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Supporting Information

New Catalytic Insights Into Acid/Base Conjugates: Highly Selective Bifunctional Catalysts for the Ring-Opening Polymerization of Lactide

*Daniel J. Coady, Kazuki Fukushima, Hans W. Horn, Julia E. Rice and James L. Hedrick**

IBM Almaden Research Center, 650 Harry Road,
San Jose, CA, USA
95120.
E-mail: hedrick@almaden.ibm.com; Fax: (1)408-927-3310

Materials:

Reagents were available commercially from Aldrich and used as received unless otherwise noted. Benzyl alcohol was dried by distillation from CaH_2. 4-Pyrene-1-butanol (99%) was dried by stirring in dry THF with CaH_2, filtering, and removing the solvent in vacuo. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (98%) was stirred over CaH_2, vacuum distilled, then stored over molecular sieves (3 Å). Benzoic acid (BA) was dried in a vacuum oven (60 °C) for 72 h. (L)-Lactide was recrytallized from dry toluene and dried in a vacuum oven (60 °C). *p*-Toluenesulfonic acid monohydrate was dried at 80 °C under high-vacuum for 48 h. Dry THF, toluene and CH_2Cl_2 were obtained by using a solvent drying system from Innovative Technologies.

Methods:

All polymerizations were carried out in a nitrogen filled glove box. ^{1}H NMR spectra were obtained on a Bruker Avance 400 instrument using $CDCl_3$ solutions. Gel permeation chromatography (GPC) was performed in THF at 30 °C using a Waters chromatograph equipped with four 5 µm Waters columns (300 mm x 7.7 mm) connected in series with increasing pore size (10, 1000, 10^5, 10^6 Å), a Waters 410 differential refractometer for refractive index (RI) detection and a 996 photodiode array detector calibrated against polystyrene standards (750 - (2 x 10^6) g/mol).

Procedures:

DBU/BA Salt (1:1): A flame dried flask was charged with benzoic acid (1.0 g, 8.18 mmol), ether (20 mL) and a stirbar under dry nitrogen atmosphere. To the stirred solution, DBU (1.2g, 8.18 mmol) was added. Instantly a white precipitate formed and stirring was continued for 1 h. The precipitate, 2.1 g (95%) of a white salt, was then washed with excess ether and isolated by decantation. The salt was

then dried under HV. %). ^{1}H NMR ($CDCl_3$) δ: 8.06 - 8.12 (bm, 2H), 7.31-7.37 (bm, 3H), 5.34 (t, 2H), 3.36-3.46 (bm, 4H), 2.92-3.02 (bm, 2H), 2.01 (p, 2H), 1.62-1.82 (b, 6H); ^{13}C NMR: 173.1, 166.0, 138.7, 129.4, 127.42, 54.1, 48.6, 38.2, 32.1, 29.2, 27.1, 24.3, 19.8.

MTBD/BA Salt (1:1): A flame dried flask was charged with benzoic acid (1.0 g, 8.18 mmol), ether (20 mL) and a stirbar under dry nitrogen atmosphere. To the stirred solution, MTBD (1.2g, 8.18 mmol) was added. Instantly a white precipitate formed and stirring was continued for 1 h. The precipitate, 2.0 g (91%) of white salt, was then washed with excess ether and isolated by decantation. The salt was then dried under HV. ^{1}H NMR ($CDCl_3$) δ: 8.07 - 8.12 (bm, 2H), 7.31-7.37 (bm, 3H), 3.53 (t, 2H), 3.20-3.33 (b, 9H), 1.92-2.02 (b, 4H); ^{13}C NMR: 172.4, 151.4, 139.1, 129.4, 129.3, 127.4, 48.1, 48.0, 47.1, 38.7, 38.6.

DMAP/BA Salt (1:1): A flame dried flask was charged with benzoic acid (1.0 g, 8.18 mmol), ether (20 mL) and a stirbar under dry nitrogen atmosphere. To the stirred solution, DMAP (1.0g, 8.18 mmol) was added. Instantly a white precipitate formed and stirring was continued for 1 h. The precipitate, 1.9 g (95%) of white salt, was then washed with excess ether and isolated by decantation. The salt was then dried under HV. ^{1}H NMR ($CDCl_3$) δ: 8.07 -8.12 (bm, 2H), 7.31-7.37 (bm, 3H), 7.38-7.52 (m, 3H), 6.66 (d, 2H), 3.11 (s, 6H); ^{13}C NMR: 171.8, 156.0, 144.1, 134.9, 131.1, 129.6, 127.9, 106.4, 39.5.

