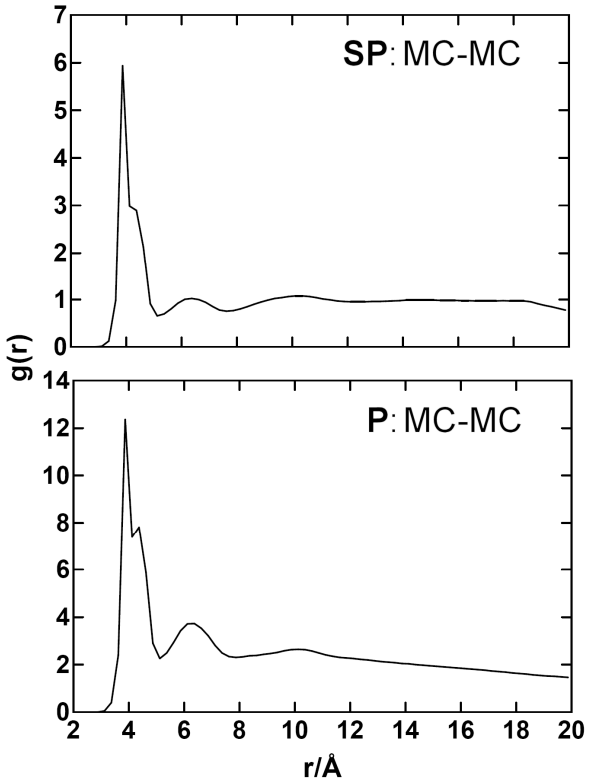


Figure S13. MAA-MAA Distributions for the different prepolymerization mixtures studied (see Chart 1 for a description of the atoms analyzed).

Template-Porogen

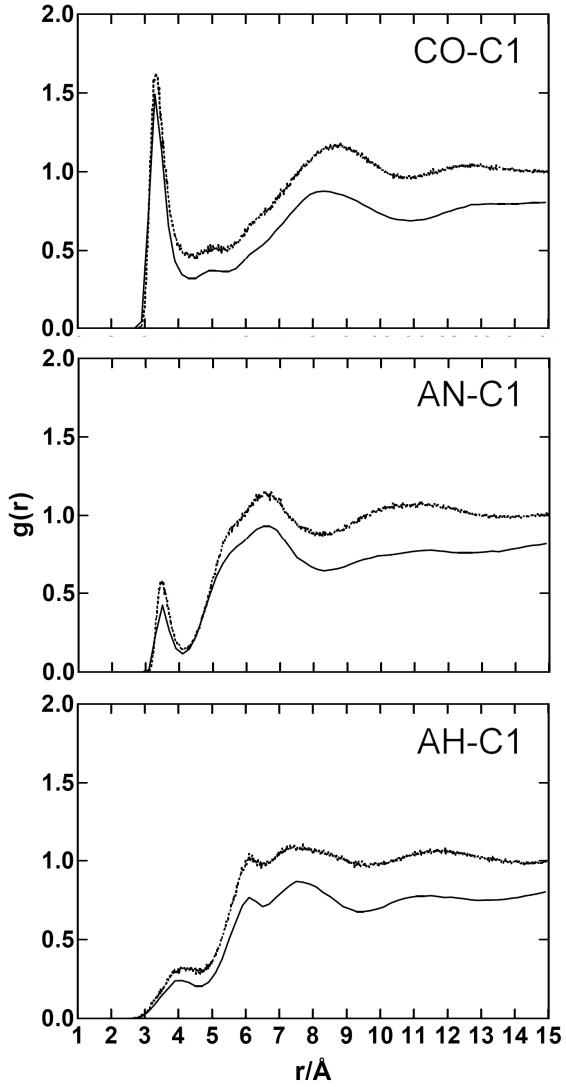


Figure S14. RDFs for the distribution of the central carbon atom (*C1*) of chloroform at the bupivacaine functional groups studied in the **SP** (solid lines) or in the **P** (dashed lines) mixtures (see Chart 1 for a description of the atoms analyzed).

