Communication

Substituent effects and mechanism in

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a mechanochemical reaction

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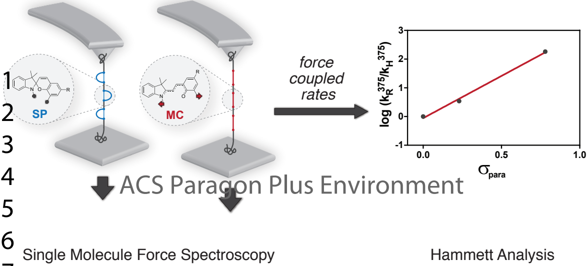
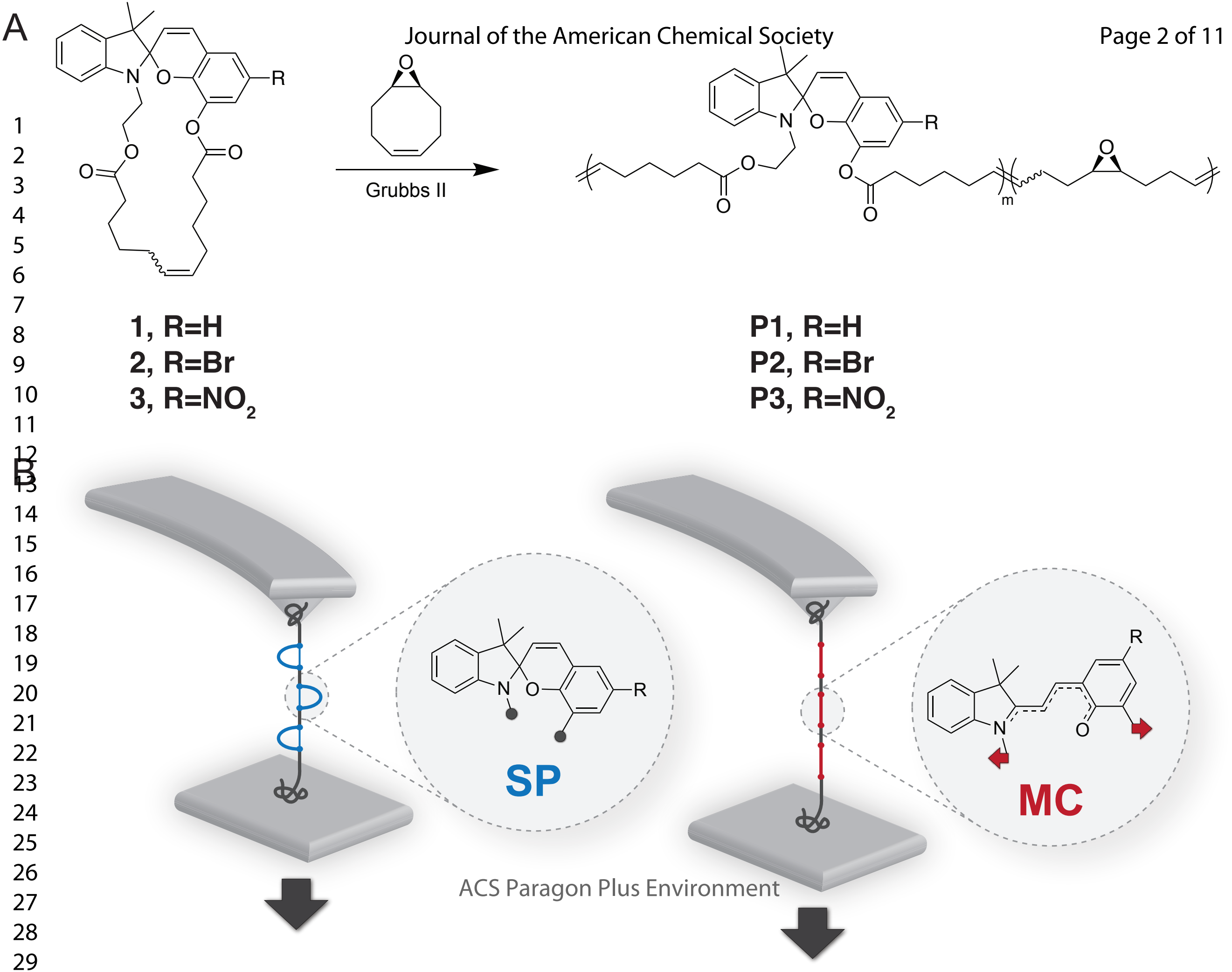

