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Supporting Information

Revealing the Nature of Thio-Click Reactions on Solid Phase

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Reagents

Pentaerythritol tetrakis-(3-mercaptopropionate) (tetra-thiol), 1,7-octadiyne (di-alkyne), 2,2-dimethoxy-2-phenylacetophenone (DMPA), dodecane-1-thiol, 10-undecylenic acid, *n*-hexyl isocyanate, *n*-hexyl isothiocyanate, methyl-2-bromopropionate, N-methylmaleimide, 1,2-epoxybutane, triethylamine (Et_3N), dimethylformamide (DMF), azidotrimethyl-silane, tetrabutylammonium fluoride (1M in THF), 2-norbornene, *n*-butyl acrylate, dimethylphenyl phosphine (DMPP), N-tosylaziridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), $ZnCl_2$, BF_3 and tri-butylphosphine were purchased from Aldrich and used as received. CuBr was washed with glacier acetic acid overnight to remove oxidized species, further washed with ethanol and DEE, and dried under vacuum. Pentamethyldiethylenetriamine (PMDETA) was distilled prior to use. Washing solvents were technical grade and used as received. Fluorogenic maleate (**3**) was synthesized according to the literature.[1] Synthesis of tris(benzyltriazolylmethyl)amine (TBTA) is reported elsewhere.[2]

Instrumentation

The size and monodispersity of the dried beads, beads in continuous phase, and beads in solvent were examined by optical microscopy, with a Nikon SMZ800 microscope, and evaluated statistically on representative samples.

The morphology of the beads has been observed by scanning electron microscopy (SEM), with a Quanta 200 FEG FEI scanning electron microscope operated at an acceleration voltage of 20 kV.

Fourier transform infrared (FTIR) spectra of polymer beads, crushed and dispersed in KBr, were recorded by a Perkin-Elmer Spectrum 1000, in order to provide relevant qualitative information about IR active groups.

Elemental analysis measurements were done in CNRS Paris (Centre National de la Recherche Scientifique).

Synthesis of 1-dodecaneazide [3]

1-dodecaneazide was synthesized by reaction of 1-iodododecane (6 ml) with azidotrimethyl-silane (5 ml, 1.5 eq), in the presence of tetrabutylammonium fluoride (36 ml, 1M in THF, 1.5 eq). This mixture is stirred at room temperature for 24h. 25 ml of THF and water were added to the crude and the aqueous phase was extracted with pentane (3x25 ml). After washing with 3x25 ml water and drying with Na_2SO_4, pentane was removed under vacuum. GC-MS spectra (negative mode) of the product has a single peak with a retention time of 11.12 min whereas the retention time of the iodide was 11.81 min. MS spectra of the product (peak at 11.12 min) showed a minor peak at 210 m/z (211.20 calculated) but there was a larger peak at 182 m/z, which is attributed to product with loss of N_2. MS of iodododecane was completely different and showed the mother peak of 296 m/z (calculated 296.24). ^1H NMR (300 MHz, $CDCl_3$): δ 3.18 (t, 2H), 1.53 (m, 2H), 1.19 (bs, 18H), 0.81 (t, 3H).

