Mechanism of the lithium–iodine exchange in an iodothiophene¹

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Abstract: Solutions of 2-lithio-5-methylthiophene (4) were characterized using DNMR techniques and shown to be a mixture of monomer and dimer in THF–Et₂O (3:2). The hypervalent iodine ate complex 5 ($Ar_2I^-Li^+$), a presumed intermediate in the Li–I exchange with 2-iodo-5-methylthiophene, was observed by ¹³C and ⁷Li NMR spectroscopy at low temperatures (-130 °C). At higher temperatures, the ate complex coalesced with 2-lithio-5-methylthiophene. A kinetic scheme was developed, which accounts for the exchange of the monomer 4M, dimer 4D, and 2-iodo-5-methylthiophene (6) with the ate complex 5. The rates of the various exchanges were obtained through a DNMR analysis of the variable temperature ¹³C and ⁷Li NMR spectra, and the thermodynamic and activation parameters were calculated. The monomer 4M and the ate complex 5 have similar reactivity as aryl donors in the Li–I exchange reaction, but 4M is at least 1000 times as reactive as the dimer 4D towards the iodide.

Key words: halogen-metal exchange, lithium iodinate, iodine ate complex, lithium reagent, aggregate reactivity.

Résumé : On a caractérisé des solutions de 2-lithio-5-méthylthiophène (**4**) en faisant appel à des techniques de RMN dynamique (RMND) et on a pu démontrer que, dans le THF–Et₂O (3 : 2), elles comprennent un monomère et un dimère. Faisant appel à la RMN du ¹³C et du ⁷Li à basse température (–130 °C), on a pu observer le complexe **5** de l'iodate hypervalent ($Ar_2I^-Li^+$), un intermédiaire supposé dans l'échange Li–I avec le 2-iodo-5-méthylthiophène. À des températures supérieures, il y a coalescence du complexe are avec le 2-lithio-5-méthylthiophène. On a développé un schéma cinétique qui permet de tenir compte de l'échange du monomère **4M**, du dimère **4D** et du 2-iodo-5-méthylthiophène (**6**) avec le complexe ate **5**. On a obtenu les vitesses des divers échanges par une analyse RMN des spectres RMN du ¹³C et du ⁷Li à des températures variables et on en a calculé les paramètres thermodynamiques et d'activation. Vis-à-vis des donneurs aryles, dans une réaction d'échange Li–I, les réactivités du monomère **4M** et du complexe ate **5** sont semblables; toutefois, vis-à-vis de l'iode, le monomère **4M** est au moins mille fois plus réactif que le dimère **4D**.

Mots clés : échange halogène-métal, iodate de lithium, complexe ate de l'iode, réactif de lithium, réactivité d'un agrégat.

[Traduit par la Rédaction]

Introduction

The lithium–metalloid exchange, independently discovered by Gilman et al. (1) and Wittig et al. (2) is an effective route for the formation of many organolithium reagents inaccessible by other methods. Understanding the mechanism of this process provides greater insight and predictability into the factors that influence reactivity. The reaction has commanded substantial research interest over the past 60 years (3*a*), where four-centered (4), SET (3*a*–3*c*, 5), S_N2 (6), and ate complex mechanisms (7*a*, 8) have been suggested. Investigation of the lithium–metalloid exchange identified ate complexes as permissible intermediates, including those of I (7*b*, 7*c*, 9), Te (7*c*–7*e*, 10*a*, 10*b*), Se (7*d*, 7*f*, 10*b*), Sn (7*g*, 11, 12), Si (13), and Hg (7*b*, 7*c*). Iodine ate complexes have

Received 25 April 2005. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 1 December 2005.

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¹This article is part of a Special Issue dedicated to organic reaction mechanisms.

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also been detected as intermediates in the Li–Mg exchange (14). Both experimental (7*e*, 15) and computational (3*d*, 8) studies have addressed the ease of formation of various ate complexes. The relative rates of the lithium–metalloid exchanges follow the trend: I > Te >> Sn >> Br > Se >> S.

In previous reports of the lithium-iodine exchange of phenyllithium (1) with iodobenzene (2) we have kinetically and spectroscopically identified the stable hypervalent ate complex **3** as present in solution (7*b*, 7*c*, 7*e*). Direct involvement of **3** in the exchange process could not be proven, since analysis of the kinetic processes was complicated by the unfavorable equilibrium between phenyllithium monomer and dimer, and the degenerate exchange between **2** and **3**.



We report here our results on the solution structure of 5methyl-2-thienyllithium (4) and its behavior in the lithium– iodine exchange using low-temperature, multinuclear NMR techniques. The use of 4, with its favorable NMR properties, ease of handling, and considerably higher monomer to dimer ratio compared to PhLi, has allowed measurement of the rates and equilibria of exchange between monomer 4M and dimer **4D** (eq. [1]), monomer and ate complex **5** (eq. [2]), and ate complex and 2-iodo-5-methylthiophene (**6**) (eq. [3]). It has also allowed an estimate of the maximum reactivity of the dimer with the iodide in the Li–I exchange (eq. [4]).



Results and discussion

The NMR study we set out to perform used four kinds of samples, all in THF–ether (3:2) solution (this mixed solvent system is close in donor strength to that of pure THF and allows the measurement of NMR spectra down to -135 °C). In each case variable temperature ⁶Li, ⁷Li, and ¹³C NMR spectra were measured. They are:

1. Solutions of the lithium reagent 4 to define the aggregates (4M and 4D) present (Figs. 1A and 2). The concentration and temperature dependence of the equilibrium constant (K_1) and the temperature dependence of the exchange rates k_1 and k_{-1} were determined from these samples (Figs. 3 and 4). **Fig. 1.** ¹³C NMR spectra in THF–ether (3:2). (A) 0.10 mol/L of **4** at -133 °C (the inset showing the C-2 signals is from a 0.2 mol/L ⁶Li-labeled sample, where the dimer C-2 signal was processed by multiplying the FID with a Gaussian function before Fourier transformation (LB = -6.1, GB = 0.1). The coupling constants are believed accurate to ±0.2 Hz (D = **4D**, M = **4M**). (B) A 1:1 ratio of **4** and **6** with 9 equiv. of HMPA (T = 2-methylthiophene, protonation product). (C) The iodide **6**.