N-Methylimidazole/BA Salt (1:1): A flame dried flask was charged with benzoic acid (1.0 g, 8.18 mmol), ether (20 mL) and a stirbar under dry nitrogen atmosphere. To the stirred solution, N-methylimidazole (0.67g, 8.18 mmol) was added. Instantly a white precipitate formed and stirring was continued for 1 h. The precipitate, 1.5 g (90%) of white salt, was then washed with excess ether and isolated by decantation. The salt was then dried under HV. ^{1}H NMR ($CDCl_3$) δ: 8.14 (bd, 2H), 7.79 (t, 1H), 7.46 (t, 1H), 7.18 (t, 1H), 6.92 (t, 1H), 3.74 (s, 3H); ^{13}C NMR: 170.4, 137.6, 132.4, 131.8, 129.8, 128.2, 127.7, 120.2, 33.7.

Triphenylphosphine/BA Salt (1:1): A flame dried flask was charged with benzoic acid (1.0 g, 8.18 mmol), ether (20 mL) and a stirbar under dry nitrogen atmosphere. To the stirred solution triphenylphosphine (2.14 g, 8.18 mmol) was added. Instantly a white precipitate formed and stirring was continued for 1 h. The precipitate, 2.9 g (92%) of white salt, was then washed with excess ether and isolated by decantation. The salt was then dried under HV. ^{1}H NMR ($CDCl_3$) δ: 8.17 (d, 2H), 7.66 (t, 1H), 7.52 (t, 2H), 7/31-7.4 (b, 12H); ^{13}C NMR: 172.2, 137.2, 137.1, 133.8, 133.6, 130.2, 129.3, 128.7, 128.5.

Triethylamine/BA Salt (1:1): A flame dried flask was charged with benzoic acid (1.0 g, 8.18 mmol), ether (20 mL) and a stirbar under dry nitrogen atmosphere. To the stirred solution triethylamine (0.83 g, 8.18 mmol) was added. Instantly a white precipitate formed and stirring was continued for 1 h. The precipitate, 1.7 g (93%) of white salt, was then washed with excess ether and isolated by decantation. The salt was then dried under HV. ^{1}H NMR ($CDCl_3$) δ: 8.08 (d, 2H), 7.38 (m, 3H), 3.09 (q, 6H), 1.30 (t, 9H); ^{13}C NMR: 172.7, 136.4, 130.4, 129.5, 127.7, 44.8, 8.8.

DBU/HCl Salt (1:1): A flame dried flask was charged with DBU (1.0 g, 6.56 mmol), ether (20 mL) and a stirbar under dry nitrogen atmosphere. With vigorous stirring, a 1M ethereal HCl solution (6.6 mL) was added to form a white precipitate. Stirring was continued for 1 hr then excess solvent was decanted to yield 1.1 g (90%). The salt was then dried under HV. ^{1}H NMR ($CDCl_3$) δ: 3.32 (bq, 6H), 2.65 (b, 2H), 1.88 (p, 2H), 1.56-1.73 (b 6H); ^{13}C NMR: 166.7, 53.5, 48.5, 41.3, 34.9, 29.4 27.8, 25.1, 21.1.

MTBD/HCl Salt (1:1): A flame dried flask was charged with MTBD (0.25 g, 1.63 mmol), ether (10 mL) and a stirbar under dry nitrogen atmosphere. With vigorous stirring a 1M ethereal HCl solution was then added to form a white precipitate. Stirring was continued for 1 hr then excess solvent was decanted to yield 0.29 g (94%). The salt was then dried under HV. ^{1}H NMR ($CDCl_3$) δ: 3.40 (t, 2H), 3.15 (m, 6H), 2.94 (s, 3H), 1.98 (p, 2H), 1.86 (p, 2H); ^{13}C NMR: 151.8, 65.8, 48.3, 48.1, 42.6, 37.7, 22.5, 15.3.

