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One-Dimensional Random Walk of a Synthetic Small Molecule Toward a Thermodynamic Sink

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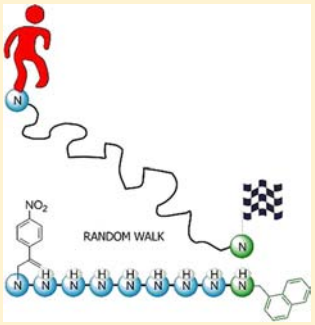
Supporting Information

ABSTRACT: We report on the spontaneous intramolecular migration of α-methylene-4-nitrostyrene from amine group to amine group along oligoethyleneimine tracks up to eight repeat units in length (number of amine footholds, n = 3, 5, 9). Each track consists of $n - 1$ aliphatic secondary amine footholds plus a naphthylmethylamine group foothold situated at one end of the track. Under basic conditions the α-methylene-4-nitrostyrene unit undergoes a series of reversible intramolecular Michael−retro-Michael reactions between adjacent amine groups that move it up and down the track. For n = 3 and 5 it is possible to monitor the population of every positional isomer on the track by ^{1}H NMR spectroscopy. On the longest track (n = 9) the fraction of walkers on each end-foothold can be quantified with respect to those on the inner footholds. In all cases the naphthylmethylamine foothold acts as a thermodynamic sink with the steady-state distribution significantly biased in favor of the walker at that site. The dynamics of the walker migration is well described by the random walk of a Brownian particle in one dimension.

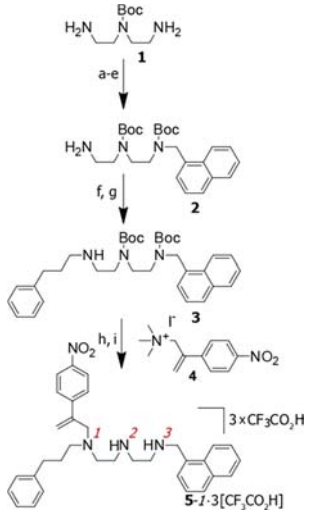


INTRODUCTION

Various motor proteins from the myosin, dynein, and kinesin superfamilies move along filaments and microtubules in the cell, transporting cargos such as membranous organelles, protein complexes, and mRNA.[1] These remarkable biological molecular machines are inspiring the invention of artificial systems that may one day be able to migrate along polymer tracks and perform similarly useful tasks.[2] In the past few years small molecules that are able to 'walk' down short molecular tracks have been described.[3,4] However, many of these systems require intervention in the form of the sequential addition of reagents (and in some cases irradiation with light) for the 'walker' to take each 'step'. Our group[4a] and that of Lehn[4b] recently reported conceptually related model compounds in which a molecular fragment can be transferred intramolecularly between adjacent amine groups on a short track without the need for the sequential addition of reagents or other forms of intervention.[4] Both systems involve dynamic covalent chemistry[5] of nitrogen-containing functional groups: the Lehn approach is based upon transimination reactions (the reversible formation of C═N bonds);[6] ours utilizes the reversible Michael addition of secondary amines to an α-methylene-4-nitrostyrene unit, chemistry that is based on the equilibrium transfer alkylating cross-linking (ETAC) reagents introduced by Lawton in the 1970s for the cross-linking of proteins under thermodynamic control.[7]

The preliminary publications from both groups focused on establishing the reversibility and intramolecular nature of the 'stepping' dynamics on model systems, demonstrating that the small-molecule fragment is randomly exchanged between adjacent amines on short (up to three or four repeat units) oligoethyleneimine tracks. Here we describe the extension of the Michael−retro-Michael walker concept to long (up to nine footholds) tracks and investigate the effect of acid and base on

Scheme 1. Synthesis of Walker−Track Conjugate 5-*1*·3[CF_3CO_2H][a]



[a]Reaction conditions: a) 1-naphthaldehyde, EtOH, RT, 16 h; b) $NaBH_4$, RT, 3 h, 34% (two steps); c) CF_3CO_2Et, CH_2Cl_2, 0 °C→RT, 16 h; d) Boc_2O, Et_3N, RT, 12 h; e) NaOH, MeOH/H_2O, RT, 5 h, 92% (three steps); f) 3-phenylpropionaldehyde, EtOH, RT, 16 h; g) $NaBH_4$, RT, 3 h, 27%, (two steps); h) **4**, MeOH, ^{i}Pr$_2$NEt, 50 °C, 24 h, 54%; i) CF_3CO_2H, CH_2Cl_2, RT, 3 h, quant.