- 2. Solutions with a 1:1 ratio of lithium reagent 4 and iodide 6 with excess HMPA present (Fig. 1B). In such solutions K_2 becomes very large, leaving 5 as the only detectable species (7*a*, 7*b*) and allowing its NMR identification and characterization.
- 3. Solutions with an excess of lithium reagent over iodide (Fig. 5). Line-shape fitting of the ⁷Li NMR spectra of these samples allow estimation of k_2 at each temperature, using as input the values of K_1 , K_2 , k_1 , and k_3 obtained from samples 1 and 4.
- 4. Solutions with an excess of iodide **6** over lithium reagent **4** (Fig. 6). In these solutions **4M**, **5**, **6**, and, at temperatures above -85 °C, **4D**, are in rapid exchange and it is possible to measure the temperature dependence of the ate complex association constant K_2 from analysis of the averaged peak positions in the ¹³C NMR spectra, using K_1 obtained from samples 1 and the chemical shifts of the individual species. Line-shape analysis of these samples also allowed measurement of k_3 and an estimate of k_4 .

The solution structure of 2-lithio-5-methylthiophene

Previous studies of 2-thienyllithium reagents have included X-ray structures of the ether solvated tetramer of 4 (7*h*), several substituted lithiothiophenes,³ and 2-lithiobenzothiophene (16*a*), as well as a report of the solution ¹³C NMR spectrum of 2-lithiothiophene itself (17). We have recently

³Several single crystal X-ray structures have been reported in the Cambridge Structural Database as private communications (1999). 3-Dimethylaminomethyl-2-lithiothiophene dimer (LEDSES): A.L. Spek, M.T. Lakin, and R. den Besten. 3-Methoxy-2-lithiothiophene (HIGPOC): A.L. Spek and N. Veldman. 3-Bromo-2-lithiothiophene TMEDA dimer (HIGXUQ): A.L. Spek. 2-Lithiothiophene dimer (JUJXER): A.L. Spek and W.J.J. Smeets.

Fig. 2. Selected ¹³C and ⁷Li NMR spectra of a variable temperature study of 0.101 mol/L 5-methyl-2-thienyllithium (4) in THF– ether (3:2). These spectra were simulated to obtain k_1 , k_{-1} , and K_1 (eq. [1]). Monomer (M), dimer (D).



Fig. 3. (A) Concentration dependence of the **4M** and **4D** ratio in THF–ether (3:2) at –121 °C. (B) Temperature dependence of free energy ($\Delta G = RT \ln(K_{eq})$) for the monomer dimer equilibrium (K_1 , eq. [1]) and the ate complex equilibrium (K_2 , eq. [2]).



reported detailed NMR studies of a series of lithiothiophenes, including some with ortho chelating groups (7i).

Clean solutions of 4 were readily available since the precursor 2-methylthiophene is easily metalated with n-BuLi (17, 18), and the pure reagent can be crystallized from THF or ether (7*h*). Figure 1A reports the 13 C NMR spectrum of 95.5% ⁶Li-labeled **4** (19) in THF-ether (3:2) at -121 °C. There are two sets of carbon signals, corresponding to two distinct lithium species (19a). Each showed fully resolved ¹³C-⁶Li scalar coupling of the ipso carbon signals at 182.3 ppm (1:1:1 triplet, ${}^{1}J = 15.3$ Hz) and 174.5 ppm (1:2:3:2:1 pentet, ${}^{1}J = 7.8$ Hz), respectively (19*b*). The assignment of the two species as monomer 4M and dimer 4D derives from the lithium-carbon coupling, as well as from a variable concentration study, which showed that the two species differ in aggregation state by a factor of two (slope of the log[M] vs. log[D] plot was 1.9 ± 0.13 , $K_1 =$ 12.6 (mol/L)⁻¹ at -128 °C, Fig. 3a) (7j, 7k, 16b). In addition, **Fig. 4.** Temperature dependence of the free energy of activation (calculated from a form of the Eyring equation, $\Delta G^{\ddagger} = RT[23.76 + \ln(T/k_{\rm r})] = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$) for the monomer–dimer exchange $(k_1 (\bullet))$ from line-shape analysis of the spectra in Fig. 2, eq. [1]), ate complex formation $(k_2 (\blacktriangle)$ from Fig. 6, eq. [2]), and ate complex – iodide exchange $(k_3 (\Box))$ from Fig. 7, eq. [3]).



Fig. 5. Variable temperature (A) 13 C and (B) 7 Li NMR spectra of a solution of 4 (0.117 mol/L) and 6 (0.046 mol/L) in THF-ether (3:2).



experiments in various mixtures of THF and ether showed that the dimer signals increasingly predominated as the fraction of ether increased. The carbon assignments in the ¹³C NMR spectra were based on identification of C-2 from the

Fig. 6. Variable temperature NMR spectra of solutions of 4 and 6 in THF–ether (3:2) with excess iodide. The two panels are from experiments with slightly different concentrations. (A) 13 C NMR spectra. The dotted spectra are simulations of the C-3 resonance, as described in the text. (B) 7 Li NMR spectra. The insets are vertical expansions showing the build-up and eventual coalescence of 4D with the average of the other signals as temperature increased.



Li–C coupling, C-5 as a quaternary carbon by an INEPT experiment, on the literature assignments for 2-lithiothiophene (17), and on the correlation between equivalent carbons of **4M**, **4D**, **5**, and **6** provided by the coalescence experiments (Figs. 2, 5, and 6). Thus, the carbons of **6** could be readily assigned from shift parameters (20), and this allowed carbon signal assignments of all of the other compounds.

A variable temperature experiment of 4 is shown in Fig. 2. Each pair of ¹³C and ⁷Li NMR signals for 4M and 4D coalesced between -120 and -91 °C. Complete line-shape simulations of these spectra were used to determine the rates of interconversion for monomer and dimer. The relationship between the pseudo-first-order NMR rate constants (k_{MD} and k_{DM}) obtained from the simulation and the mechanistic rate constants k_1 and k_{-1} of eq. [1] is straightforward: k_{-1} is also a first-order rate constant (it is best to think of a first-order rate as the fraction of substrate converted per unit time), so $k_{-1} = k_{\rm DM}$. The monomer to dimer conversion k_1 is a secondorder rate constant (fractional conversion per unit time per molar concentration of reactant), and thus $k_{\rm MD} = k_1[4M]$. The activation parameters in eq. [1] were calculated from the temperature dependence of k_1 and k_{-1} (see Fig. 4). The simulation also gave the concentration of monomer and dimer as a function of temperature (for the four low temperature points from the areas of the two C-3 peaks, for the five high temperature points from the peak position of the averaged C- 3 signals), and hence the thermodynamic parameters for the dimer–monomer equilibrium (Fig. 3B).