Atomic Densities

TABLE S5: Data Obtained from the RDF Analysis[a]

		Peaks: r(Å) [g(r)]							n(r) [R_{cut}(Å)][b]					
		SP			P				SP			P		
Molecules	Atom Pair													
BUP-MAA	CO-MH	1.7 [33]	4.9 [1.9]	6.1 [1.2]	1.7 [81]				0.70 [2.5]	1.3 [5.3]	2.1 [6.5]	0.37 [2.6]		
BUP-MAA	AN-MH	1.9 [14]	4.7 [2.4]		5.1 [6.0]	8.8 [3.0]			0.33 [2.5]	1.9 [5.6]		1.0 [6.4]	5.7 [12]	
BUP-MAA	AH-MO	1.9 [12]	4.1 [2.0]	5.7 [1.4]	2.5 [1.7]	5.6 [3.8]			0.38 [2.7]	1.1 [4.7]	2.5 [6.7]	0.044 [3.4]	0.86 [6.5]	
BUP-EDMA	CO-EO				5.5 [0.79]							1.2 [6.9]		
BUP-EDMA	CO-EO1				4.4 [0.72]							0.38 [5.5]		
BUP-EDMA	CO-EO2				4.4 [0.73]							0.46 [5.9]		
BUP-EDMA	CO-EO3				*n.a.*							*n.a.*		
BUP-EDMA	AN-EO				4.5 [0.88]							0.62 [5.7]		
BUP-EDMA	AN-EO1				*n.a.*							*n.a.*		
BUP-EDMA	AN-EO2				*n.a.*							*n.a.*		
BUP-EDMA	AN-EO3				*n.a.*							*n.a.*		
BUP-EDMA	AH-EO				2.5 [1.2]							0.24 [4.1]		
BUP-EDMA	AH-EO1				4.2 [1.6]							0.29 [5.1]		
BUP-EDMA	AH-EO2				*n.a.*							*n.a.*		
BUP-EDMA	AH-EO3				2.3 [0.54]							0.081 [3.9]		
BUP-AIBN	BC-IN				8.0 [2.8]							0.25 [9.5]		
BUP-AIBN	BC-IN1				8.2 [2.5]							0.24 [9.7]		
BUP-AIBN	BC-IN2				11.7 [2.9]							1.2 [16]		
BUP-AIBN	BC-IN3				7.2 [2.5]							0.15 [8.7]		
BUP-$CHCl_3$	CO-C1	3.3 [1.6]	8.7 [1.2]		3.3 [1.5]	8.3 [0.87]			0.98 [4.3]	25 [11]		0.48 [4.2]	11 [11]	
BUP-$CHCl_3$	AN-C1	3.5 [0.60]	6.6 [1.1]		3.5 [0.43]	6.6 [0.93]			0.26 [4.1]	10 [8.1]		0.11 [4.0]	4.9 [8.2]	
BUP-$CHCl_3$	AH-C1	*n.a.*			*n.a.*				*n.a.*			*n.a.*		
BUP-BUP	BC-BC	*n.a.*			5.1 [41]				*n.a.*			0.40 [6.1]		
MAA-MAA	MC-MC	3.9 [6.0]	4.4 [3.0]	6.3 [1.0]	3.9 [12]	4.4 [7.9]	6.3 [3.8]		0.72 [4.2]	1.4 [5.2]	3.1 [7.5]	0.45 [4.2]	0.82 [5.2]	2.0 [7.5]

[a] Data are presented for the two molecular systems simulated: The simplified prepolymerization mixture (SP) in which the crosslinker EDMA and the initiator AIBN have been excluded and the full-scale prepolymerization mixture (P). [b] Values were obtained through numerical integration using the sum of g(r) from r=0 up to the cutoff value. n.a.means not analyzed

MD - Grid Density Analysis
Simplified Prepolymerization Mixture (SP)