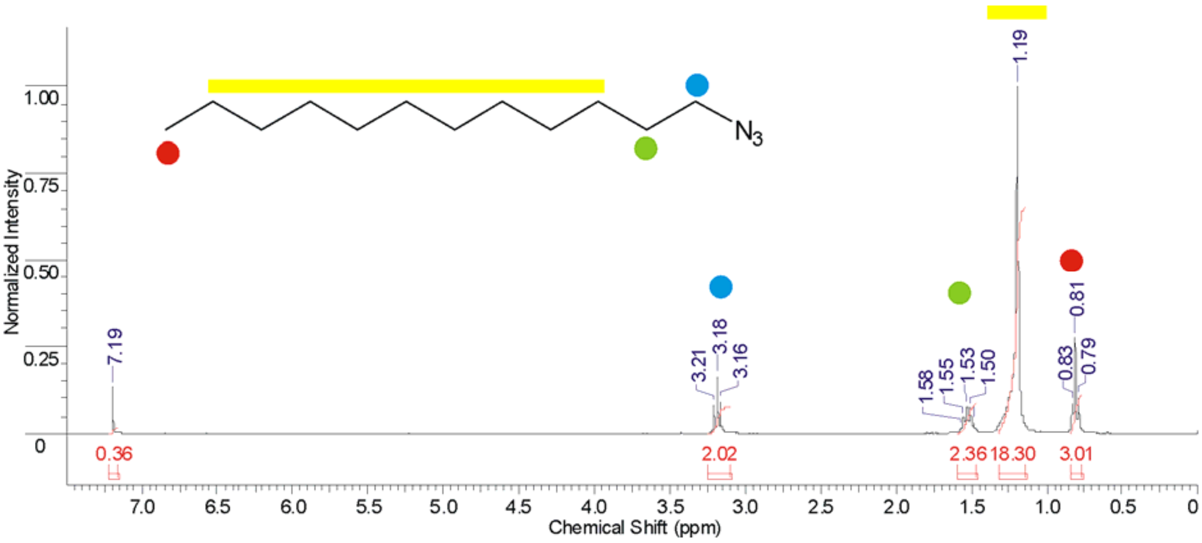


Fig S1. NMR of 1-dodecaneazide

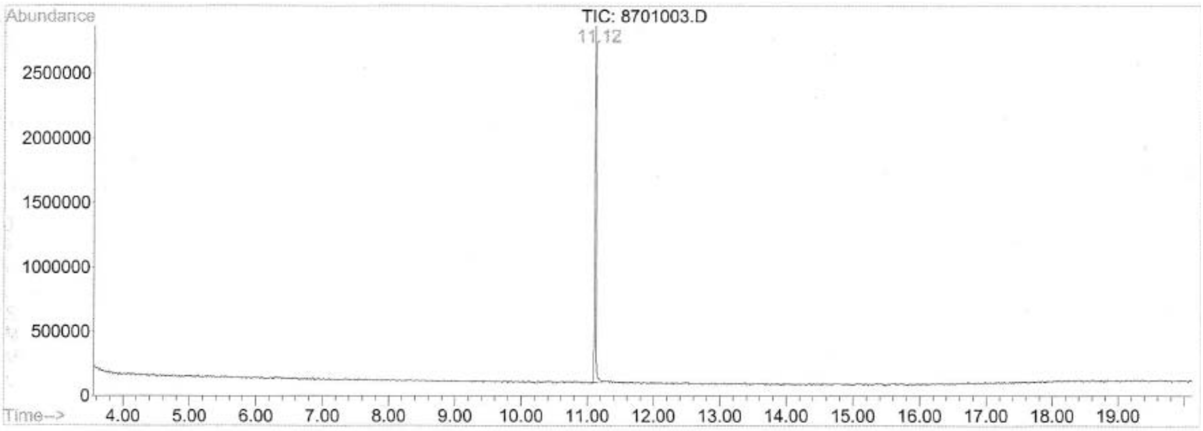
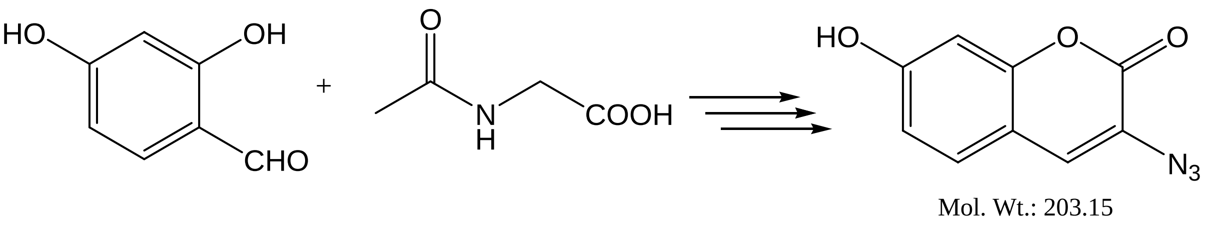


Fig. S2. GC chromatogram for 1-dodecaneazide

Synthesis of 3-azido-7-hydroxycoumarin (compound 4 in the paper)

According to literature[4]



2.76g (20 mmol) 2,4-dihydroxy benzaldehyde, 2.34g (20 mmol) N-acetylglycine and 4.92g sodium acetate (60 mmol) was refluxed (140-150 °C) in 100 mL acetic anhydride at for 4h. There was some solid on the bottom at the end. The reaction mixture was poured onto ice (300-400 mL) to give a yellow precipitate. Precipitation was sluggish. After filtration, the yellow solid was washed by ice-water before it was refluxed in a mixture of concentrated HCl and ethanol (2:1, 30 mL) for 1 hour (mixture turns into dark red when the acid is added), then ice-water (40 mL) was added to dilute the solution. The solution was then cooled in an ice bath and $NaNO_2$ (40 mmol, 2.76g) was added. The mixture was stirred for 5-10 minutes and NaN_3 (60 mmol, 3.90g) was added in portions. After stirring for another 15 minutes, the resulting precipitate was filtered off, washed with water, and dried under reduced pressure to afford a brown solid; 215 mg (5% overall yield)