Lithium-iodine exchange of 2-lithio 5-methyl-thiophene

Solutions containing both 4 and 5 show complex DNMR behavior because of the presence of four species (4M, 4D, 5, and 6) whose relative concentrations are strongly temperature dependent and which are all undergoing mutual exchange involving at least three different rate constants (k_1 , k_2 , and k_3). Figure 1 shows spectra of 4 and 6 and a 1:1 mixture of the two, the latter with 9 equiv. of hexamethylphosphoric triamide (HMPA) present, which has the effect of greatly increasing K_2 (7*a*, 7*b*). The presence of a new species in Fig 1B, the ate complex 5, can be readily seen, since the ¹³C signals for C-3, C-4, and C-5 are upfield of all three constituents, and so cannot simply be a dynamic average of them.

Examination of samples in THF–ether (3:2) with varying ratios of iodide and lithium reagent revealed that there were two limiting behaviors. With excess lithium reagent the signals of three of the components present (4D, 4M, and 5) could be decoalesced. There is not a detectable amount of 6 at the lower temperature limit of the solvent system (Fig. 5). On the other hand, when iodide was in excess there was (with a minor exception) a single, strongly temperature dependent set of ${}^{13}C$ and ${}^{7}Li$ signals throughout the accessible temperature range (Fig. 6).

The spectra of Fig. 5 can be interpreted as follows. At the lowest temperatures the signals of the ate complex 5 are decoalesced from those of the monomer 4M and dimer 4D. The formation constant (K_2) of 5 is high, and since there is excess lithium reagent, there is no detectable iodide 6. Between -130 and -115 °C the signals of 5 and 4M coalesce (eq. [2]). The signals of 4D are not appreciably affected by this process. Between -110 and -90 °C the 4D signals coalesce with the averaged signals of 5 and 4M. Starting at ca. -110 °C, the shift of the equilibrium of eq. [2] (K_2) away from ate complex toward the iodide and lithium reagent becomes apparent as indicated by the downfield shift of the three visible signals (the C-3, C-4, and C-5 signals of 5 are all upfield of those of 4M, 4D, and 6).

Figure 6 cannot be interpreted with only the eq. [1] and [2] processes, since the lowest temperature spectrum should show excess iodide 6 and the ate complex 5 in slow exchange, just as was seen for excess 4 in Fig. 5 (the process k_2 is slow on the NMR timescale at this temperature). We propose that here, as seen for the PhLi–PhI system (7b, 7c), there is another exchange process that averages the signals of 5 and 6. The ate complex is behaving as a carbanion donor, and transferring an aryl group to the iodide to form a new ate complex (k_3 , eq. [3]). When there is a stoichiometric excess of lithium reagent, there is no corresponding process that can average the lithium reagent and ate complex signals, and so the signals can be decoalesced (Fig. 5).

We will perform a quantitative analysis of the thermodynamics and kinetics of the Li–I exchange as revealed by the spectra of Figs. 5 and 6. First, we will determine the ate complex association constant K_2 from an analysis of chemical shifts and peak positions in the ¹³C NMR spectra of Fig. 6 using the information on k_1 and K_1 gleaned from Fig. 2 and similar experiments. This allows us to extract the

Fig. 7. Exchange matrix used for the simulation of the 7 Li NMR spectra of Fig. 5B.

	A (5)	D (4D)	M (4M)		$k_{\rm AD} = k_{-4} [4M]$
A (5)	$\begin{bmatrix} i2\pi(v_A) \\ -1/T-\Sigma k_{AX} \end{bmatrix}$	k _{AD}	k _{AM}]	$k_{\text{DA}} = \frac{k_4 [6]}{2}$ $k_{\text{AM}} = k_2$
D (4D)	k _{DA}	i2π(v _D) -1/T-Σk _{DX}	k _{DM}	= E	$k_{\rm MA} = k_2 [6]$
M (4M)	k _{MA}	$k_{\rm MD}$	i2π(v _M) -1/T-Σk _{MX}		$k_{\text{DM}} = k_{-1} + \frac{4}{2} k_{\text{MD}} = k_1 [4\text{M}] + k_{-4} [5]$

Li–I exchange rate constant k_2 from the spectra of Fig. 5, and sets the stage for determining k_3 as well as estimating the maximum rate of exchange of the dimer **4D** with the iodide **6** (k_4).

Determination of the ate complex association constant (K_2)

We have used the chemical shift of the C-3 signal in the ¹³C NMR spectra of an experiment like the one in Fig. 6A to determine the composition of the sample. At each temperature above coalescence (-87 to -59 °C) an iterative computer program was used to calculate the concentration of all species for a series of trial ate complex concentrations until the calculated averaged ¹³C NMR chemical shift matched the experimental one. These calculations used the previously determined values of K_1 (eq. [1]), the concentrations of the component species, and the chemical shifts of each compound as input. The shifts of **4M**, **4D**, and **5** were found to be temperature independent and those of **6** were extrapolated from spectra of pure **6** taken at a series of temperatures.

Two additional data points were derived from the ⁷Li NMR spectra. At -117, -107, -102, and -98 °C it was possible to detect the signal of **4D** (see insets, Fig. 6B). The area of this signal was determined at the two temperatures at which it is best defined (-102 and -107 °C), and these values were then used to calculate the concentrations of the other species using the known value of K_1 .

From the concentrations, K_2 can be calculated at each temperature and the thermodynamic parameters for the ate complex equilibrium determined (see eq. [2], Fig. 3B). The large negative entropy of formation of the ate complexes (-48.6 eu) is similar to that found for the formation of lithium diphenyliodinate **3** (-44 eu) (7c) and other systems (7d, 7f, 13). This loss of entropy derives from loss of translational and rotational motion for the component iodide and lithium reagent, as well as the extra THF molecules frozen by the very electrophilic free lithium cation of the ate complex (7b, 7c), compared to the strongly C-bound cation of the aryllithium reagent (7l).