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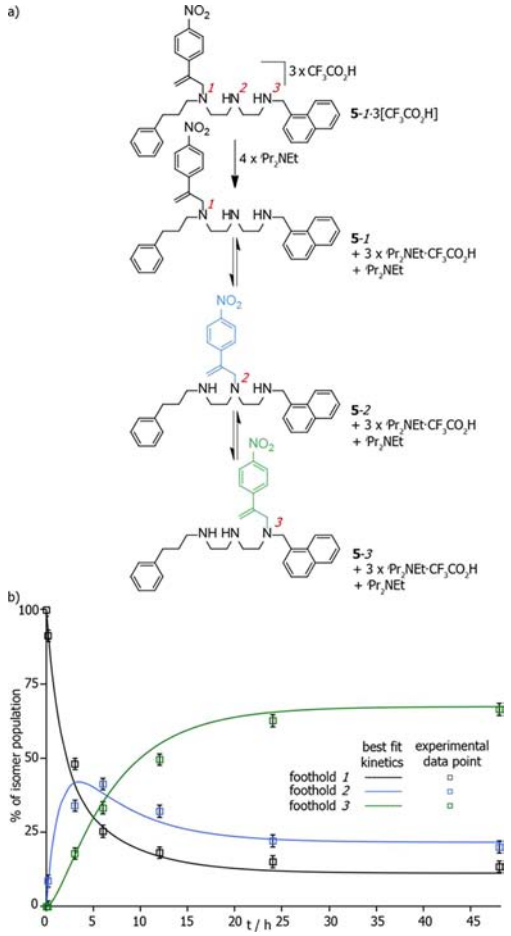

Figure 1. (a) Intramolecular migration of the α-methylene-4-nitrostyrene unit of **5**-*1*·3[CF_3CO_2H] in the presence of 4 equiv of $^{i}Pr_2NEt$. (b) Population of isomers (^{1}H NMR integration; see Figure 2). After 48 h, 67 ± 3% of walkers are positioned on foothold 3 of the track (isomer **5**-3). Lines show the best fit of the experimental data to the kinetics of exchange between **5**-*1*, **5**-*2*, and **5**-3 using SimFit[9] (see Supporting Information for details). Error bars are indicative of the error associated with ^{1}H NMR integration using equivalent protons in each positional isomer.

migration. Moreover, we show that under basic conditions a naphthylmethylamine foothold introduced at one end of the oligoethyleneimine track acts as a thermodynamic sink for the walker. Although the steps taken on the internal regions of the track proceed at the same rate in either direction, the rate that the walker departs from the naphthylmethylamine site is significantly slower than from the other footholds, meaning that the walker distribution is biased toward this site generating net directional transport from one end of the track to the other even on long (up to nine footholds) tracks. The α-methylene-4-nitrostyrene walker migrates from one end of a nine-foothold track to the other under dynamics that correspond well to the theoretical description of a one-dimensional random walk of a Brownian particle.[8]

RESULTS AND DISCUSSION

Influence of Acid and Base on Michael and retro-Michael Reactions of α-Methylene-4-nitrostyrene on a Diethylenetriamine Track. We previously investigated the migration of α-methylene-4-nitrostyrene walker unit between adjacent amine groups of short oligoethyleneimine tracks under neutral conditions. To probe the effect of acid and base on these reactions a three-foothold walker–track conjugate **5**-*1* was synthesized as the *tris*-trifluoroacetic acid salt (Scheme 1). Boc-protected diethylenetriamine **1** was desymmetrized through reductive amination with 1-naphthaldehyde (Scheme 1 a,b), followed by a sequence of Boc-protection–deprotection reactions (Scheme 1 c–e) to yield free primary amine **2**, which after reductive amination with 3-phenylpropionaldehyde (Scheme 1 f,g) afforded track **3** featuring a single site for walker attachment. The α-methylene-4-nitrostyrene walker unit **4** was subsequently introduced exclusively at foothold 1 (Scheme 1 h). Removal of the Boc group gave compound **5**-*1* as the *tris*-trifluoroacetic acid salt. With all of the amine groups of the track protonated, the α-methylene-4-nitrostyrene group does not migrate away from its original position.

Walker Migration on a Diethylenetriamine Track in the Presence of One Equivalent of Excess Base. Treatment of **5**-*1*·3[CF_3CO_2H] in DMSO-d_6 (20 mM, 298 K) with 4 equiv of diisopropylethylamine ($^{i}Pr_2NEt$), i.e. one equiv