NMR (DMSO) peaks fit with the original report. [4]

The product was analyzed with LCMS as well. In positive mode, we obtained 176 and 148 m/z peaks, the latter being the larger peak. 176 peak should correspond to the product with $-N_2$ loss. This kind of N_2 loss is very usual for azides. Later, we clicked it with phenyl acetylene and obtained single large peak with a value of 304 m/z in negative mode. MW of the clicked product should be 305 g/mol.

Detailed bead manufacture

Beads were synthesized using a home-made microfluidic setup where the reagent phase was injected into the continuous phase , MilliRo grade water containing 3 wt% surfactant sodium dodecyl sulfate (SDS), flowing through a UV transparent tube (Tygon - Φ_{intern} = 0.8 mm, L = 2 m), by use of a blunt bent needle (32G - Φ_{intern} =

110 µm). The continuous and reagent phases were pumped using a syringe pump, respectively with a syringe of 100 ml and 1 ml capacities, at flow rates of 120 ml/h and 1 ml/h.

The droplets were polymerized on-flight by UV irradiation in a metalight box fitted with 12 lamps (Philips 9W, I = 2.5 mW/cm^2, λ = 320-400 nm) and exposed for one more hour after collection. The beads, with a size of around 400 µm, were then washed with 3 x 5 ml of water, methanol, dichloromethane, acetone, and diethyl ether, and dried under vacuum at 90 °C overnight. Solvents were technical grade and used as received to wash the beads.

The monomer phase for the *thiol beads* was prepared as follows: 0.375 g (5 mol% compared to the total thiol functions) photoinitiator DMPA is dissolved in a mixture of 3.666 g tetrathiol (7.502 mmol) and 0.545 g 1,7-octadiyne (5.133 mmol).

For the *yne beads*, 0.133 g (5 mol% compared to the total thiol functions) photoinitiator DMPA is dissolved in a mixture of 1.297 g tetra-thiol (2.654 mmol) and 0.424 g 1,7-octadiyne (3.994 mmol).

Theoretical Loading Calculations

Thiol bead:

Thiol loading $= (n_{\text{remaining thiol groups after bead formation}}) / (\text{total mass of ingredients})$

$= (n_{\text{initial thiol groups}} - n_{\text{initial }\pi\text{-bonds}}) / (\text{total mass of ingredients})$

$= (4\text{x } n_{\text{tetrathiol}} - 4\text{x } n_{\text{dialkyne}}) / (m_{\text{tetrathiol}} + m_{\text{dialkyne}} + m_{\text{DMPA}})$

$= (4\text{x } 7.502\text{ mmol} - 4\text{x } 5.133\text{ mmol}) / (3.666\text{g} + 0.545\text{g} + 0.375\text{g})$

$= 2.067\text{ mmol/g}$

Yne bead:

Yne loading $= (n_{\text{remaining yne groups after bead formation}}) / (\text{total mass of ingredients})$

$= [0.5\text{x } (n_{\text{remaining }\pi\text{-bonds after bead formation}})] / (\text{total mass of ingredients})$

$= [0.5\text{x } (n_{\text{remaining }\pi\text{-bonds after bead formation}})] / (m_{\text{tetrathiol}} + m_{\text{dialkyne}} + m_{\text{DMPA}})$

$= [0.5\text{x } (n_{\text{initial }\pi\text{-bonds}} - n_{\text{initial thiol groups}})] / (m_{\text{tetrathiol}} + m_{\text{dialkyne}} + m_{\text{DMPA}})$

$= [0.5\text{x } (4\text{x } n_{\text{dialkyne}} - 4\text{x } n_{\text{tetrathiol}})] / (1.297\text{g} + 0.424\text{g} + 0.133\text{ g})$

$= [0.5\text{x } (4\text{x } 3.994\text{ mmol} - 4\text{x } 2.654\text{ mmol})] / (1.854\text{g})$

$= 1.446\text{ mmol/g}$

Post-modifications of beads

Note: Samples were prepared individually for each time scale of every reaction, instead of preparing one batch per reaction and taking samples from the same batch. Namely, for the thiol-norbornene reaction for instance, 5 vials were prepared containing exactly the same ingredients. The first one is stopped via washing after 30 min, second after 1h and so on. DMF was selected as the solvent because of its high solvating capability and its ability to swell the beads.