Determination of the rate of Li–I exchange (k_2)

We next simulated the NMR spectra of Fig. 5 to determine values for k_2 and k_{-2} . The ¹³C signals were rather noisy, and simulations were not very well defined. However, the ⁷Li NMR signals had superb signal-to-noise and had the decisive advantage that the degenerate exchange of iodide and ate complex (eq. [3]) does not affect the ⁷Li line shape, since this process leaves the lithium signal unchanged.

A significant problem for simulations of the ⁷Li spectra is the quite variable quadrupolar T_1 relaxation rates (21), which could not be independently measured because of interfer**Fig. 8.** Line-shape simulation of the variable temperature ${}^{7}\text{Li}$ NMR spectra of Fig. 5B (**4** (0.117 mol/L) and **6** (0.046 mol/L) in THF–ether (3:2)). Lower lines are experimental data, upper dotted lines are simulations using the rate constants shown and the exchange matrix of Fig. 7.



ence from dynamic effects. Since the lines were fifty to several hundred Hz wide in the crucial part of the simulation, we anticipated that errors in line width would not greatly affect the accuracy of the rate constants determined. We assigned inherent line widths of 4 Hz for 5, 8 Hz for 4D, and 10 Hz for 4M based on the low temperature spectra and the behavior of other related aryllithium species. An iterative process was used to establish optimum populations and rates (see the Experimental section) using the exchange matrix shown in Fig. 7. The exchange matrix includes contributions from the reaction of dimer with iodide (k_4 process, eq. [4]). The values of k_{-1} in solutions containing 6 were actually smaller than those determined for solutions of just the lithium reagent. Since no detectable contribution from k_4 is present, it was set to zero, leaving only $k_{\text{DM}}(k_{-1})$ and $k_{\text{AM}}(k_{-2})$ to be adjusted (7m).

The simulations are presented in Fig. 8. An excellent match between experimental and calculated spectra was achieved, with k_{-1} within a factor of two of those values determined from solutions of 4 (Fig. 2) and K_2 values within a factor of four of those determined from analysis of the previous ¹³C NMR shifts of Fig. 6 (see Fig. 4). There are a number of potential reasons for these discrepancies: the chemical shifts may have a slight temperature dependence, the assumption of T_1 values for the three lithium species may have been too crude, and there may have been small variations in solvent composition between experiments. Both K_1 and K_2 are very solvent sensitive. For example, K_1 decreased by a factor of 5.7 between 60% and 80% THF in ether at -117 °C. The values for k_2 and k_{-2} as a function of temperature are shown in an Eyring plot in Fig. 4, leading to the activation parameters reported in eq. [2].

Rate of exchange of ate complex with iodide (k_3)

We are now in a position to attempt a simulation of the ¹³C NMR line shifts of Fig. 6, which involves, in addition to

Fig. 9. (A) Spectrum of a solution of **4** and **6** at -131 °C. (B) Optimal simulation. (C) Simulation with no contribution from the process of eq. [3] (k_3) (7m). See Fig. 10 for the definitions of k_{AI} and k_{AM} .



the eq. [1] and [2] processes, the bimolecular exchange between ate complex and iodide $(k_3, eq. [3])$. We used the values of k_1 , k_2 , K_1 , and K_2 calculated from the thermodynamic and activation parameters in eqs. [1] and [2] to determine the NMR rates and populations of 4M, 4D, 5, and 6 at each temperature. Neither the populations nor the k_1 and k_2 rate constants were allowed to vary in the simulation. Any excess broadening of the iodide 6 and ate complex 5 signals over that predicted by k_2 can then be assigned to k_3 , the iodide - ate complex exchange of eq. [3]. This is illustrated in Fig. 9, which shows simulations of the -131 °C spectrum. At this temperature the iodide signal would be decoalesced if $k_{AI} = k_{AM}$ (Fig. 9C), i.e., if k_2 was the only mechanism for exchange. This can be compared with the simulation in Fig. 9B, which has the rate k_{AI} optimally adjusted to fit the actual spectrum.

The exchange matrix and the relationship between firstorder NMR rate constants $(k_{AD}, k_{AM}, k_{AI}, \text{ etc.})$ and their mechanistic equivalents $(k_1, k_2, k_3, k_4, \text{ etc.})$ is shown in Fig. 10. This simulation is complicated by the fact that temperatures low enough for decoalescence cannot be achieved. In addition, values for k_3 and k_{-3} are calculated from k_2 and k_{-2} $(k_3 = (k_{IA} - k_2[4M])/[5], k_{-3} = (2k_{AI} - k_{-2})/[6])$, and so the limited accuracy of k_2 because of the small temperature range and scatter of the ΔG^{\ddagger} vs. T plot (Fig. 4) directly affects the accuracy of the k_3 values.

The simulation worked reasonably well (insets in Fig. 6A), although there were small errors in the chemical shift of the averaged signal, which is not surprising considering the accumulation of calculated values that comprise the input. The most likely source is small errors in the value of K_2 used to calculate the concentrations. Only at the four lowest temperatures in Fig. 6 were the spectra significantly affected by the value of k_3 , so we report data only at these temperatures. Although there is significant broadening at intermediate temperatures (-87 and -81 °C), this is largely due to the monomer-dimer exchange (k_1) and is not very sensitive to k_3 . Activation parameters are shown in eq. [3]. We did not perform experiments to verify that the k_3 process was first order in 6 by repeating this experiment with variable iodide concentrations. However, such an experiment was previously performed for a PhLi-PhI solution in THF-HMPA Fig. 10. Exchange matrix for the interactions between 4M, 4D, 5, and 6. See eqs. [1]–[4] for definitions of the rate constants.

(7b), where first-order behavior in iodide was demonstrated by a DNMR study.