DBU/TsOH Salt (1:1): A flame dried flask was charged with PTSA (1.0 g, 5.81 mmol), ether (20 mL) and a stirbar under dry nitrogen atmosphere. To the stirred solution, DBU (0.88 g, 5.81 mmol) was added. Instantly a white precipitate formed and stirring was continued for 1 h. The precipitate, 1.5 g (81%) of white salt, was then washed with excess ether and isolated by decantation. The salt was then dried under HV. ^{1}H NMR ($CDCl_3$) δ: 7.75 (d, 2H), 7.16 (d, 2H), 4.33 (bs, 2H), 3.43 (m, 6H), 2.75 (b, 2H), 2.34 (s, 3H), 1.96 (p, 2H), 1.56-1.73 (b, 6H); ^{13}C NMR: 166.3, 142,6, 139.8, 128.8, 125.9, 54.4, 48.6, 38.2, 32.6, 28.9, 26.7, 23.9, 21.3, 19.4.

MTBD/TsOH Salt (1:1): A flame dried flask was charged with PTSA (0.28 g, 1.63 mmol), ether (20 mL) and a stirbar under dry nitrogen atmosphere. To the stirred solution, MTBD (0.25 g, 1.63 mmol) was added. Instantly a white precipitate formed and stirring was continued for 1 h. The precipitate, 0.47 g (88%) of white salt, was then washed with excess ether and isolated by decantation. The salt was then dried under HV. ^{1}H NMR ($CDCl_3$) δ: 7.75 (d, 2H), 7.16 (d, 2H), 3.42 (t, 2H), 3.25 (q, 6H), 3.06 (s, 3H), 2.33 (s, 3H), 2.00 (p, 2H), 1.92 (p, 2H); ^{13}C NMR: 151.2, 143.4, 139.3, 128.6, 125.9, 48.1, 47.9, 47.2, 39.3, 38.0, 21,3, 21.2, 20.9.

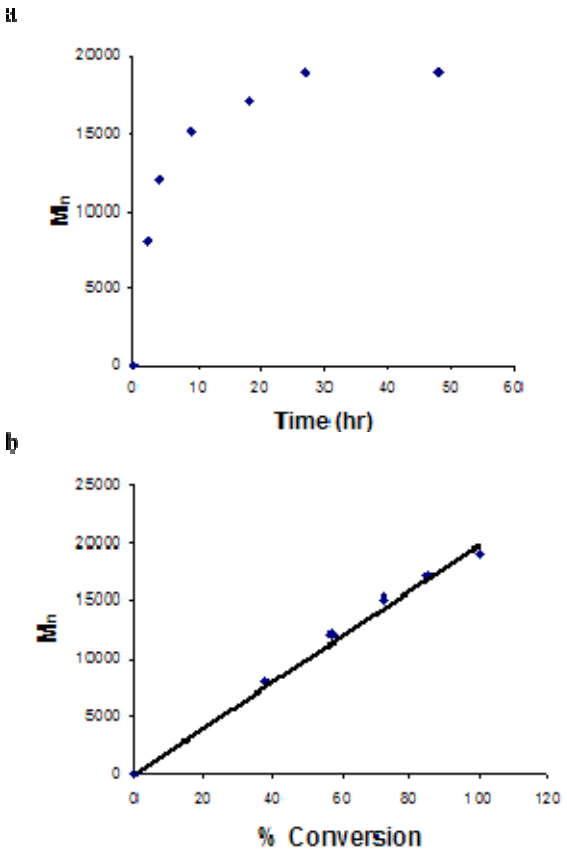
DBU/Acetic Acid Salt (1:1): A flame dried flask was charged with acetic acid (0.099 g, 1.64 mmol), DCM (10 mL) and a stirbar under a dry nitrogen atmosphere. To the stirred solution, DBU (0.25 g, 1.64 mmol) was added and stirring continued for 1 h. The solvent was removed under vacuum to yield 0.34 (98%) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 3.30-3.55 (m, 6H), 2.85 (bs, 2H), 1.90-2.04 (bm, 6H), 1.58-1.77 (bm, 6H); ^{13}C NMR: 177.1, 166.0, 54.3, 48.6, 38.0, 32.0, 29.1, 26.9, 24.1, 23.8, 19.6.