SP
MC
force coupled rates
log (k_R^{375}/k_H^{375})
σ_{para}
3
2
1
0
-1
0.0
0.5
1.0
Single Molecule Force Spectroscopy
Hammett Analysis


A
R
N
O
O
O
O
O
Grubbs II
O
R
N
O
O
O
O
O
m
O
1, R=H
2, R=Br
3, R=NO2
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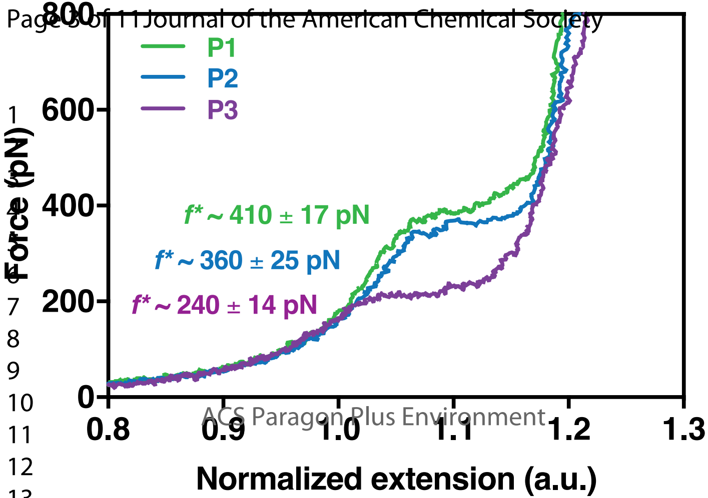
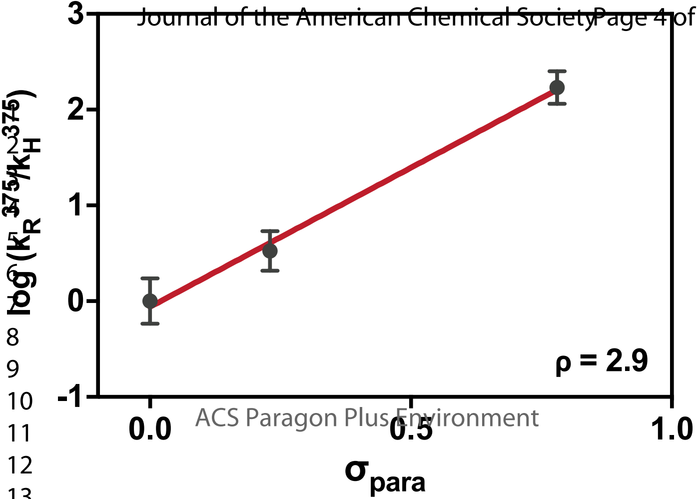
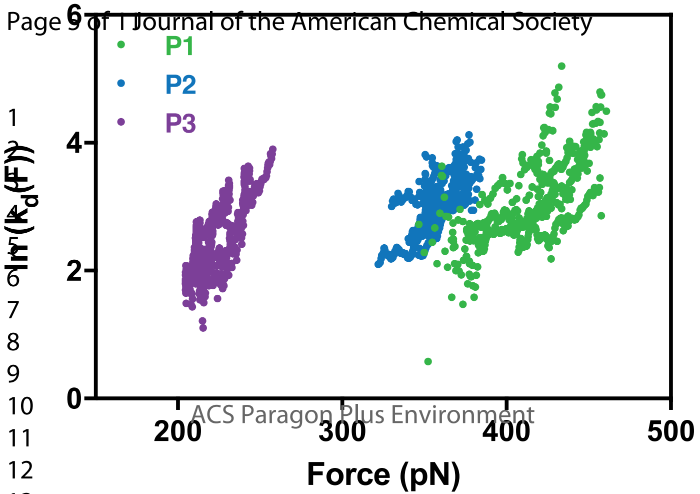
P2, R=Br
P3, R=NO2
B
N
O
R
SP
R
N
O
MC


800
600
400
200
0
Force (pN)
P1
P2
P3
f* ~ 410 ± 17 pN
f* ~ 360 ± 25 pN
f* ~ 240 ± 14 pN
0.8
0.9
1.0
1.1
1.2
1.3
Normalized extension (a.u.)