The data obtained show the astonishing result that the monomeric lithium reagent and the ate complex have comparable reactivity as donors in the Li-I exchange. In another test of ate complex reactivity, the reaction of PhLi-PhI with hexamethyldisiloxane in THF-HMPA, PhLi is at least a factor of 10^5 more reactive than Ph₂I⁻Li⁺ (7*a*). This estimate is based on the reduction in k_{obs} for the silulation reaction when excess PhI was added to a solution of PhLi in THF-HMPA. Of course, in this case the PhLi has been greatly activated by complexation to HMPA (by a factor of 10^3 or more) (7j), so a direct comparison is not very meaningful. We considered that the k_2 process might be approaching diffusion control, and thus suffer from rate compression, but diffusion-controlled processes at -102 °C in THF-ether should have rates of ca 1×10^9 s⁻¹ (mol/L)⁻¹, about 10^3 times faster than the measured bimolecular rate (k_2) . A more likely explanation is that the rate-limiting (or partiallimiting) step for the Li-I exchange (eq. [2]) is C-Li bond dissociation (CIP to SIP) or solvent association with or dissociation from the lithium cation. Barriers to dissociation of THF from lithium species can be substantially higher than the activation energies of the Li-I exchange measured here (7n, 22, 23). This is in principle testable (the Li–I exchange should have fractional or zero order in iodide) by repeating the experiment of Fig. 5 at various concentrations, to establish whether consistent rates would be obtained. Unfortunately, the concentration of iodide is not easily manipulated in solutions with excess lithium reagent, the only conditions where k_{-2} can be measured.

It is the interference by the process of eq. [3] that prevents us from demonstrating by DNMR techniques whether the ate complex is an obligatory intermediate in the Li–I exchange. This would require showing that the exchange rates of iodide and lithium reagent were the same and that the ate complex lifetime was correctly predicted from the lifetimes of the reaction partners. To achieve this, signals for all three components (**4M**, **5**, and **6**) must be visible in a sample so that lifetimes of all three can be simultaneously measured. As can be seen from Figs. 5 and 6, at no point can ¹³C signals of all three species be seen. This is in part because at the low temperatures where rates are slow enough to observe individual signals, K_2 is so large that the concentrations of **4M** or **6** (whichever is stoichiometrically limiting) is too small to detect, and in part because k_3 is too large.

Rate of Li–I exchange for the dimer (k_4)

The observation that the ⁷Li NMR signal of the dimer **4D** could be decoalesced from the averaged signal comprising the lithiums of 4M and 5 in Fig. 6B shows that the dimer is not undergoing Li-I exchange (eq. [4]) under conditions where exchange of monomer is rapid. The 'Li NMR signal of 4D at -102 °C is 60 Hz wide. At the same temperature the ¹³C NMR signal of **4D** in a sample containing only **4** is 80 Hz (Fig. 2), so there is no detectable broadening assignable to the Li–I exchange of dimer, the k_4 process. If we estimate that no more than 10 Hz of the 60 Hz line width of the lithium signal could be due to the k_4 process, then the NMR rate constant $k_{\text{DA}} \le 31 \text{ s}^{-1} (\pi \Delta \nu)$, and the physical rate constant $k_4 = k_{\text{DA}}/[\mathbf{6}] \le 670 \text{ s}^{-1} (\text{mol/L})^{-1}$. Since the rate of exchange of the iodide with monomer (k_2) is 6.7×10^6 s⁻¹ $(mol/L)^{-1}$ at -102 °C (see eq. [2]), reaction of dimer with the iodide is at least a factor of 1000 slower than reaction of the monomer. Although many reactivity effects of organolithium reagents have been ascribed to aggregation phenomena, determination of quantitative and qualitative differences between reactivity of different aggregates of an organolithium species under the same conditions has rarely been reported (24, 25). This result shows that the common assumption that higher aggregates are less reactive than lower ones holds well in this monomer-dimer case, and that the differences can be quite large.

Summary

A DNMR investigation of 2-lithio-5-methylthiophene (4) showed this lithium reagent to be a mixture of monomer and 4-center dimer in THF-ether (3:2). Solutions of 4 and the corresponding iodide 6 undergo Li-I exchange on the NMR timescale. The ate complex 5, a probable intermediate in the exchange, is formed with a high association constant at low temperature (-130 °C), but is largely dissociated at temperatures above -70 °C. A variable-temperature DNMR kinetic analysis showed that three exchange processes occurred on the NMR timescale, the monomer dimer exchange (eq. [1]), the Li-I exchange of the monomeric lithium reagent (eq. [2]), and direct exchange between the ate complex and the iodide (eq. [3]). The ate complex 5 is comparable in reactivity to the monomeric lithium reagent 4M in the Li-I exchange process. The data obtained also allowed an estimate of the upper limit of a fourth process, the Li-I exchange of the dimer (eq. [4]). The bimolecular rate constants at -102 °C are shown in the following:

Rate constant	$k \; ((\text{mol/L})^{-1} \; \text{s}^{-1})$	$k_{\rm rel}$
k_1 (eq. [1])	6.8×10 ³	1/100
k_2 (eq. [2])	6.7×10^5	1.0
k_3 (eq. [3])	1.3×10^{6}	1.9
k_4 (eq. [4])	$<6.6 \times 10^{2}$	<1/1000

The lithium iodine exchange reaction has been mechanistically controversial since its discovery in 1938. The present DNMR investigation, together with other related papers (7*a*– 7*c*), places aryl iodine ate complexes (**5**) firmly into the mechanistic picture in two roles: as a permissible intermediate in the exchange itself (our results do not make it an obligatory intermediate), and as a reactive partner in its own right in donating a thienyl anion to iodothiophene (eq. [3]). The latter observation suggests that ate complexes may be reactive partners in reactions when lithium reagents are prepared by Li–I exchange. The fact that solutions of iodide and lithium reagent are stable in samples where upwards of 10⁹ Li–I exchanges have occurred during an experiment provides a strong argument that single electron transfer reactions involving aryl radical intermediates play no role in the reaction, since cage effects of this magnitude would seem impossible.

Experimental section

General

All glassware was dried in an oven at 110 °C for at least 2 h and flushed with N_2 for at least 5 min. All reactions were performed under an atmosphere of dry nitrogen.

Instrumentation

GC analyses were performed using a 12 m × 0.32 mm SE-30 capillary column, with He pressure of 6.0 psi (1 psi = 6.894 757 kPa), column flow rate (split ratio 300:1) of 3 mL/min, and column temperature of 90 °C. Retention times and response factors with respect to *n*-undecane are as follows: 2-iodo-5-methylthiophene (2.77 min, 2.39), 2-(methylthio)-5-methylthiophene (2.87 min, 1.99), *n*-undecane (2.67 min, 1.00). For a 1:1 molar solution of compound: $C_{11}H_{24}$, the response factor = (peak area $C_{11}H_{24}$)/(peak area compound).