Representative Base Saturation Procedure: A flask was charged with dry ether (20 mL), BA (1.00 g, 8.19 mmol) and a stirbar under a nitrogen atmosphere. DBU (0.25 g, 1.64 mmol) was then added dropwise to a stirred solution. Immediately a white precipitate began to form and stirring was continued for 1 hr. The precipitate was then filtered off and washed with excess dry ether to yield 0.59 g (90%) white powder. ^{1}H NMR ($CDCl_3$) δ: 8.10 - 8.15 (bm, 4H), 7.37-7.49 (bm, 6H), 3.56 (t, 2H), 3.25-3.41 (bm, 4H), 2.92-2.97 (bm, 2H), 2.00 (p, 2H), 1.62-1.82 (b, 6H); ^{13}C NMR: 171.3, 166.2, 134.8, 131.2, 129.7, 127.9, 54.2, 48.6, 38.2, 32.4, 29.2, 27.0, 24.1, 19.6.

Representative Lactide Polymerization: In a nitrogen filled glovebox a vial was charged with benzyl alcohol (3.6 μL, 0.0347 mmol), (*L*)-lactide (0.50 g, 3.47 mmol), catalyst (DBU/BA Salt (1:1)) (0.010 g, 0.0347 mmol) and a stirbar. The polymerization was then initiated by the addition of DCM (3.5 mL). After 48 h complete monomer consumption was observed and the resultant mixture was precipitated into cold 2-propanol yielding 0.35 g (71%) of white polymer Mn-18100, PDI-1.07. ^{1}H NMR ($CDCl_3$) δ: 5.21 (bq, 2H), 1.42 (bd, 6H).

Representative Lactide Depolymerization: In a nitrogen filled glovebox a vial was charged with poly((L)-lactide) (0.1 g, M_n – 18100, PDI – 1.06), catalyst (DBU/BA (1:1)) (0.0047 g, 0.0173 mmol), and a stirbar. The depolymerization was then initiated by the addition of DCM (0.8 mL). After 24 and 48 hr aliquots were removed and examined by GPC. After 48 h no discernible change was observed.

Figure S1. Graphical representations of (a) M_n versus time for DBU/BA and (b) M_n versus conversion for DBU/BA catalyzed polymerizations.



Computational Methods:

Quantum-chemical calculations on a representative molecular model system were carried out at the B3LYP density functional level with a continuum dielectric model (IEF-cPCM [1]) for CH_2Cl_2 (dielectric=8.9) as implemented in GAMESS-US.[2] Geometries of stationary points along the reaction pathway were optimized using an aug-VTZP basis[3,4] and single point energies for the optimized geometries were obtained using an aug-cc-pVTZ basis [5].

In order to rationalize and understand some of the experimental observations (such as the catalytically required DBU:BA ratio), we explored possible adducts between DBU, BA and alcohol (here we replaced BnOH with MeOH), the geometries and energetics of which are shown in Fig. S2. This study lent credibility to our suspicion about the catalytically active species to be the $DBUH^+$,BA^- ion pair (Fig. S2a). Further evidence for this was drawn from a study of the dissociation energetics of the ion pair, which showed that a dissociation into either neutral species as well as into separated ions is energetically not favored in a medium with a dielectric of 8.9 (dissociation energies ~ 16 kcal/mol; Fig. S3). The geometry of the catalytic inactive species at DBU/BA saturation is shown in Fig. S2c (see footnote 4). The geometry of the activated initiator in presence of the $DBUH^+$,BA^- ion pair is shown in Fig. S2b, highlighting the carboxylic oxygen of BA^- to be the nucleophilic site of this novel bifunctional catalyst.

For pathway studies we used the model system (Fig. S4) which replaced BA with formic acid (FA), BnOH with MeOH, and simplified DBU by replacing the 7-membered ring with two CH_3 groups. The reaction studied was the initial step of the ring-opening polymerization of L-lactide, resulting in a reaction pathway (Fig. S5 and Fig. 2 in text) with a rate-determining step (nucleophilic attack of activated alcohol at activated lactide carbonyl-C) of ~18kcal/mol. Note that there are two barriers (TS1 and TS2) (Fig. S5) that differ in energy by only ~1 kcal/mol. Due to approximations inherent in the methods used (e.g. DFT, continuum solvent) either barrier could potentially be the rate-determining one. Fig. S6 (animation) shows the structure of an activated complex involving $DBUH^+$/FA^--MeOH-Lactide (located between "**RC**" and "**INT0**" species of Fig. S5). This highlights $DBUH^+$ as hydrogen-bonding species of this novel bifunctional catalyst.