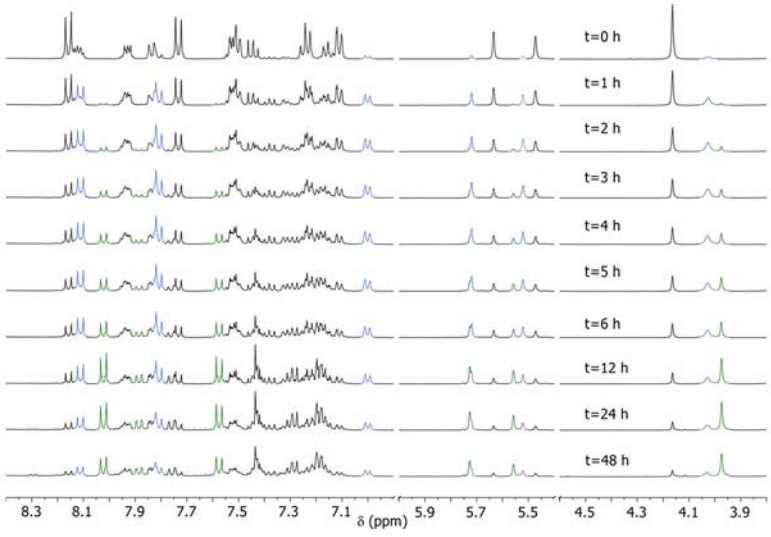

Figure 2. Partial ^{1}H NMR spectra (400 MHz, 20 mM, DMSO-d_6, 298 K) of **5**-*1*·3[CF_3CO_2H] + 4 equiv of $^{i}Pr_2NEt$, showing the interconversion of **5**-*1* (black resonances), **5**-*2* (blue resonances), and **5**-3 (green resonances) over 48 h.

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excess of base, led to spontaneous migration of the α-methylene-4-nitrostyrene unit along the track (Figures 1 and 2). The reaction was monitored by ^{1}H NMR spectroscopy (Figure 2). Under these conditions the initial migration from foothold 1 to foothold 2 is fast, with more than half of the walkers having left foothold 1 after 4 h (Figures 1 and 2). The steady-state is reached after 24−48 h, with 67 ± 3% of walkers ultimately located at the naphthylmethylamine foothold (foothold 3). The dynamics of the exchange of the positional isomers was simulated using the SimFit program[9] (Figure 1b; see Supporting Information for details).

Walker Migration on a Diethylenetriamine Track under Neutral Conditions. Treatment of **5**-*1*·3[CF_3CO_2H] in DMSO-d_6 (20 mM, 298 K) with 3 equiv of ^{i}Pr$_2$NEt (i.e. just sufficient to deprotonate all of the ammonium groups of the track) also led to spontaneous migration of the α-methylene-4-nitrostyrene unit along the track (Figure 3). Initial migration away from foothold 1 occurs at a rate similar to that in the presence of excess base, but at the steady-state, footholds 2 and 3 are populated to a comparable extent (43 ± 3% and 47 ± 3%, respectively).

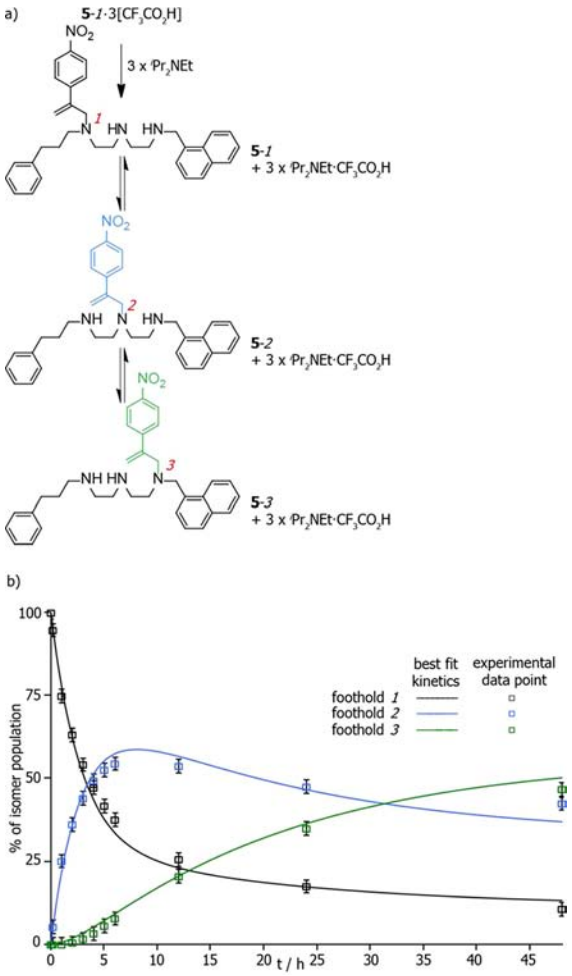

Figure 3. (a) Intramolecular migration of the α-methylene-4-nitrostyrene unit of **5**-*1*·3[CF_3CO_2H] in the presence of 3 equiv of ^{i}Pr$_2$NEt. (b) Population of isomers (^{1}H NMR integration). After 48 h, 47 ± 3% of walkers are positioned on foothold 3 of the track (isomer **5**-*3*) and 43 ± 3% on position 2 (isomer **5**-*2*). Lines show the best fit of the experimental data to the kinetics of the exchange between **5**-*1*, **5**-*2*, and **5**-*3* using SimFit[9] (see Supporting Information for details). Error bars are indicative of the error associated with ^{1}H NMR integration using equivalent protons in each positional isomer.