Template-Monomer

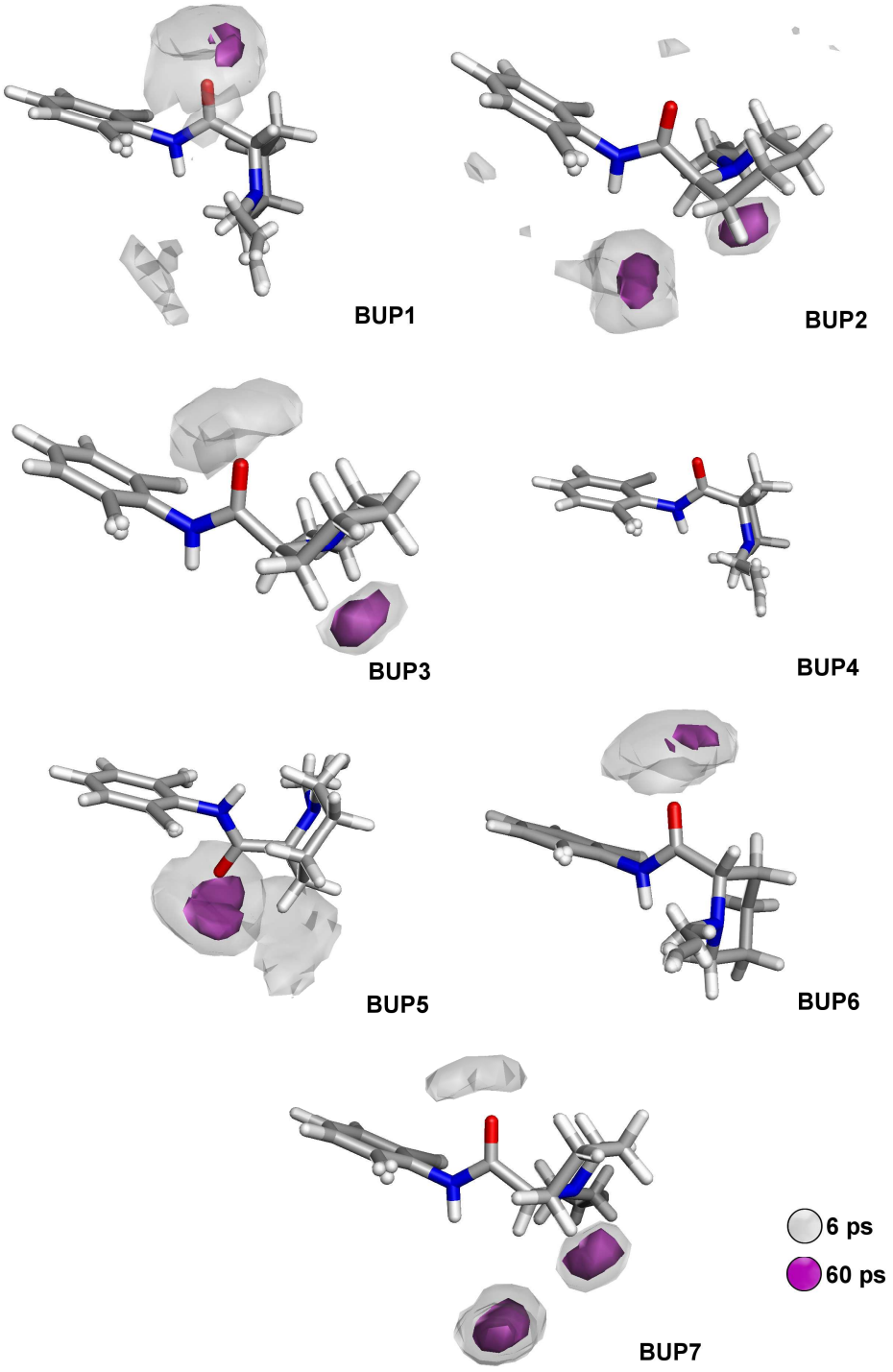


Figure S15. 3-D grid density representations showing probabilities of finding the acidic proton of MAA (*MH*, Chart 1) around each of the seven studied time-averaged stable structural conformations of bupivacaine that are present in the **SP** system (see Chart 1 for a description of the atoms analyzed).