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[1] Barone, V.; Cossi, M. *J. Phys. Chem. A*, **1998**, *102*, 1995.

[2] Schmidt, M. W. ; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comp. Chem.*, **1993**, *14*, 1347.

[3] Schaefer A.; Horn H.; Ahlrichs R. *J. Chem. Phys.* **1992**, 97, 2571. diffuse functions added via extrapolation

[4] We emphasize that due to the charged nature of the reactive species involved the use of the popular 6-31+G* basis[6] is insufficient. Certain adducts (e.g. $(DBUH_2)^{2+}(BA)_2^{2-}$ with protonation at both nitrogens of DBU) were found to be local minima when using a 6-31+G* basis while they were not bound when using the more flexible aug-VTZP basis.

[5] Woon, D. E.; Dunning, T. H. *J. Chem. Phys.*, **1995**, *103*, 4572.

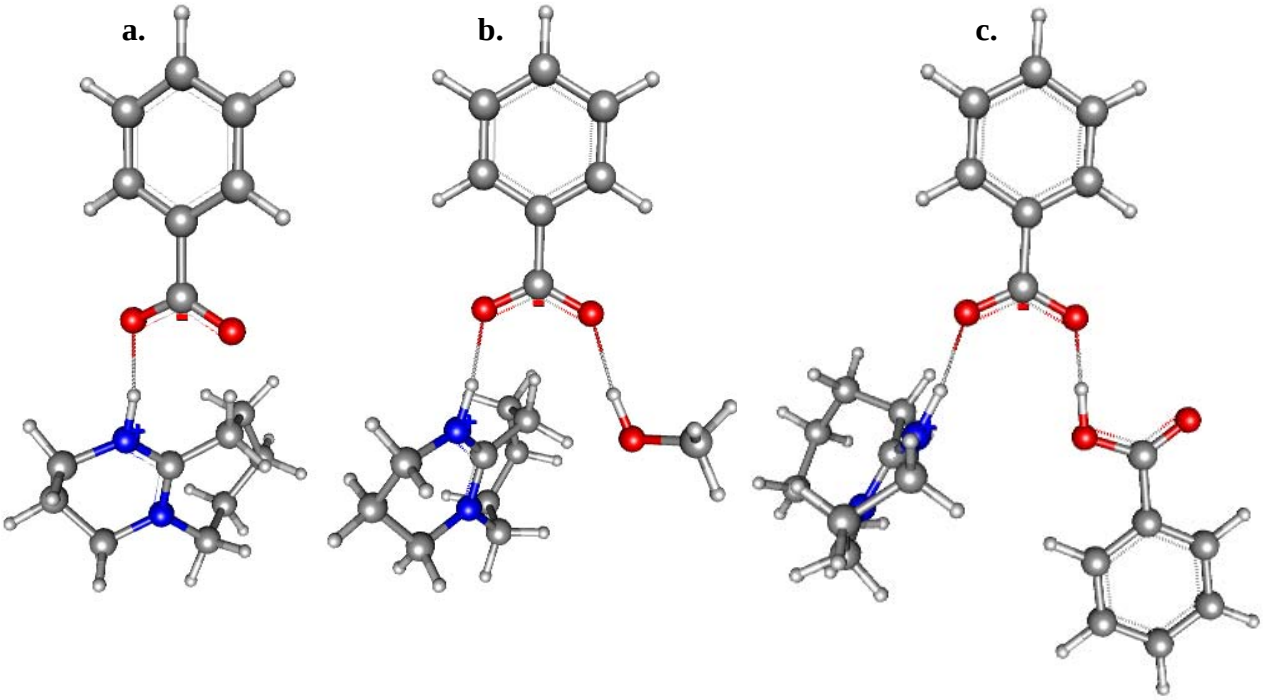

Figure S2. Select Adducts between DBU, BA and MeOH or BnOH

- **a.** DBU/BA; binding energy -16.3 kcal/mol; this species ($DBUH^+$,BA^- ion pair) is the catalytically active species with the carboxylic oxygen of BA^- being the nucleophilic site and $DBUH^+$ being the hydrogen-bonding site of this novel bifunctional catalyst.
- **b.** DBU/BA/MeOH; binding energy -22.1 kcal/mol; this shows the nucleophilic activation of the initiating alcohol in presence of the $DBUH^+$,BA^- ion pair
- **c.** DBU/2*BA; binding energy -25.0 kcal/mol; this is the catalytic inactive species at DBU/BA saturation (the 2*BA moiety is reminiscent of a BA dimer)