CuAAC on yne beads: 20 mg yne beads (28.8 µmol theoretical yne groups) were weighed into a 5 ml vial, followed by addition of a solution of 1-dodecaneazide (12.2 mg, 57.6 µmol), copper bromide (0.8 mg, 5.58 µmol) and PMDETA (2.5 µL, 11.97 µmol) in DMF (0.5 mL). Reaction with 3-azido-7-hydroxycoumarin was performed in a similar way using TBTA as the ligand instead of PMDETA.

Thiol-yne on yne beads: 20 mg beads were weighed into a 5 ml vial, followed by addition of a solution of dodecanethiol (23.3 mg, 115.1 µmol) and DMPA (1.5 mg, 5.85 µmol) in DMF (0.5 mL). The reaction setup was then exposed to the same UV lamps as used to perform beads synthesis.

Representative base mediated thiol-X reaction on thiol beads: A solution of *n*-hexyl isocyanate (12 µL, 82 µmol) and NEt_3 (0.56 µL, 4 µmol) in DMF (0.5 mL) was added on 20 mg of the thiol-containing bead (theoretically 41 µmol) in a glass vial and capped. Instead of 0.56 µL NEt_3, 5.6 µL NEt_3 was used for the methyl-2-bromopropionate reaction and 0.57 µL DMPP (4 µmol) was used for the thiol-acrylate reaction. Reaction with fluorogenic maleate was performed in a similar manner by using NEt_3.

Representative radical mediated thiol-ene on thiol beads: 20 mg thiol beads (41 µmol theoretical thiol groups) were weighed into a 5 ml vial, followed by addition of a solution of 2-norbornene (0.5 ml, 82 µmol) and DMPA (0.53 mg, 2 µmol) in DMF. The reaction setup was then exposed to the same UV lamps as used to perform beads synthesis. Reaction with 10-undecylenic acid is performed in a similar manner.

After the necessary time passed, all the beads were washed with 3 x 5 ml of methanol, dichloromethane, acetone, and diethyl ether, and dried under vacuum at 90 °C overnight. The beads are mixed with some KBr, crushed together and IR pellets were prepared.

Thiol-aziridine literature

DBU,[5] $ZnCl_2$,[6] BF_3,[7] tri-butylphosphine[5]

Elemental analysis calculations for loading

2.05% = Amount of nitrogen found by elemental analysis after fully treating the thiol bead with N-methyl maleimide (further denoted here as maleimide)

0.0205g nitrogen in 1 g final maleimide capped bead

$n_{nitrogen} = m_{nitrogen} / 14\ g\ mol^{-1} = 0.0205\ g / 14\ g\ mol^{-1} = 0.00146\ mol$

$n_{nitrogen} = n_{maleimide} = n_{SH\ groups} = 0.001464\ mol$

$m_{maleimide} = n_{maleimide} \times MW_{maleimide} = 0.001464\ mol \times 111.10\ g\ mol^{-1} = 0.163\ g$

$m_{untreated\ bead} = m_{final\ bead} - m_{maleimide} = 1\ g - 0.163\ g = 0.837\ g$

Initial SH loading = $n_{SH\ groups} / m_{untreated\ bead} = 1.464\ mmol / 0.837\ g = 1.75\ mmol\ g^{-1}$