Walker Migration on a Diethylenetriamine Track in the Presence of One Equivalent of Excess Acid. When **5**-*1*·3[CF_3CO_2H] was treated with 2 equiv of ^{i}Pr$_2$NEt (i.e. only sufficient to deprotonate two of the three ammonium groups of the track), the dynamic behavior of the walker was very different from that under neutral or basic conditions (Figure 4).

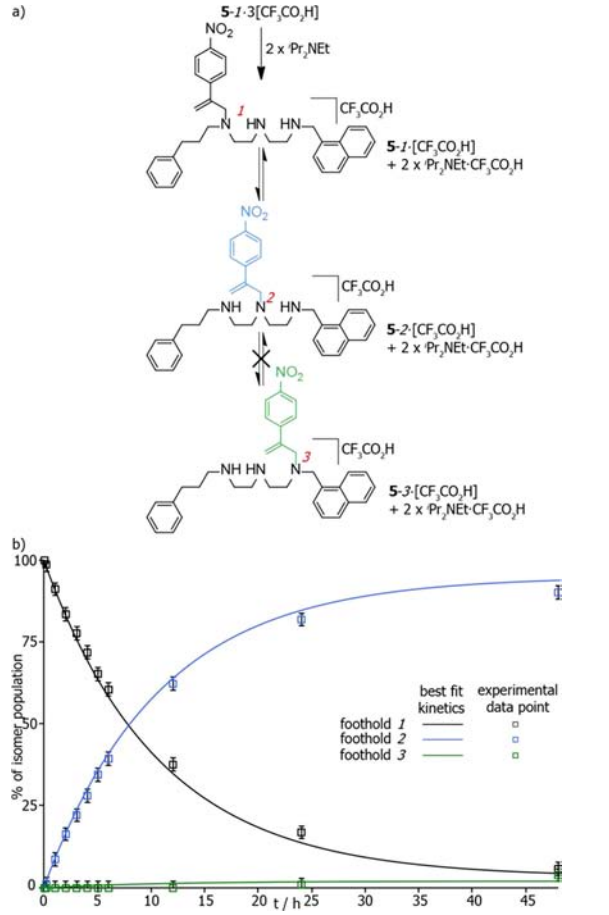

Figure 4. (a) Intramolecular migration of the α-methylene-4-nitrostyrene unit of **5**-*1*·3[CF_3CO_2H] in the presence of 2 equiv of ^{i}Pr$_2$NEt. (b) Population of isomers (^{1}H NMR integration). After 48 h, 90 ± 3% of walkers are positioned on foothold 2 of the track (isomer **5**-*2*). Lines show the best fit of the experimental data to the kinetics of the exchange between **5**-*1*, **5**-*2*, and **5**-*3* using SimFit[9] (see Supporting Information for details). Error bars are indicative of the error associated with ^{1}H NMR integration using equivalent protons in each positional isomer.

The kinetics of the initial migration from foothold 1 to foothold 2 is significantly slower: after 4 h only ∼30% of walkers had left foothold 1. Furthermore, even after 48 h only a trace of walker units (<3%) could be detected on foothold 3 with the majority (88 ± 3%) situated on foothold 2. This is presumably a result of the relative basicity of the three amine groups of the track, with the most basic naphthylmethylene secondary amine[10] remaining protonated and thus unavailable to take part in Michael reactions.

Walker Migration on a Tetraethylenepentamine Track. Given the ability of the naphthylmethylamine foothold to act as a thermodynamic sink for the α-methylene-4-nitrostyrene walker on a three-foothold track in the presence of excess base (Figure 1), we investigated the walker's behavior

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on longer, five- and nine-foothold tracks (Figures 6–9). A walker–five-foothold-track conjugate was prepared as the penta-trifluoroacetic acid salt, **6**-*1*[5 × CF_3CO_2H], according to Scheme 2 (see Supporting Information). Upon treatment with 6 equiv $^iPr_2NEt$ in DMSO-d_6 (20 mM, 298 K) the walker processively[11] migrated along the track. ^1H NMR signals diagnostic for each positional isomer could be identified (Figure 5b) and thus the population of each positional isomer monitored over time (Figure 6). After 48 h the steady-state had been reached with 46 ± 3% of the walkers having taken a net four steps directionally along the track to be positioned on the naphthylmethylamine foothold.