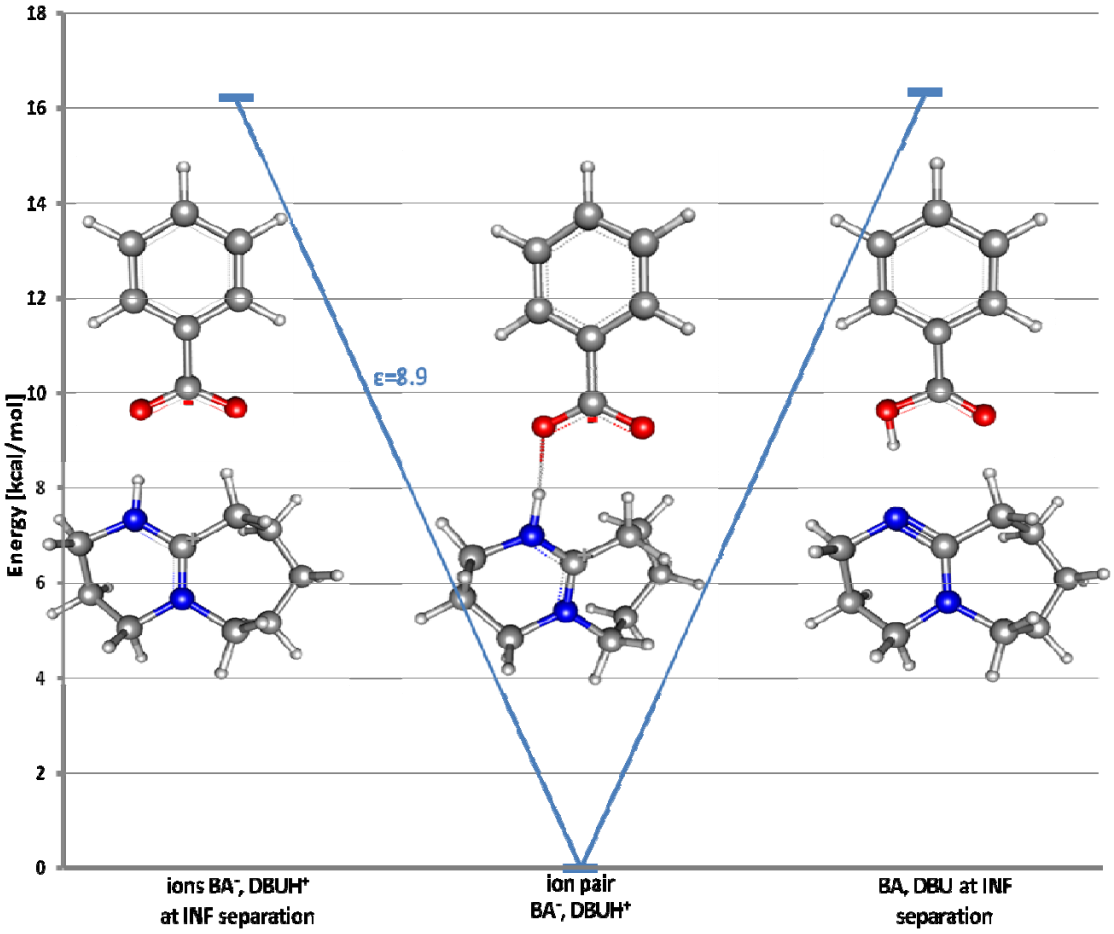

Figure S3. Dissociation energetics of the $DBUH^+$, BA^- ion pair.