3
2
1
0
-1
log (k_R^375/k_H^375)
0.0
0.5
1.0
σ_para
ρ = 2.9


P1
P2
P3
ln (k$_d$(F))
0
2
4
6
200
300
400
500
Force (pN)

Substituent effects and mechanism in a mechanochemical reaction

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Supporting Information Placeholder

ABSTRACT: We report the effect of substituents on the force-induced reactivity of a spiropyran mechanophore. Using single molecule force spectroscopy, force-rate behavior was determined for a series of spiropyran derivatives substituted with H, Br, or NO_2 para to the breaking spirocyclic C-O bond. The force required to achieve the rate constants of ~ $10\ s^{-1}$ necessary to observe transitions in the force spectroscopy experiments depends on the substituent, with the more electron withdrawing substituent requiring less force. Rate constants at 375 pN were determined for all three derivatives, and the force-coupled rate dependence on substituent identity is well explained by a Hammett linear free energy relationship with a value of $\rho = 2.9$, consistent with a highly polar transition state with heterolytic, dissociative character. The methodology paves the way for further application of linear free energy relationships and physical organic methodologies to mechanochemical reactions, and the characterization of new force probes should enable additional, quantitative studies of force-coupled molecular behavior in polymeric materials.

The potential to use mechanochemistry, either in isolated polymers or in polymeric materials, to trigger a programmed, desirable covalent molecular response was first revealed only a decade or so ago. Since that time, covalent polymer mechanochemistry[1] has undergone a renaissance in which it has been extensively explored by a number of research groups and for a variety of purposes, including (but not limited to): biasing and probing reaction pathways,[1b, 2] trapping transition states and intermediates,[3] catalysis,[4] release of small molecules and protons,[5] stress reporting,[6] stress strengthening,[6d, 7] and soft materials and devices.[8] Increasingly creative mechanophore designs and new properties continue to emerge at an ever-accelerating pace.[9]

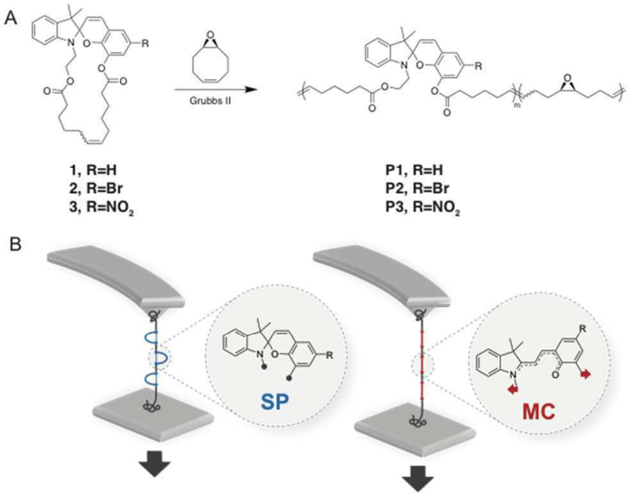

Figure 1. (A) Multi-mechanophore polymers with substitutions as indicated by R synthesized for this study. (B) A schematic of the single molecule force spectroscopy (SMFS) experiment and ring-opening of spiropyran (SP) to merocyananine (MC).

The precision with which mechanophores can be predictively designed has increased as quantitative experimental and computational studies have provided insights into structure-activity relationships.[2e] For example, it has been shown that even reactions with very similar force-free activation barriers can have very different force-coupled reactivities as a result of the polymer structure and attachment point through which force is delivered.[1c, 10]Additional benefits will be realized as these emerging quantitative relationships are mapped onto existing, intuitive physical organic frameworks. Here, we report the effect of substituent on the tension-driven ring-opening reaction of the classic mechanophore spiropyran (SP) to the (longer) merocyanine (MC).[11] Single molecule force spectroscopy is used to quantify force-rate relationships for three spiropyran derivatives with the same attachment points, and the qualitative and quantitative reactivity trends are well explained by Hammett linear free energy relationships.