Theoretical loading = 2.067 mmol/g   Found = 84.7%

IR spectra for thiol and yne beads

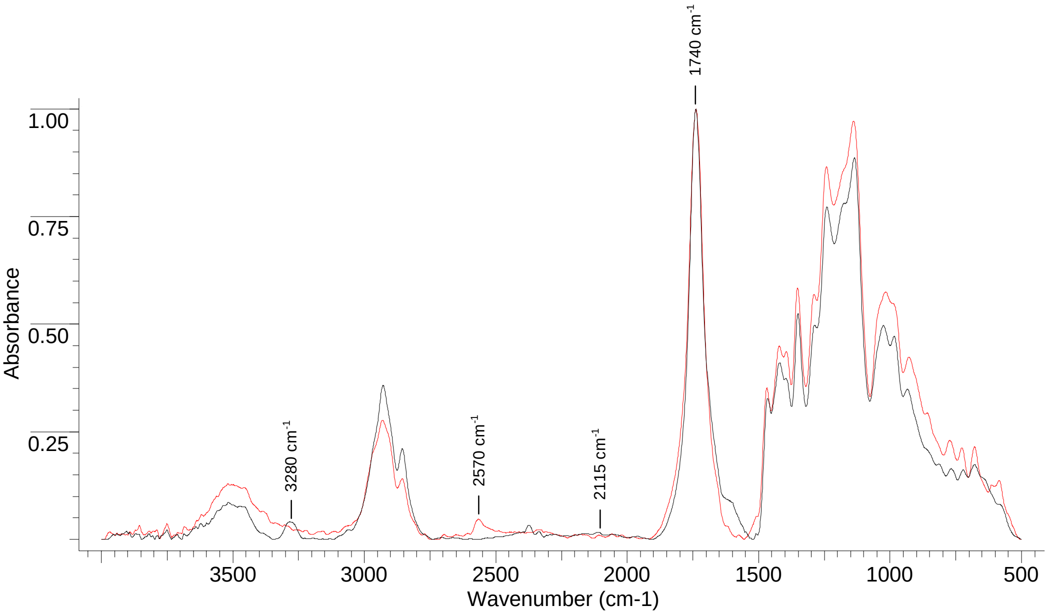


Fig. S3. IR spectra of intact yne (black spectrum) and thiol (red spectrum) beads