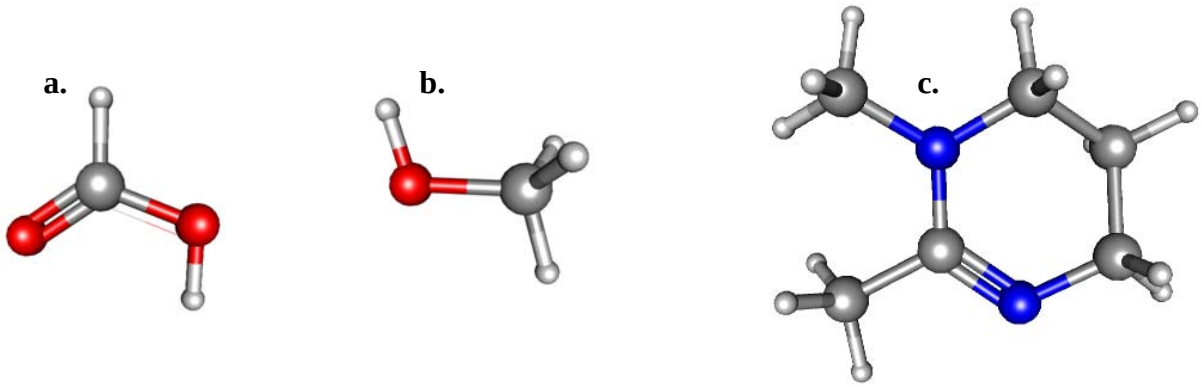

Figure S4. Model compounds for BA, BnOH and DBU used in computational study of ring-opening polymerization pathway of L-lactide. Include (a) Formic acid (FA) for benzoic acid, (b) Methanol for benzyl alcohol and (c) DBU was simplified by replacing the 7-membered ring with two CH_3 groups.