Our approach is described in Figure 1. Multi-mechanophore polymers of the three SP derivatives were synthesized through previously established entropy driven ring-opening metathesis co-polymerization.[12] Epoxidized cylcooctadiene is used as a co-monomer for better adhesion to the cantilever tip.[10a] Polymers were deposited in dilute solution of tetrahydrofuran and dried after drop casting onto a silicon surface. Toluene was placed onto the surface, then constant velocity (300 nm s^{-1}) single molecule force spectroscopy measurements were conducted to measure force as a function of tip-surface separation.[13]

The ring-opening of SP to MC releases stored length, which results in a characteristic plateau in the force-distance curves (Figure 2). Following previously published procedures,[14] the change in contour length of the polymer is determined by fitting to the extended freely jointed chain model of polymer elasticity. The experimental results (Table 1) are consistent with extension ratios based on the polymer's mechanophore content and calculated contour length before and after ring-opening from SP to the possible MC isomers.[13, 15] Similarity in the contour lengths of the MC isomers precludes an exact assignment of MC geometry (Table S4).

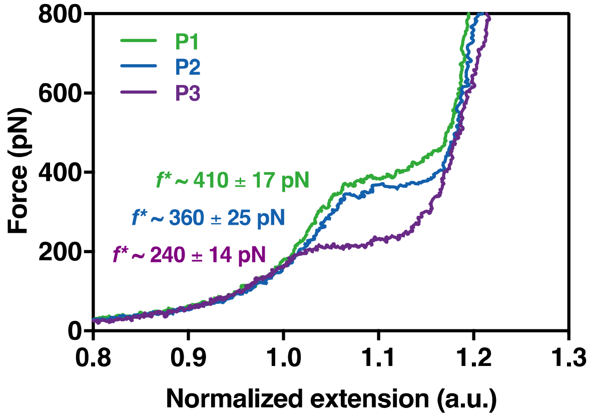

Figure 2. Representative SMFS curves for **P1-3**. The plateau corresponds to an extension of polymer contour length upon ring-opening of SP to MC. The transition force f^* is the midpoint of each plateau and is calculated as an average from multiple force curves collected at a pulling rate of 300 nm s^{-1}.

The force-distance curves of all three polymers show identical extension as a function of SP content, as expected since each of the substituted monomers have the same end to end length in the extended MC. Each SP derivative, however, shows a different critical force f^*, of around 410 pN, 360 pN, and 240 pN for **P1**, **P2**, and **P3**. Actual rate constant calculations (see below) are not derived from f^*, however, but are based on fits to the force curves that account for measurement-to-measurement variation in the contour length of the detected polymer. The nature of the (force-free) SP-to-MC reaction has been the subject of prior work that suggests that relative contributions of a less polar electrocyclic reaction and more polar, heterolytic mechanism depend on solvent and substituent.[16] The nature of the mechanochemical reaction has not been previously addressed experimentally, and the trend in f^* (H > Br > NO_2) is consistent with a transition state that is largely heterolytic and polar in character, as electron withdrawing groups para to the spirocyclic O atom should stabilize the developing negative charge separation at that position as the spirocyclic C-O bond is broken.[16]

To confirm that the reaction is under kinetic, not thermodynamic control on the timescale of the SMFS experiment,[17] we conducted a "retracing" experiment using **P1**, which is the fastest derivative to close back to SP. The cantilever, with polymer still attached after being pulled through the SP-to-MC transition, was returned to just above the surface. The approach curves obtained showed no evidence of a plateau, and they instead were fully hysteretic (Figure S14, ESI) with no evidence of ring closing. Even after waiting 2 s (in comparison to forward transition time scales of ~0.1 s) at the surface following re-approach, a second extension of the same polymer shows only partial recovery of the SP (56%) under effectively force-free (< 5 pN) conditions. The back reaction of MC to SP therefore does not need to be considered when analyzing the chain extension kinetics.