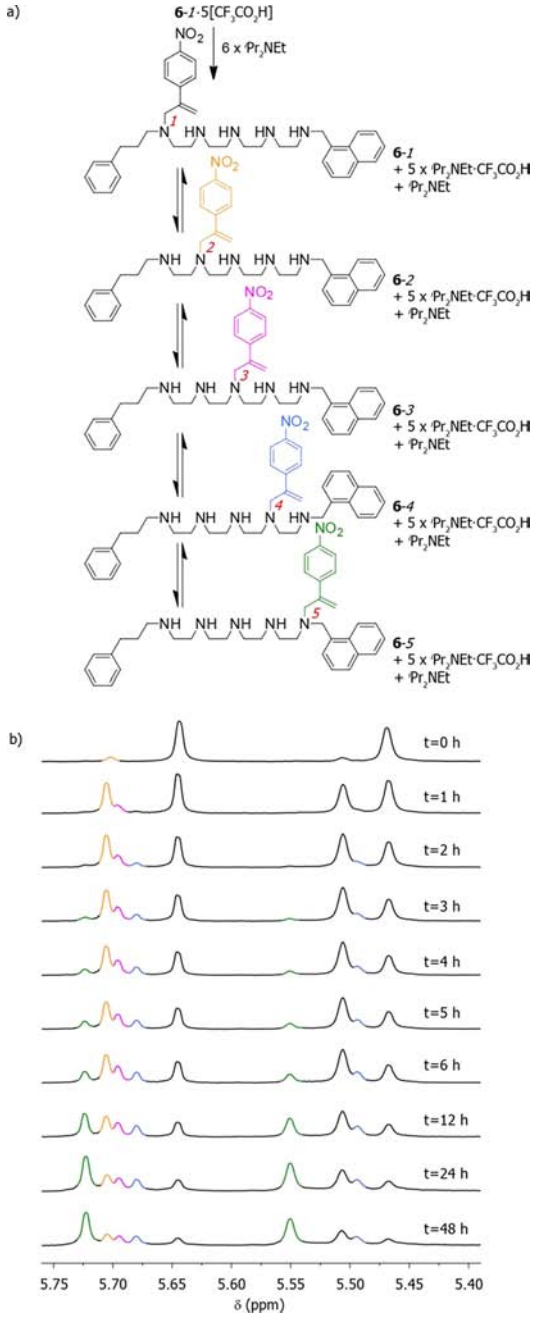


Figure 5. (a) Walking of **6**-*1*·5[CF_3CO_2H] in the presence of 6 equiv of $^iPr_2NEt$. (b) Partial ^1H NMR spectra of of **6**-*1*·5[CF_3CO_2H] + 6 equiv of $^iPr_2NEt$ (400 MHz, 20 mM, DMSO-d_6, 298 K) showing the successive formation of the five positional isomers (the colors of the signals corresponds to the structures shown in part (a)).

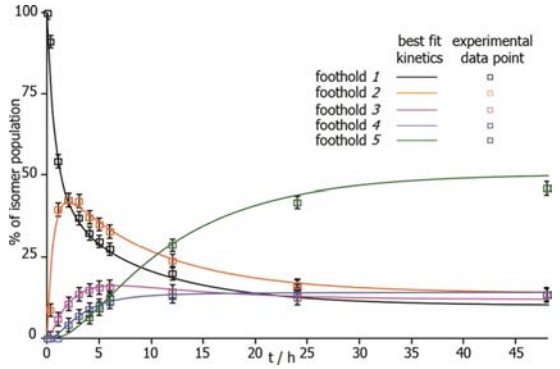
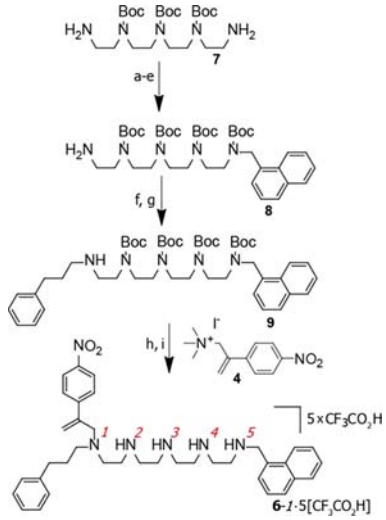


Figure 6. Intramolecular migration of the α-methylene-4-nitrostyrene unit of **6**-*1*·5[CF_3CO_2H] in the presence of 6 equiv of $^iPr_2NEt$. Population of isomers (^1H NMR integration). After 48 h, 46 ± 3% of walkers are positioned on foothold 5 of the track (isomer **6**-*5*). Lines show the best fit of the experimental data to the kinetics of the exchange between **6**-*1*, **6**-*2*, **6**-*3*, **6**-*4* and **6**-*5* using SimFit[9] (see Supporting Information for details). Error bars are indicative of the error associated with ^1H NMR integration using equivalent protons in each positional isomer.

Scheme 2. Synthesis of a Walker–Track Conjugate 6-*1*[a]



[a]Reaction conditions: a) 1-naphtaldehyde, EtOH, RT, 16 h; b) $NaBH_4$, RT, 3 h, 34% (two steps) c) CF_3CO_2Et, CH_2Cl_2, 0 °C→RT, 16 h; d) Boc_2O, Et_3N, RT, 12 h; e) NaOH, MeOH/H_2O, RT, 5 h, 74% (three steps); f) 3- phenylpropionaldehyde, EtOH, RT, 16 h; g) $NaBH_4$, RT, 3 h, 35%, (two steps); h) **4**, MeOH, $^iPr_2NEt$, 50 °C, 24 h, 49%; i) CF_3CO_2H, CH_2Cl_2, RT, 3 h, quant.