Template-Porogen

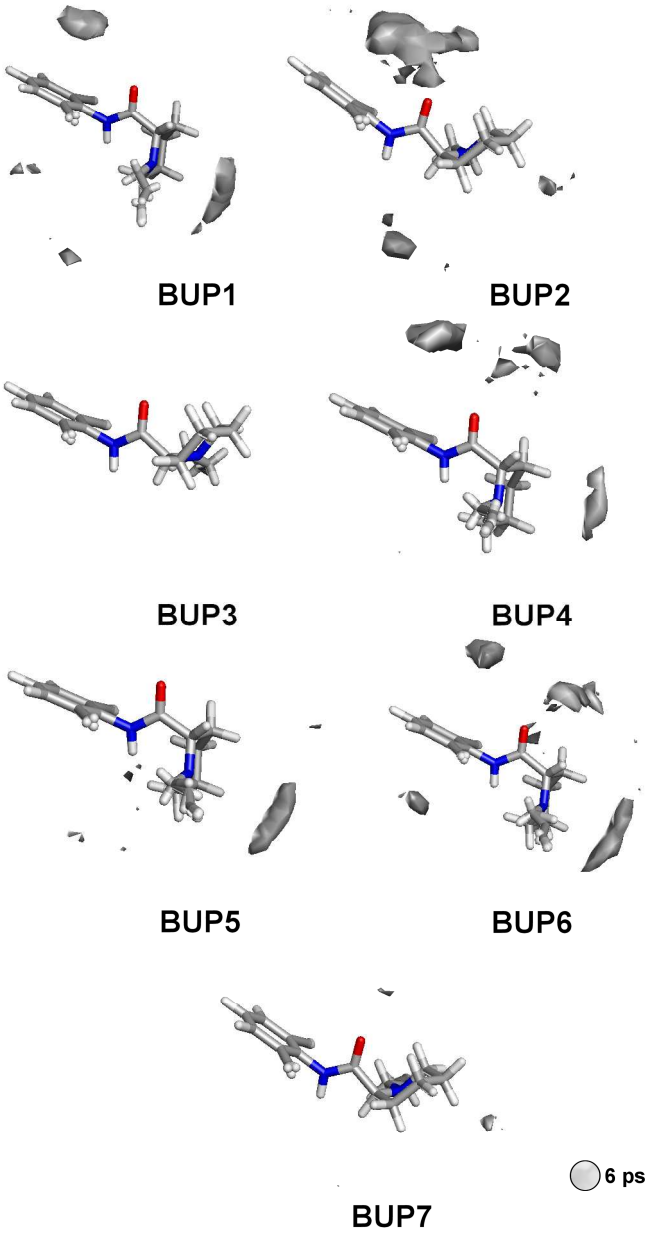


Figure S16. 3-D grid density representations showing probabilities of finding the central carbon of chloroform (*C1*, Chart 1) around each of the seven studied time-averaged stable structural conformations of bupivacaine that are present in the **SP** system (see Chart 1 for a description of the atoms analyzed).

Prepolymerization Mixture (P)