Quantitative kinetic information is extracted from the force curves of each polymer by fitting the transitions to the Bell[18] and Cusp[19] models of force-modified chemical reactivity, as done previously.[10a, 13-14] The force-free activation energy of each SP derivative is obtained from its force-free reverse rate constant and equilibrium constant (Tables S6 and S7). The fits give $\Delta x^{\ddagger}$, the change in length of the stretched polymer as an embedded SP moves from the ground to transition state. The $\Delta x^{\ddagger}$ values of the three SPs are effectively indistinguishable, given the uncertainties associated predominantly with the force-free equilibrium constants. This homology between reaction mechanism and force sensitivity is consistent with accepted models of mechanochemical coupling[1e] and is reminiscent of an earlier study of mechanistically similar ligand displacement reactions.[20]

A more direct kinetic analysis of the force-coupled reactions is possible without independent characterization of the force-free pathways, by extracting the rate constant of the ring-opening reaction as a function of force directly from the single molecule force curve (Figure 3), where the inferred force-rate relationship is independent of the velocity of the SMFS experiment.[21] For example, at a force of 375 pN, rate constants of 9 s^{-1} and 32 s^{-1} can be obtained directly for **1** and **2**, respectively (Figures S20 and S21). In the constant velocity experiments, SP **3** has already fully ring-opened by the time the force reaches 375 pN, and so we extracted rate constant as a function of force for **P3** over a range from 205 to 257 pN, and extrapolated up to 375 pN to get a force-coupled rate constant of 1600 s^{-1} (Figure S22).

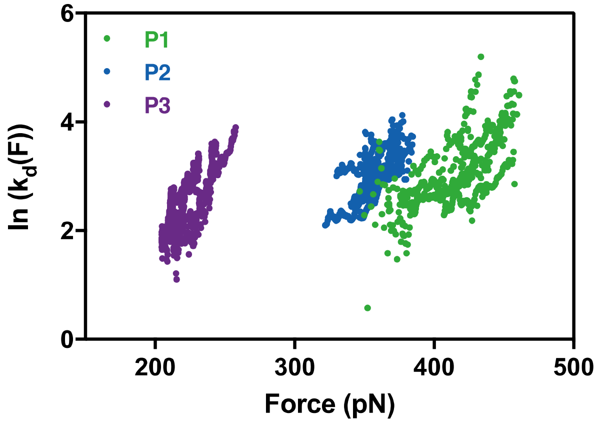

Figure 3. The rate constant as a function of force for **P1-3**, extracted directly from multiple single molecule force curves for each derivative. For **P1** and **P2**, rate constants at 375 pN can be obtained directly. For **P3**, the data is fit to a log-linear regression and extrapolated to 375 pN.

Substituent effects on a wide range of conventional, force-free reactions have been successfully interpreted through linear free energy relationships. Of these, Hammett equations are perhaps the most pervasive and useful.[22] The rate constants obtained at 375 pN (k^{375}) provide an opportunity to apply the Hammett methodology to a force-coupled reaction for the first time. As shown in Figure 4, the Hammett plot of k^{375} vs. σ_{para} for these spiropyrans returns a value of ρ = 2.9.

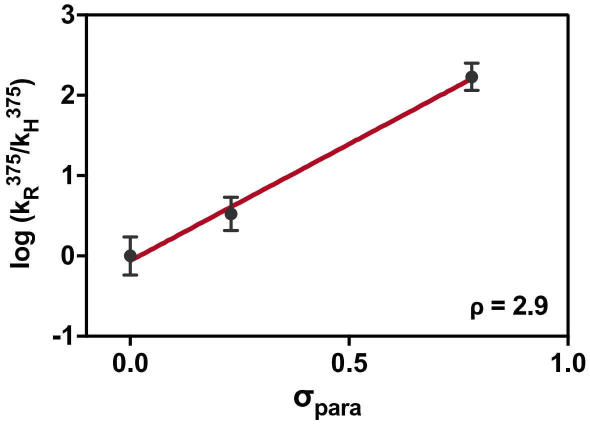

Figure 4. Hammett plot of log (k_R^{375}/k_H^{375}) vs. σ_{para} for **P1-3**, where σ_{para} is 0, 0.23, and 0.78.