Walker Migration on an Octaethylenenonamine Track. A nine-foothold walker–track conjugate **10** was synthesized starting from commercially available 2-(2-aminoethylamino)ethanol (**11**), which was subjected to a sequence of protection–deprotection reactions (Scheme 3 a–c) to give **12**. Reductive amination of **12** with 3-phenyl-propionaldehyde afforded **13** (Scheme 3 d,e). Subsequent Cbz protection and oxidation using Dess–Martin periodinane (DMP) yielded the aldehyde building block **14** (Scheme 3 f,g). The second half of the track was synthesized, starting from the reductive amination of **11** with 1-naphthaldehyde (Scheme 3 h,i) followed by selective Boc protection to give **15** (Scheme 3 j). The primary alcohol was oxidized to aldehyde **16** (Scheme 3 k) and then subjected to reductive amination with commercially

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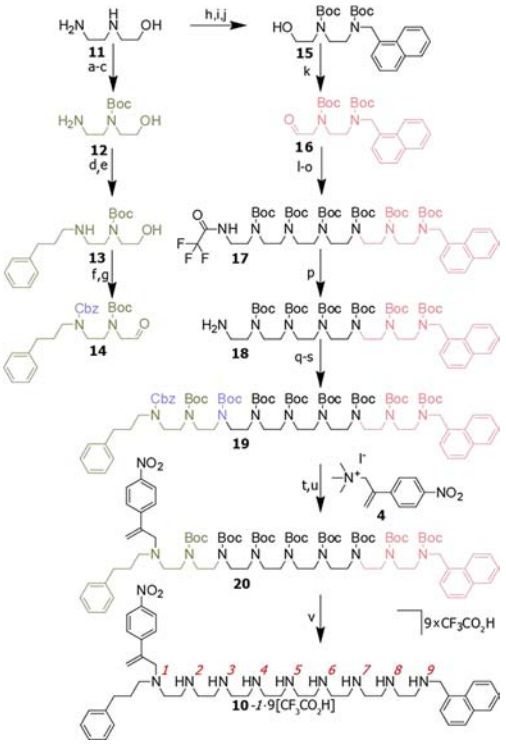
Scheme 3. Synthesis of a Walker−Track Conjugate 7-*1*[a]



[a]Reaction conditions: a) CF_3CO_2Et, CH_2Cl_2, 0 °C→RT, 3 h; b) Boc_2O, Et_3N, RT, 12 h, 60% (two steps); c) NaOH, $MeOH/H_2O$, RT, 5 h, 73%; d) 3-phenylpropionaldehyde, EtOH, RT, 16 h; e) $NaBH_4$, RT, 3 h, 36% (two steps); f) CbzCl, Et_3N, CH_2Cl_2, RT, 4 h, 68%; g) DMP, CH_2Cl_2, RT, 12 h, 81%; h) 1-naphthaldehyde, EtOH, RT, 16 h; i) $NaBH_4$, RT, 3 h; j) Boc_2O, MeCN, RT, 12 h, 64% (three steps); k) DMP, CH_2Cl_2, RT, 12 h, 68%; l) tetraethylenepentaamine, EtOH, RT, 16 h; m) $NaBH_4$, RT, 3 h; n) CF_3CO_2Et, CH_2Cl_2, 0 °C→RT, 16 h; o) Boc_2O, Et_3N, RT, 12 h, p) NaOH, $MeOH/H_2O$, RT, 5 h, 20% (five steps); q) **14**, EtOH, RT, 16 h; r) $NaBH_4$, RT, 3 h; s) Boc_2O, Et_3N, RT, 12 h, 30% (three steps); t) Pd/C, H_2, THF, RT, 20 h, 50%; u) **4**, MeOH, $^{i}Pr_2NEt$, 50 °C, 48 h, 50%; v) CF_3CO_2H, CH_2Cl_2, RT, 7 h, quant.

available tetraethylenepentaamine (Scheme 3 l,m). The primary amine was protected as the trifluoroacetate, followed by quadruple Boc protection of the remaining secondary amines to give **17** (Scheme 3 n,o). Deprotection of the primary amine (Scheme 3 p) afforded **18** and reductive amination with **14** furnished the nine-foothold track with one 'free' secondary amine (Scheme 3 q,r), which was subsequently Boc-protected to give **19** (Scheme 3 s). The Cbz group was reductively cleaved (Scheme 3 t) and the walker was attached and the protecting groups were removed (Scheme 3 u,v) to give **10**-*1*·9[CF_3CO_2H] (see Supporting Information for experimental procedures and characterization data).