Template-Porogen

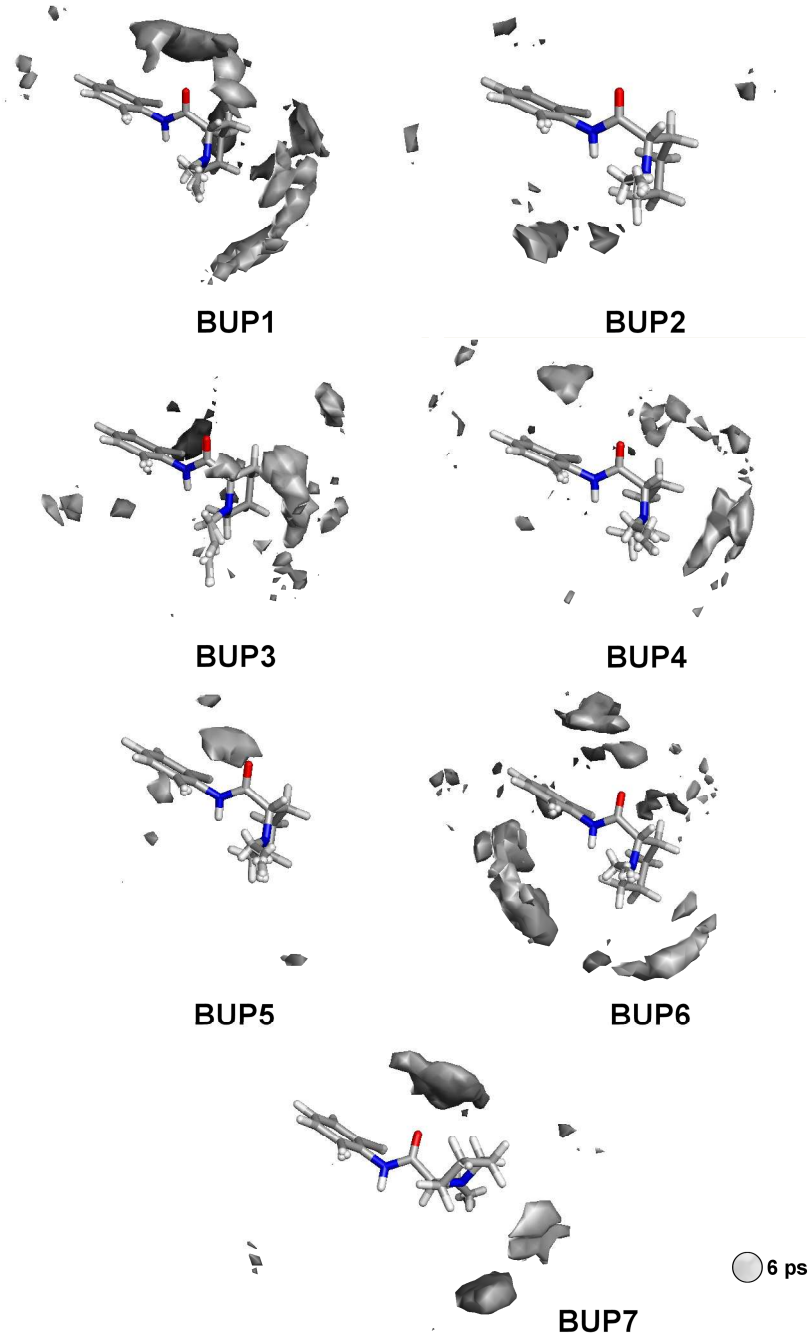


Figure S17. 3-D grid density representations showing probabilities of finding the central carbon of chloroform (*C1*, Chart 1) around each of the seven studied time-averaged stable structural conformations of bupivacaine that are present in the prepolymerization mixture (**P**) (see Chart 1 for a description of the atoms analyzed).