¹³C, ⁷Li, and ⁶Li NMR spectra were obtained on a Bruker AM-360 spectrometer operating at 90.56, 139.96, and 53.00 MHz, respectively. The NMR spectra were acquired unlocked and in non-deuterated solvents unless otherwise stated. For ¹³C NMR, a 30° pulse of 5 µs repeated every 2.9 s was used. An exponential line broadening of 2-5 Hz was used, and a 64 K transform was carried out over a spectral width of 20 800 Hz. ¹³C NMR chemical shifts are reported in ppm relative to TMS (δ 0.0), using THF as an internal reference. ⁷Li NMR spectra were recorded over a spectral width of 1400 Hz (8K data points) using a 10 µs pulse and ⁶Li NMR spectra over a spectral width of 2907 Hz (8K data points) with a pulse width of 10 µs and a recycle delay of 4 s. Both ⁷Li and ⁶Li NMR chemical shifts were referenced to external 0.30 mol/L LiCl in MeOH (δ 0.0 \approx -100 °C) (19c). n-Bu-⁶Li (95.5% enriched) was prepared by literature procedures (7l).

Probe temperatures were measured (decoupler turned off) by replacing the sample with an open tube containing the same solvent and the sensor of a RTD (platinum resistance) thermometer, which was designed to measure temperatures from -150 °C to 50 °C, and was calibrated using ice water (0.01 °C) and CO₂ (-78.5 °C). The accuracy of the resistance thermometer was checked with the melting points of toluene (-95.00 °C) and methylcyclohexane (-126.6 °C) and were found to be within 0.4 °C of the reported value. Samples were allowed to equilibrate for at least 8 min in the probe prior to tuning the spectrometer and acquiring the spectrum. Probe temperatures were confirmed following the acquisition of each spectrum.

DNMR simulations were performed with the Binsch DNMR program (26) and with WINDNMR (7m).

Solvents

THF and Et_2O were freshly distilled from sodium benzophenone ketyl prior to use. The THF still was recharged every 3 weeks to insure that no benzene (formed by cleavage of benzophenone) accumulated in the THF. Solutions of organolithium reagents were titrated by use of 1-propanol with 1,10-phenanthroline as the indicator (27). 2-Methylthiophene was commercially available.

Preparation of stock solutions of 2-lithio-5methylthiophene (4)

To a solution of 2-methylthiophene (2.4 mL, 25 mmol) in 5 mL of THF at -78 °C was added 13.3 mL of a 1.88 mol/L solution of *n*-BuLi or *n*-Bu⁶Li (25 mmol). The reaction mixture was warmed to 0 °C for 10 min, then cooled to -78 °C. Crystals formed in the centrifuge tube within 10 min. The supernatant was removed from the crystals, which were washed two times with 6 mL of THF, each time removing the excess solvent by cannula. The crystals were dissolved in ca. 15 mL of THF to give a solution of **4** in THF, which was determined to be 0.95 mol/L. The solution of **4** was stable for several months at -20 °C.

2-Iodo-5-methylthiophene (6)

To a solution of 2-methylthiophene (96.8 µL/mmol, 1.94 mL, 20 mmol) in 20 mL of THF at -78 °C was added a solution of n-BuLi (1.88 mol/L, 10.6 mL, 20 mmol). The solution of 4 was warmed to 0 °C and added dropwise to a suspension of 1,2-diiodoethane in THF at -78 °C. The mixture was stirred at -78 °C for 1 h, warmed to 0 °C for 2 h, and partitioned between 200 mL of Et₂O-pentane (1:1) and 150 mL of NaHCO₃. The organic layer (purple) was washed with 50 mL of 0.5 mol/L Na₂S₂O₃, 200 mL of water, 150 mL of brine, and passed through a cone of Na₂SO₄. Evaporation of the solvent gave a light brown liquid (4.34 g, 97%), which was purified by Kugelrohr distillation (bp 40-60 °C (1 mm Hg)) giving a colorless liquid. ¹H NMR $(CDCl_3, 200 \text{ MHz}) \delta$: 2.46 (d, J = 0.94 Hz, 3H), 6.45 (dq, J = 3.7, 0.9 Hz, 1H), 7.01 (d, J = 3.67 Hz, 1H). ¹³C NMR (THF-Et₂O (60:40), -116 °C, 90.556 MHz) δ: 15.4, 73.2, 128.34, 137.4, 146.3 (28).

The preparation of NMR samples of 2-lithio-5-methylthiophene (4)

To a septum-capped 10 mm NMR tube under N₂ was added 0.05 mL of a 1.42 mol/L solution of 2-lithio-5methylthiophene (4) and 1 mL of THF. The NMR tube containing the dilute solution of 4 was rolled so that all of the surface of the NMR tube and septum came in contact with the organolithium solution (to dry the NMR tube). The solution of 4 was removed from the NMR tube with a syringe. A solution of 4 in THF (1.42 mol/L, 0.20 mL, 0.288 mmol) was added to the NMR containing a static N₂ needle. THF (1.8 mL) and Et₂O (1.2 mL) was added to the tube and the solution was mixed with a vortex mixer. The contents of the tube were cooled to -78 °C and the septum was sealed with parafilm.

The determination of concentration for NMR samples

To the NMR solution was added Me₂S₂ and 25 μ L (0.118 mmol) of *n*-undecane. The mixture was added to

Table 1. Data for the plot of ln[monomer] vs. ln[dimer] at -121 °C.

[4] (mol/L)	Peak ratio (4D/4M)	[4D] (mol/L)	[4M] (mol/L)	K_1 ((mol/L) ⁻¹)
0.21	1.845	0.0681	0.0783	12.5
0.12	1.332	0.0343	0.0515	12.9
0.094	1.190	0.0255	0.0429	13.9
0.062	0.739	0.0132	0.0357	10.4
0.028	0.510	0.0047	0.0185	13.8

10 mL of pentane and 1 to 2 drops of 30% NaOH and the mixture dried with Na_2SO_4 . The organic solution was analyzed by GC to determine the relative concentrations of the components vs. *n*-undecane.

Concentration dependence of 4

Seven samples of **4** in THF–ether (3:2) were prepared by appropriate dilution of a 0.78 mol/L sample of **4** in THF. Spectra (¹³C, ⁷Li) of each sample were taken at -121 °C. After the experiment, the concentration of **4** in each sample was determined by quenching with Me₂S₂ and GC analysis. The spectra from the five samples with the highest concentrations were integrated (C-3) by line-shape simulation. The data are shown in Table 1 and Fig. 3A.