The small data set of three substituents precludes a detailed evaluation of potentially subtle contributions; nonetheless, some insights are possible. The positive slope is consistent with the expected increase in rate as electron withdrawing substituents stabilize the developing negative charge on the spirocyclic oxygen.[16a] The product MC has a contributing resonance structure that is a phenoxide, and so it is noteworthy that ρ here is roughly half the value ρ = 5.3 for phenol acidity in dimethyl sulfoxide.[23] We expect that ρ for phenol activity in toluene would be slightly higher, given its calculated value in a vacuum (ρ =14.3),[23] and estimates based on solvent descriptors (ε, Z, and E_T(30), see Figure S23-25) range from ~7.3 to ~13.3. This finding is therefore consistent with a transition state that is intermediate to reactant and product phenoxide structure.

Substituent effects on the spiropyran ring-opening reaction have been well studied,[16b, 24] and our measured value of ρ also correlates well to trends in ρ seen in similar spiropyran racemization reactions, which also proceed through a transition state where the C(sp^3-O) bond is cleaving.[16a] Racemization rates from Swansburg et al.[16a] for spiropyrans with the same substituents as in **P1-3** in acetonitrile and 90:10 hexanes/isopropanol give ρ = 2.2 and ρ = 1.5. The larger ρ value obtained in our SMFS experiments can again largely be attributed to the less polar medium (toluene) employed, although for force-free racemizations in cyclohexane, ρ is negative over a large series of compounds, and for the spiropyrans corresponding to **P1-3** there is weak correlation. The present SMFS analysis is limited in that there are only 3 SP derivatives, and so this study may not fully capture subtle aspects of the structure-property relationships.

Beyond the mechanistic insights into the mechanochemical reaction mechanism, the quantitative linear free energy relationship will guide the choice of spiropyran derivatives as a function the desired force and time regimes of various material applications. For example, the quantitative data on this series of spiropyrans, which have different force-rate behaviors, will allow us to use them as probes to correlate SMFS and bulk response (e.g., to quantify the fraction of polymer chains experiencing certain forces within polymer networks) as a function of material composition, including polarity. Additionally, differences in decoloration rate for these SPs allow us to select the derivative with a specific application in mind. These H- and Br- substituted mechanophores have an additional advantage in that the SP form is not photoactive and has negligible background color relative to the NO_2- analog, which might provide advantages in some situations. Comparative applications using these mechanophores will be facilitated by the fact that for this series of spiropyrans, the attachment points are held constant, but the intrinsic reactivity is modified with local substituent effects.

To the best of our knowledge, this analysis is the first application of linear free energy relationships to mechanochemical processes. The results of the Hammett analysis are consistent with a force-coupled reaction mechanism and evolution in electronic structure that is polar in nature, as suggested by prior studies of the force-free reaction. The methodology reported here should be broadly applicable in a manner that serves the increasing desire to apply physical organic insights and chemical intuition to mechanophore design.

ASSOCIATED CONTENT

Supporting Information. Synthetic details, additional SMFS curves and fitting. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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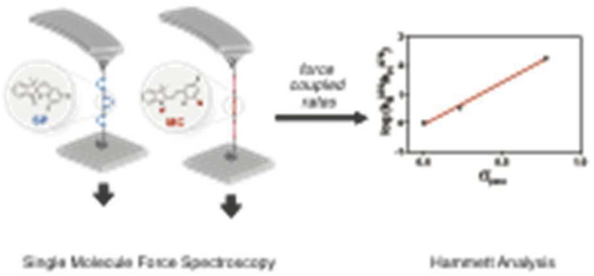
Table 1. Polymer Characterization and Force Curve Fitting

a. Determined from previously published data.[13]
b. Mole fraction by ^{1}H NMR.

Polymer	SP content[b]	L_f/L_i (calc) (CTC)	L_f/L_i (calc) (TTT)	L_f/L_i (obs)	*f**	$\Delta x^‡$ (BE), nm	$\Delta x^‡$ (Cusp), nm
1	0.46	1.11	1.17	1.15±0.03	410±17	0.19±0.006	0.22±0.0009
2	0.48	1.11	1.17	1.15±0.04	358±25	0.22±0.008	0.25±0.009
3[a]	0.45	1.11	1.13	1.15±0.02	240±14	0.19±0.012	0.21±0.013


SP
MC
force coupled rates
σ_{para}
Single Molecule Force Spectroscopy
Hammett Analysis