IR spectra for kinetic analysis

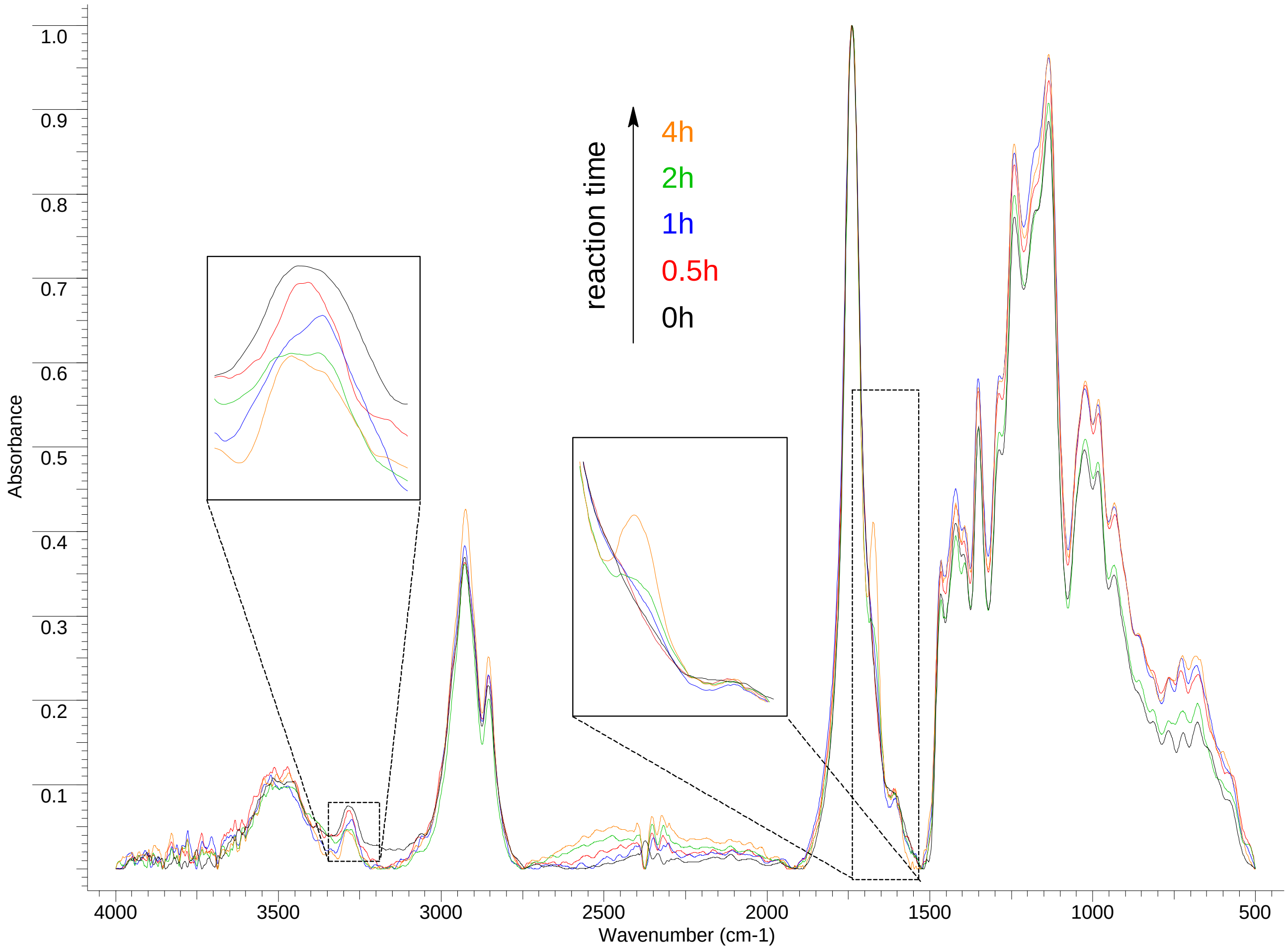


Fig. S4. Evolution of IR spectra for the reaction between yne bead and 1-dodecaneazide. Both the yne peak (left) and the forming double bond[8] peak (right) have been zoomed.