In order to investigate the processive[11] walking process on the nine-foothold track, **10**-*1*·9[CF_3CO_2H] was treated with 10 equiv of $^{i}Pr_2NEt$ in DMSO-d_6 (10 mM, 298 K), and the reaction monitored by ^1H NMR spectroscopy (Figures 7 and 8). Although the assignment of each of the nine positional isomers is not possible, we were able to quantify the number of walkers on each of the terminal footholds (i.e., **10**-*1* and **10**-*9*) and compare each of those to the number sited on the internal footholds (i.e., **10**-*2*−**10**-*8*). After 15 h, signals corresponding to **10**-*9* (the walker molecule reaching the last foothold of the track) were apparent (green resonances, Figures 7 and 8b) and gradually increased in intensity until after 90 h (Figure 8b) 19 ± 3% of the walker units were present on the last foothold.

Intramolecular Migration As a One-Dimensional Random Walk toward a Thermodynamic Sink. Figure 10 shows the rate of diffusion of the walker along the various length tracks (compounds **5**, **6**, and **10**) and confirms that the net distance varies as the square root of the elapsed time.[12] The rate constants for the interconversion of adjacent positional isomers (e.g., between **10**-*3* and **10**-*2* and **10**-*4*) suggested by SimFit are similar for almost all exchanges between amine groups on the internal positions of the track (Figure 8a). Although the influence of the naphthylmethylamine group is diminished in the presence of eight alternative amine footholds, there is still a significant bias for the site, resulting in net directional walking of the α-methylene-4-nitrostyrene unit

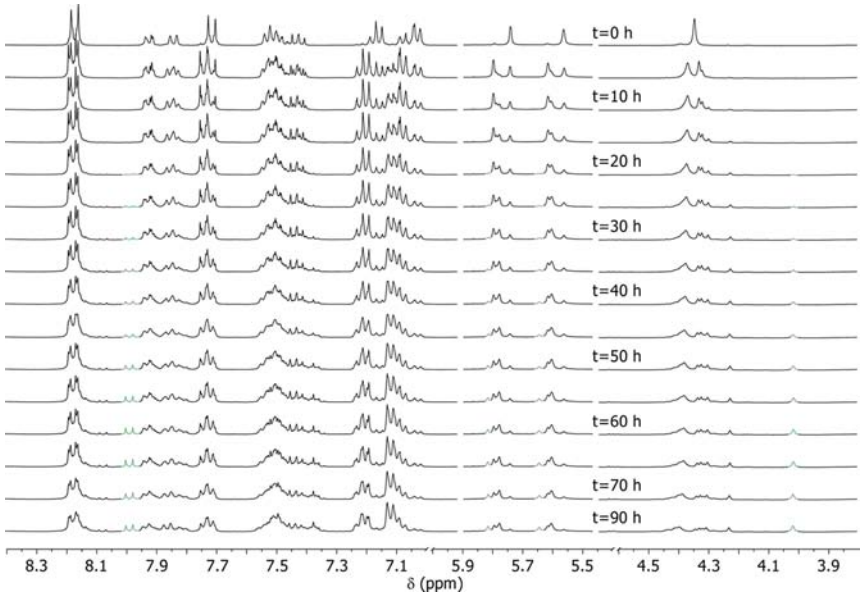


Figure 7. Partial ^1H NMR spectra (400 MHz, 10 mM, DMSO-d_6, 298 K) monitoring the intramolecular exchange of **10**-*1*·9[CF_3CO_2H] (black resonances at t = 0 h) in the presence of 10 equiv of $^{i}Pr_2NEt$, showing the disappearance of **10**-*1* and formation of positional isomers **10**-*2*−**10**-*8*. Resonances corresponding to **10**-*9* are shown in green.

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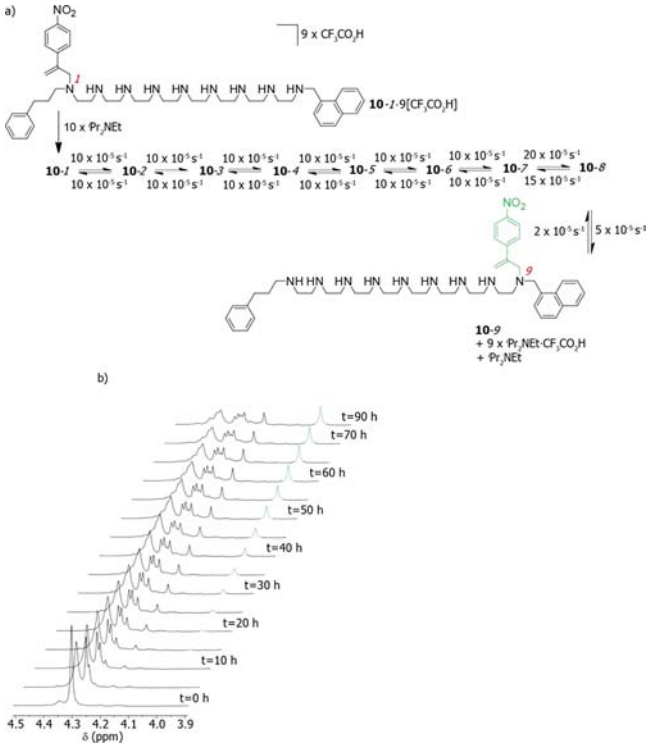