Template-Initiator

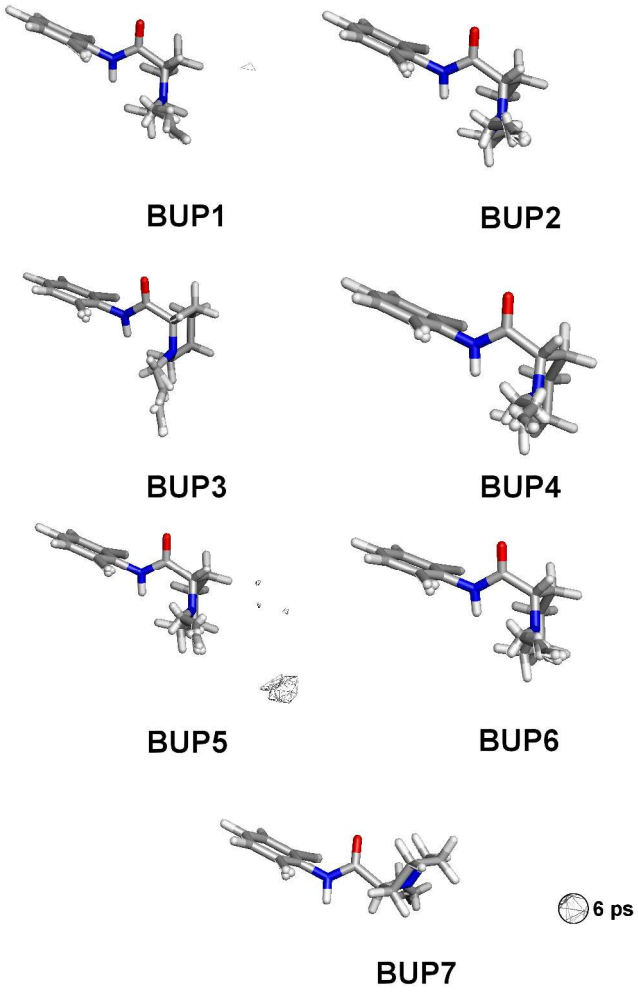


Figure S18. 3-D grid density representations showing probabilities of finding the *IN* (see Chart 1) atom of the initiator 2,2'-azo-bis(isobutyronitrile), AIBN, around each of the seven studied time-averaged stable structural conformations of bupivacaine that are present in the **P** mixture (see Chart 1 for a description of the atoms analyzed).

Polymer-Template Rebinding Study

Polymer Titration Data

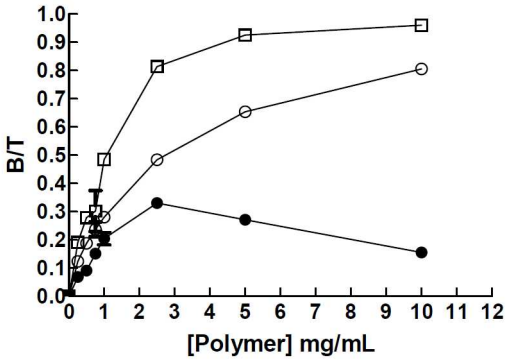


Figure S19. Data from the polymer titration experiment performed in toluene at 298 K. The specific binding of bupivacaine (●) is presented as the difference in the binding to the MIP (□) and the binding to the blank reference polymer (○). The polymer concentration used to obtain 50% template binding, PC_{50}, was found to be ~2.5 mg/mL for the REF (R^2=0.985) and 0.9 mg/mL for the MIP (R^2=0.986) (values obtained from a log[Polymer] versus logitB/T plot).

BET analysis of the polymers resulted in a surface area of the REF of 251.78 ± 1.11 m^2/g and MIP of 104.83 ± 2.60 m^2/g. The average pore sizes diameters were found to be 5.8 nm for the MIP and 6.1 nm for the REF polymer, respectively.

The Affect on Unsaturation on Functional Monomer-Template Binding
^{1}H NMR Titration Experimental Info and Titration Data

Aliquots of a stock solution containing 2.31 M isobutyric acid and 34 mM bupivacaine were added to an NMR tube containing 0.7 mL of 34 mM of bupivacaine. Changes in the chemical shifts of selected bupivacaine Δδ (ppm), were determined and plotted as a function of the concentration of isobutyric acid added (3.30 mM – 1.05 M).