Temperature dependence of 4

A 0.101 mol/L sample of 4 in THF-ether (3:2) was prepared and a series of ¹³C and ⁷Li NMR spectra were taken at accurately determined temperatures. Sample spectra are shown in Fig. 2. The spectra of the C-3 carbons were simulated. Line widths in the absence of exchange were determined from the solvent peaks. Below coalescence the line positions and populations of 4M and 4D were allowed to vary in the simulation. For determination of the thermodynamic parameters above coalescence, the populations were calculated from the chemical shift of the averaged peaks. Several experiments were performed to determine ΔH_1 and ΔS_1 at various concentrations: the ΔH_1 values varied from 0.8 to 1.4 kcal/mol and the ΔS_1 values from 10.5 to 14.5 eu, giving some measure of the reproducibility of these experiments. One significant variable may be accurately reproducing solvent composition for the NMR samples, since the K_1 values are very sensitive to the ratio of THF to ether.

For determination of the kinetic parameters, the populations during and above coalescence were calculated from the ΔH_1 and ΔS_1 values given in eq. [1]. Data used and derived from the simulations are shown in Table 2. Activation parameters were determined from the values of k_1 and k_{-1} and are shown in eq. [1].

The preparation of NMR samples of 4 containing 2iodo-5-methylthiophene (6)

The sample preparation is the same as described in the previous section, except after the NMR tube was dried, Et_2O was added (22 °C) followed by **6**. The sample was mixed with a vortex mixer, cooled to -78 °C, then a solution of **4** in THF was added. The sides of the NMR tube were washed with the THF, which was added last.

	[4D]	[/]]	1.	1.	l.	V
T (K)	[4D] (mol/L)	(mol/L)	$(s^{-1})^a$	$((\text{mol/L})^{-1} \text{ s}^{-1})^{b}$	$(s^{-1})^c$	$((\text{mol/L})^{-1})^d$
139.9	0.0242	0.0526	20	386	22	8.7
153.1	0.0278	0.0457	57	1 246	47	13.3
163.0	0.0308	0.0394	116	2 931	74	19.8
170.4	0.0307	0.0396	293	7 400	189	19.6
182.0	0.0315 ^e	0.0379 ^e	1 654	43 600	995	21.9
192.5	0.0325^{e}	0.0360 ^e	3 859	107 000	2 134	25.1
200.7	0.0332^{e}	0.0346 ^e	6 405	175 000	3 350	27.7
210.9	0.0340^{e}	0.0331 ^e	19 260	582 000	9 380	31.0
220.6	0.0346 ^e	0.0311 ^e	36 820	1 180 000	16 900	35.8
231.0	0.0352^{e}	0.0306 ^e	101 000	3 300 000	43 950	37.6
241.7	0.0357^{e}	0.0295 ^e	248 300	8 410 000	102 600	41.0

Table 2. Data for DNMR simulation of the spectra in Fig. 2.

^aDNMR rate constant for conversion of monomer to dimer nuclei.

 ${}^{b}k_{1} = k_{\text{MD}}/[4\text{M}] \text{ (s}^{1} \text{ (mol/L)}^{-1}\text{)}.$

^cDNMR rate constant for the conversion of dimer to monomer nuclei $k_{-1} = k_{DM}$ (s⁻¹).

 ${}^{d}K_{1} = [\mathbf{4D}]/[\mathbf{4M}]^{2} ((\text{mol/L})^{-1}).$

^eThese concentrations were calculated from ΔH_1 and ΔS_1 (eq. [1]).

Table 3. Input and output data for determination of K_2 in THF–ether (3:2).

			<i>K</i> ₁	[4D]	[4M]	[5]	[6]	<i>K</i> ₂
T (K)	δ for 6	δ obs	$((mol/L)^{-1})$	(mol/L)	(mol/L)	(mol/L)	(mol/L)	$((mol/L)^{-1})$
214.4	137.33	136.34	32.14	0.041 7	0.0360	0.0037	0.152	0.67
209.3	137.32	136.20	30.50	0.040 5	0.0394	0.0057	0.150	1.02
203.6	137.30	135.91	28.94	0.038 2	0.0365	0.0144	0.145	1.91
200.1	137.29	135.61	27.53	0.035 9	0.0361	0.0150	0.141	2.95
197.0	137.28	135.19	26.57	0.032 9	0.0352	0.0219	0.134	4.66
194.1	137.28	134.69	25.66	0.029 4	0.0338	0.0304	0.126	7.15
191.8	137.27	133.94	24.93	0.024 3	0.0312	0.0433	0.113	12.3
186.2	137.25	132.67	23.17	0.015 9	0.0262	0.0651	0.091	27.4
180.8	137.24	131.60	21.54	0.009 3	0.0207	0.0838	0.072	55.9
175.2	137.22	130.90	19.82	0.005 3	0.0163	0.0962	0.060	98.8
171.2		а	18.64	0.001 9	0.0101	0.109	0.047	229
166.2		а	17.11	0.000 78	0.0067	0.115	0.042	397

^aConcentrations calculated from the fraction of dimer in the ⁷Li NMR spectra.

Determination of the ate complex association constant (K_2)

A sample 0.156 mol/L in 6 and 0.123 mol/L in 4 was prepared using the previous procedure. ¹³C and ⁷Li NMR spectra were taken at 13 temperatures between -117 and -59 °C (Fig. 6). The ¹³C NMR chemical shift of the averaged C-3 carbon in the spectra from -87 to -59 °C was used to determine the concentrations of 4M, 4D, 5, and 6. Input parameters were the values of the chemical shifts of the individual compounds (δ 132.6 for 4M, δ 136.8 for 4D, δ 128.7 for 5, the shifts of 6 were temperature dependent and calculated using the formula $\delta = 0.002 815(T \circ C) + 137.500$, the observed chemical shift in the averaged spectrum, the stoichiometric concentrations of **4** and **6**, and the value of K_1 calculated from ΔH_1 and ΔS_1 . The input data were then used to iteratively calculate values for all concentrations using test values of K_2 until the average δ for all species matched observed δ for C-3. Data are presented in Table 3.