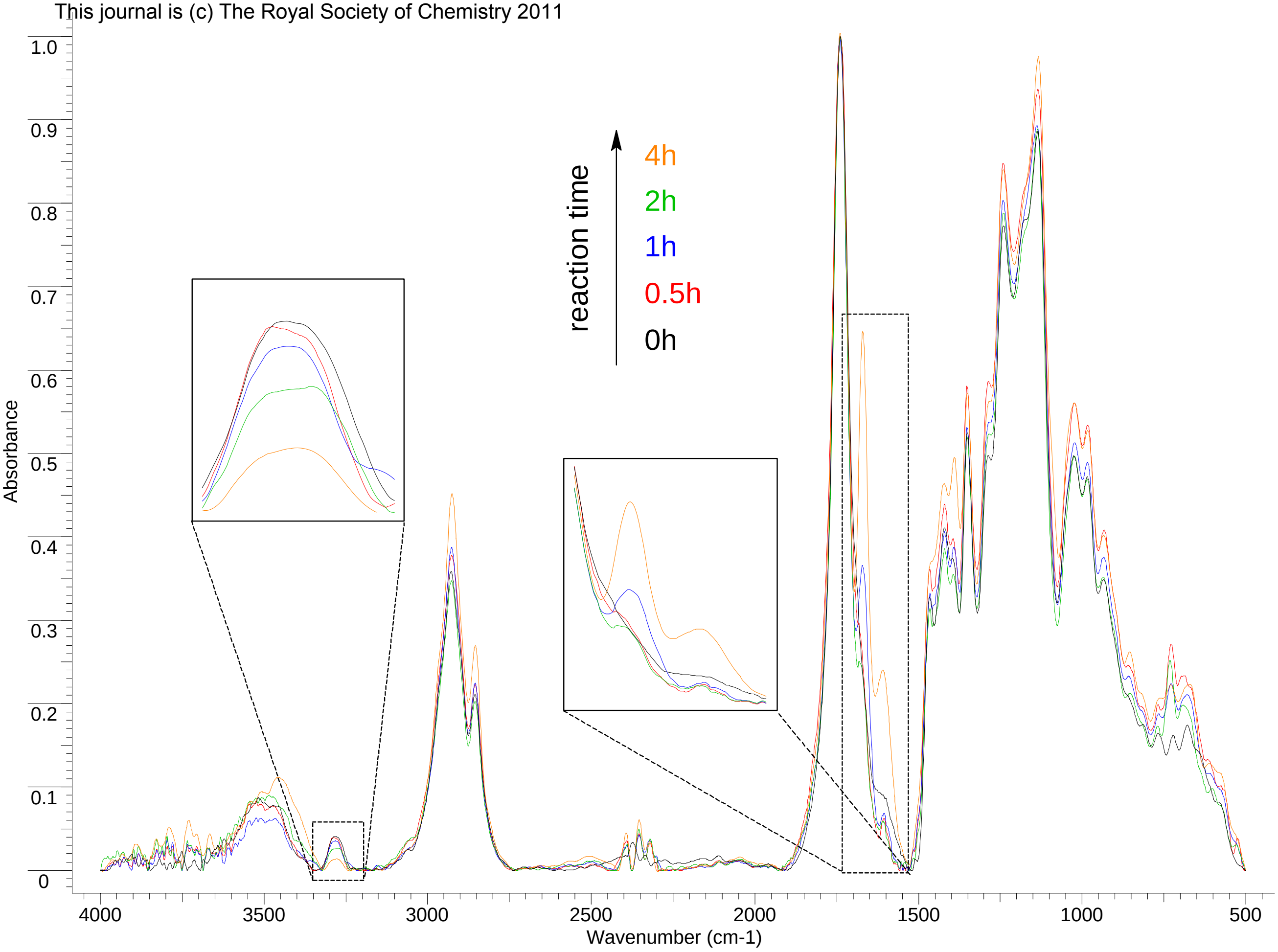


Fig. S5. Evolution of IR spectra for the reaction between yne bead and dodecane thiol. Both the yne peak (left) and the forming double bond peak (right) have been zoomed.

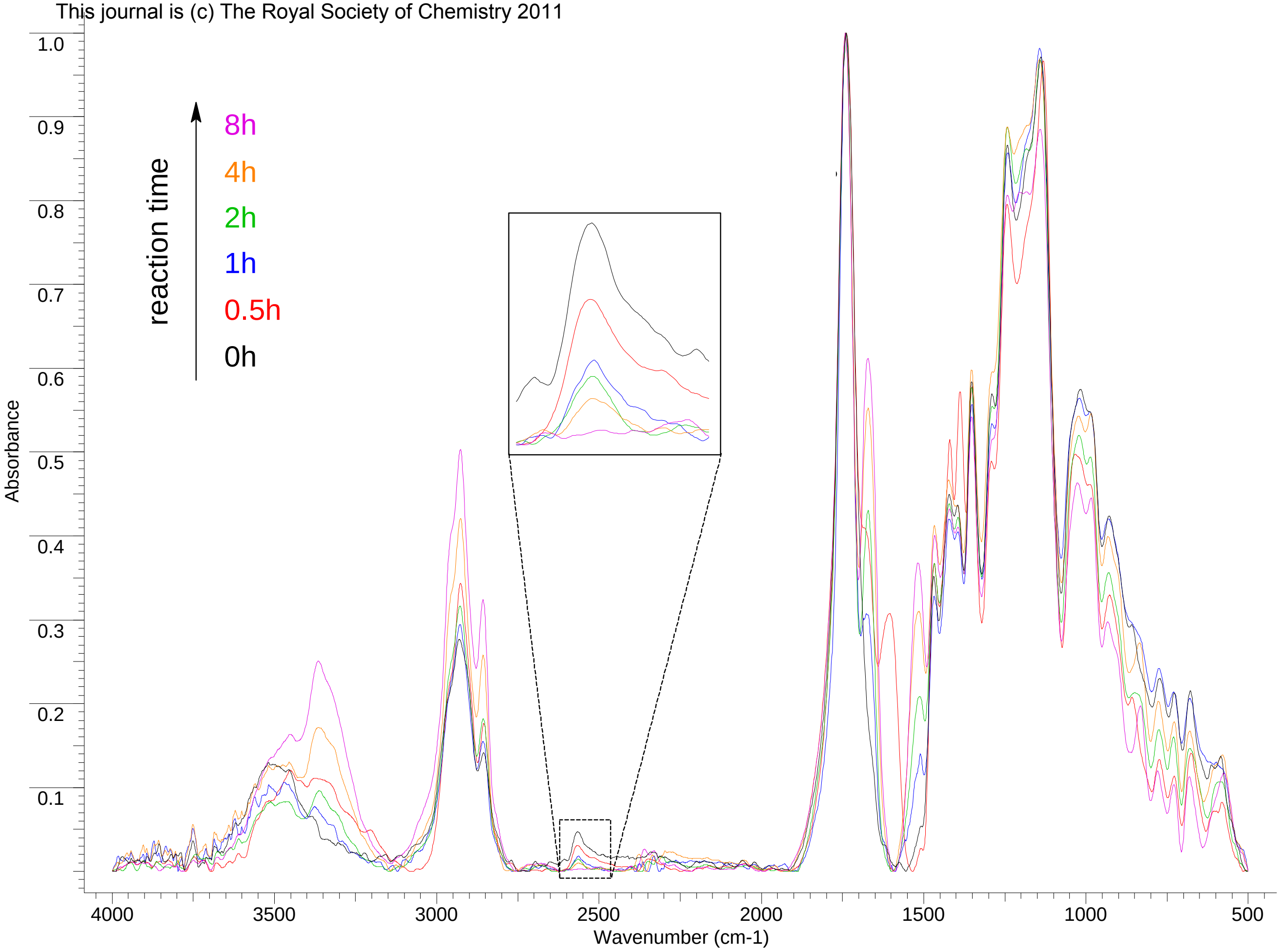


Fig. S6. Evolution of IR spectra for the reaction between the thiol bead and isocyanate.