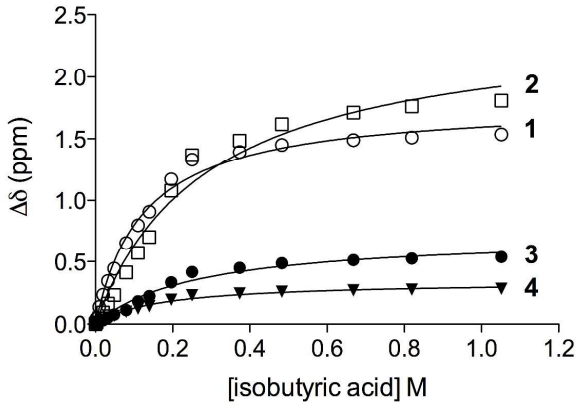


Figure S20. Isobutyric acid-bupivacaine ^{1}H NMR titration experiment in $CDCl_3$ at 293 K. Analysis of the bupivacaine protons studied (see Chart 2) using a non-linear one-site binding model yielded:
R^2*>0.99* and K_D= *0.125 ± 0.011 M* for **1** (□),
R^2*>0.99* and K_D= *0.267 ± 0.043 M* for **2** (○),
R^2*>0.99* and K_D= *0.287 ± 0.045 M* for **3** (●),
R^2*>0.99* and K_D= *0.172 ± 0.016 M* for **4** (▼).

MD Simulation Setup and Grid Density Data

The simulated methacrylic acid or isobutyric-bupivacaine mixtures (6 bupivacaine, 61 methacrylic acid and 476 chloroform molecules or 6 bupivacaine, 64 isobutyric acid and XXX chloroform molecules) were prepared identically as being described under the *materials and methods section*. After equilibration for 250 ps under conditions of NPT (P=1 bar and T=293 K), to assure stable values in density and energy, grid density data was extracted for the distribution of functional monomer around the six bupivacaine molecules present in each system during a 5 ns production phase at NVT. The non-bonded used in the simulations was 9.0 Å and data was saved every 0.2 ps.

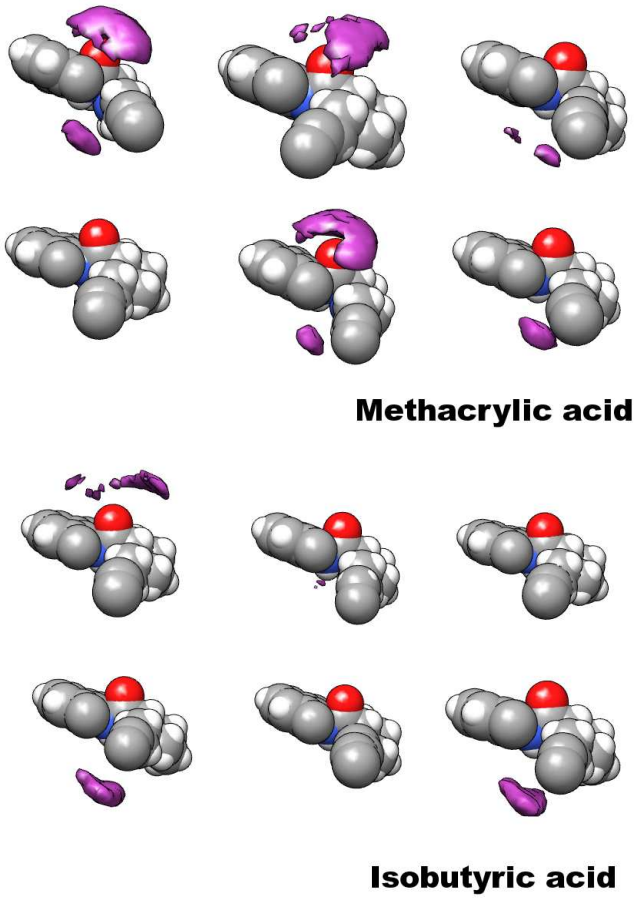


Figure S21. Grid density representation of the distribution of the acidic proton of methacrylic acid (MAA, top) or isobutyric acid (bottom) around the six template molecules present in each **SP** system during a 5 ns production phase at NVT in chloroform. Purple surfaces represent densities of functional monomer of ≥ 6 ps.