Figure 8. (a) Walking of **10**-*1*·9[CF_3CO_2H] in the presence of 10 equiv of $^iPr_2NEt$. (b) Partial ^1H NMR spectra (400 MHz, 10 mM, DMSO-d_6, 298 K) of the reaction mixture over time. After 90 h of exchange, 19 ± 3% of walkers are positioned on the 9th foothold of the track (**10**-*9*). Green resonances correspond to **10**-*9*. Rate constants obtained from the fitting of the experimental values to a kinetic model using SimFit[9] (see Figure 9 and Supporting Information for details).

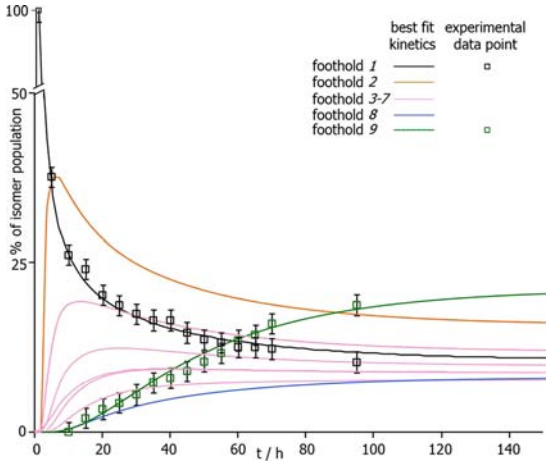

Figure 9. Intramolecular migration of the α-methylene-4-nitrostyrene unit of **10**-*1*·9[CF_3CO_2H] in the presence of 10 equiv of $^iPr_2NEt$. Population of isomers (^1H NMR integration). After 90 h, 19 ± 3% of walkers are positioned on foothold 9 of the track (isomer **10**-*9*). Lines show the best fit of the experimental data to the kinetics of the exchange between **10**-*1*, **10**-*2*, **10**-*3*, **10**-*4*, **10**-*5*, **10**-*6*, **10**-*7*, **10**-*8*, and **10**-*9* using SimFit[9] (see Supporting Information for details). Error bars are indicative of the error associated with ^1H NMR integration using equivalent protons in each positional isomer. Error of fit ±10%.

along the track. Interestingly, however, the preference for the walker to spend more time toward one end of the track appears to be a result of kinetics associated with foothold 8, the amine adjacent to the naphthylamine group, as well as the

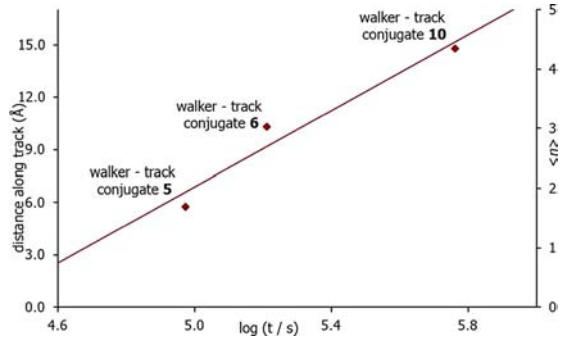

Figure 10. Calculated net displacement (distance along the vector of the track, Å, left-hand axis; average number of footholds traveled, <*n*>, right-hand axis) of α-methylene-4-nitrostyrene walker as a function of time.

naphthylamine foothold itself. Due to the track's architecture, the walker unit can only take forward and backward steps of equal distance, and therefore the migration is well described as a one-dimensional random walk toward a modest thermodynamic sink.[8,12]

CONCLUSIONS

We have shown that the migration of α-methylene-4-nitrostyrene along oligoethyleneimine tracks by Michael–retro-Michael reactions is hindered in the presence of acid but occurs readily under neutral and basic conditions. The intramolecular transfer from amine group to adjacent amine group is not limited to short model systems but also occurs on extended tracks up to nine footholds long. Moreover, under basic conditions a naphthylmethylamine foothold can act as a thermodynamic sink, leading to net directional migration of the walker even in the presence of eight other amine footholds. Directional movement along tracks over significant distances may enable synthetic small-molecule systems to transport cargoes and perform other useful tasks[13] at the molecular level.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, synthesis and characterization data, processivity experiments, kinetic measurements, and rate constant determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Processivity is the tendency of the molecular fragment (i.e., the walker) to remain attached to the track during operation, i.e. to migrate along a molecular scaffold without detaching or exchanging with other molecules in the bulk (ref 2a). We previously reported[3a] that α-methylene-4-nitrostyrene takes an average of 530 steps between adjacent amines on model (up to four repeat units) oligoethyleneimine tracks before detaching. Mass spectrometry was used to confirm high processivity during migration on the longer tracks used in this paper in the presence of excess base (see Supporting Information).

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