Two additional K_2 values were determined at -107 and -102 °C, where it is possible to detect the signal of **4D** (see Fig. 6B and insets). From the relative area of the dimer peak

the concentrations of the other species could be determined by a similar iterative process. The area of this signal was determined at the two temperatures at which it is best defined (-102 and -107 °C), where **4D** corresponds to 1.4% and 0.6% of total peak area. These values were then used to calculate the concentrations of the other species using the known value of K_1 .

Determination of ate complex association and dissociation rate constants (k_2 and k_{-2})

A sample 0.117 mol/L in 4 and 0.046 mol/L in 6 in THF– ether (3:2) was prepared by the general procedure, and ⁷Li and ¹³C NMR spectra were measured at a series of accurately measured temperatures (Fig. 5). The ⁷Li signals were simulated as follows. The population of the exchanging species (4M, 4D, 5, and 6) were calculated from the known concentrations and the values of K_1 and K_2 at each temperature, and values for k_1 and k_{-1} were calculated from the activation parameters of eq. [1]. These were used to start the simulation. The line width in the absence of exchange for the simulations was problematic, since it is likely to be both

T (K)	[4D] (mol/L) ^a	[4M] (mol/L) ^a	[5] (mol/L) ^a	[6] (mol/L) ^a	$k_{ m DM} \ ({ m s}^{-1})^b$	$k_{ m AM} \ ({ m s}^{-1})^b$	k_2 ((mol/L) ⁻¹ s ⁻¹) ^c
148.5	0.0171	0.0370	0.0456	0.0004	12	127	3.70×10 ⁵
154.6	0.0182	0.0358	0.0446	0.0014	29	369	3.32×10^{5}
159.5	0.0194	0.0354	0.0427	0.0032	52	849	3.16×10^5
162.2	0.0202	0.0353	0.0410	0.0049	109	1 750	4.12×10^5
164.9	0.0213	0.0353	0.0388	0.0073	181	3 100	4.68×10^5
170.5	0.0244	0.0361	0.0319	0.0142	336	12 200	7.61×10^5
175.9	0.0281	0.0372	0.0235	0.0225	356	27 300	7.67×10^5

Table 4. Data for the DNMR simulation of the ⁷Li NMR spectra of Fig. 5B (determination of k_2 and k_{-2}).

^aCalculated from K_1 (eq. [1]) and K_2 (Li) at each temperature and fixed during the simulation (pop(dimer) = 2[dimer]).

^bDetermined by simulation NMR.

 ${}^{c}k_{2} = k_{\text{MA}}/[6].$

Table 5. Input and output data for simulation of the ¹³C NMR spectra in Fig. 6 (determination of k_3 and k_{-3}).

T (K)	[4D] (mol/L) ^a	[4M] (mol/L) ^a	[5] (mol/L) ^a	[6] (mol/L) ^a	$k_{AI} \over (s^{-1})^b$	k_{-2} (mol/L) ^c	k_{-3} (mol/L) ^d	$k_{\mathrm{IA}} \ (\mathrm{s}^{-1})^e$	k_2 (mol/L) ^c	k_3 (mol/L) ^f
141.9	0.0018	0.0035	0.127	0.0394	2.65×10^{3}	16.5	1.34×10^{5}	1.70×10^4	2.25×10^{5}	1.28×10^{5}
152.5	0.0015	0.0041	0.124	0.0426	7.31×10^{3}	230	3.38×10^{5}	4.24×10^{4}	3.50×10^5	3.32×10^{5}
163.7	0.0015	0.0086	0.117	0.0490	1.98×10^{4}	2 581	7.56×10^5	9.45×10^4	5.27×10^{5}	7.69×10^5
173.8	0.0041	0.0146	0.105	0.0606	5.62×10^4	17 570	1.57×10^{6}	1.96×10^{5}	7.31×10^{5}	1.76×10^{6}
183.0	0.0109	0.0222	0.084	0.0820	4.80×10^5	84 100	1.07×10^{7}	9.85×10 ⁵	9.58×10 ⁵	1.15×10 ⁷

^{*a*}Calculated from K_1 (eq. [1]) and K_2 (eq. [2]) at each temperature and fixed during the simulation (pop(dimer) = 2[dimer]). ^{*b*}NMR rate for conversion of ate complex nuclei to iodide nuclei determined by line-shape simulation.

^cCalculated from the activation parameters in eq. [2].

^dCalculated: $k_{-3} = (2k_{AI} - k_{-2})/[6]$.

^eFrom line-shape fitting: $k_{IA} = k_{AI}(\text{Pop A})/(\text{Pop I})$.

^{*f*}Calculated: $k_3 = (k_{IA} - k_2[4M])/[5].$

compound specific (different rates of quadrupolar relaxation for different lithium environments) and temperature sensitive. In the absence of actual information, the line widths were set at 4, 8, and 10 Hz for 5, 4D, and 4M, respectively, based on values for several related species. The simulations were performed with the program WINDNMR (7m) using the exchange matrix of Fig. 7. The relative values of 4M and 4D fit well, but small changes in the relative populations of 5 were required for a good fit for all nuclei. Chemical shifts were assumed to be temperature independent (no actual measurements could be performed because dynamic broadening occurred at too low a temperature) and were set by fitting the spectrum at 142 K. After an optimal fit was achieved, we redetermined K_2 at each temperature, shown as K_2 (Li) in Fig. 3B ($\Delta H_2 = -8.8 \pm 1$ kcal/mol, $\Delta S_2 = -43.3 \pm 1$ 1 eu). New concentrations of all species were calculated with these parameters, and a final fitting was performed with the calculated concentrations frozen, modifying only k_{AI} and $k_{\rm AM}$. Only the spectra from -124 to -97 °C provided good definition for the individual rates, and data for these temperatures are shown in Table 4 and Fig. 4.

Determination of rate constants for ate complex exchange with iodide (k_3, k_{-3})

The ¹³C NMR spectra in Fig. 6A were simulated to extract values for the rate of **5**/6 exchange. A sample was prepared 0.166 mol/L in **6** and 0.128 mol/L in **4** in THF–ether (3:2). In the simulations the population of all of the species was calculated from the values of K_1 and K_2 determined from ΔH_1 and ΔS_1 , and values of k_1 , k_{-1} , k_2 , and k_{-2} were calculated from the values for the activation parameters in

eqs. [1] and [2]. The exchange matrix is shown in Fig. 10, the numeric data in Table 5, and the simulated spectra in Fig. 6A.

Acknowledgement

We thank the National Science Foundation (NSF) for financial support.

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