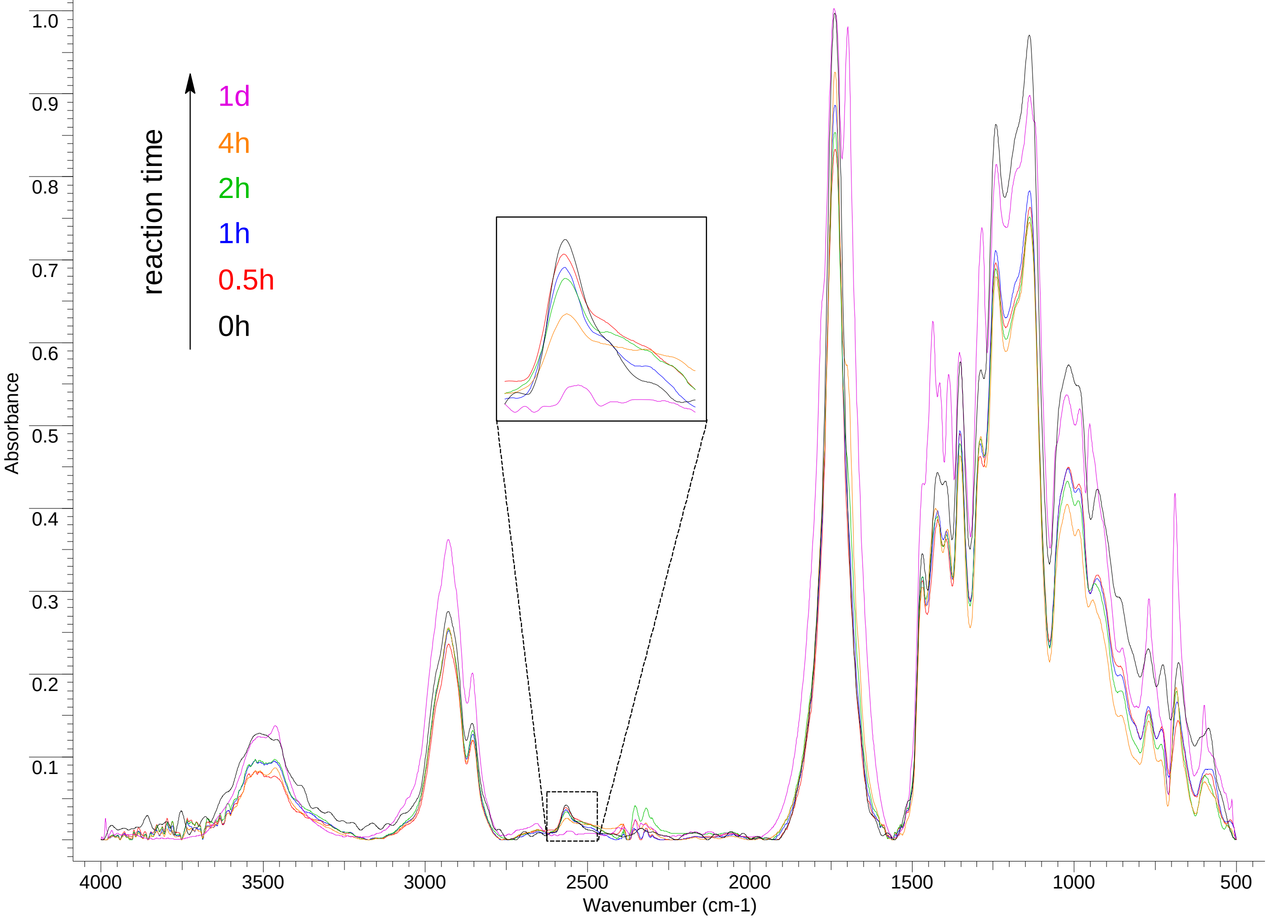


Fig. S7. Evolution of IR spectra for the reaction between thiol bead and maleimide.

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