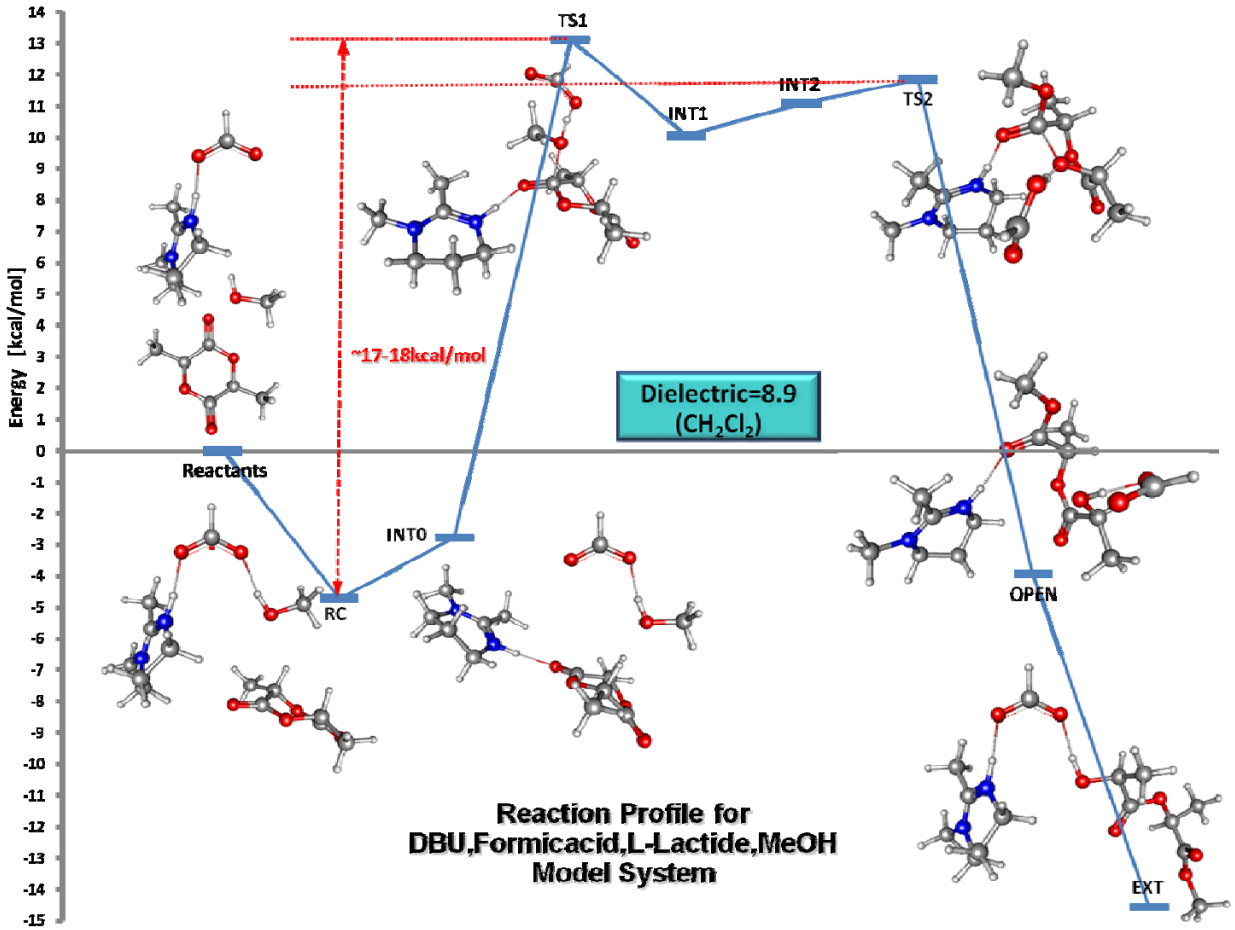

Figure S5. Initial step of the ring-opening polymerization of L-lactide in presence of $DBUH^+/FA^-$ model catalyst and MeOH as initiator (images of structures "INT1" and "INT2" have been omitted for clarity). High-resolution version of Figure 2 in text

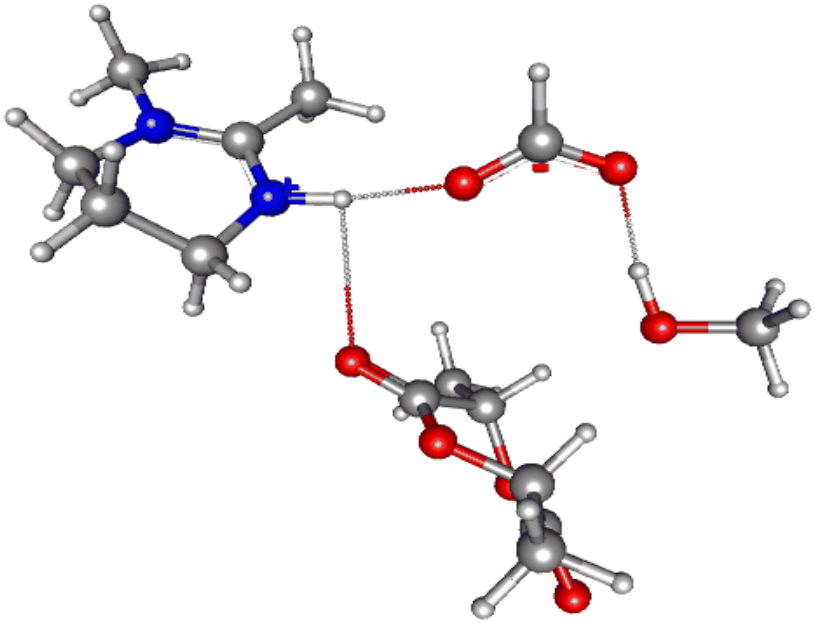

Figure S6. Activated complex involving $DBUH^+/FA^-$-MeOH-Lactide (animation; located between "RC" and "INT0" species of Fig. S5).

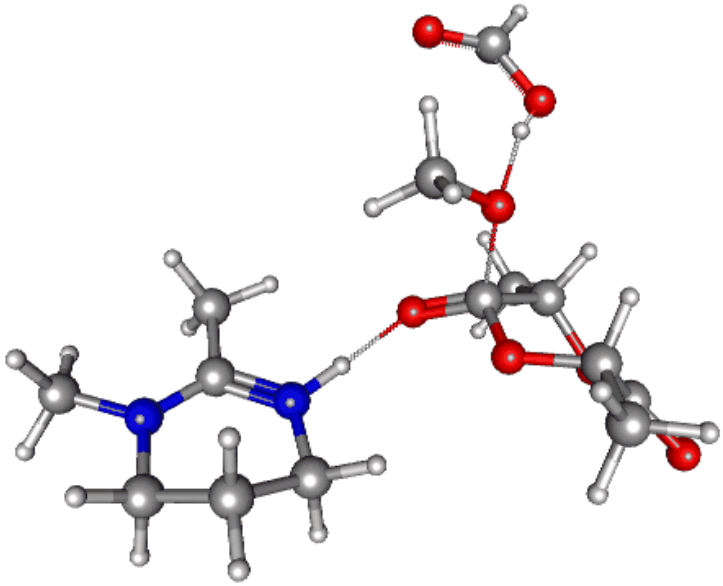

Figure S7. Geometry of transition state "TS1" of Fig. S5 (animation).