Is Experimental Evidence Sufficient Enough To Account for the Stabilization Effect of Bisnitroxide on the Fate of NMP Experiments?

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Recently, Braslau[1] reported nitroxide-mediated polymerization (NMP) experiments performed with the couple **1**/**3** (Figure 1) as initiating agent/controller. They reported investigations on the homolysis process, on the stabilities of both **1** and **3**, and on the electron paramagnetic resonance (EPR) analysis of the nitroxide **3**. In this Note, we would like to provide some density functional theory (DFT) calculations on the possible conformations of **3** and to comment on the Arrhenius parameters of unimolecular alkoxyamine homolysis, on the procedures of measurements of the C−ON bond homolysis rate constants k_d, and on the EPR results. Our comments will show that the stabilization effect for bisnitroxide **3** as proposed by Braslau[1] is likely not involved in the reactivity.

DFT Calculations on 3

To account for the results observed during the alkoxyamines' decomposition and the polymerization, Braslau[1] proposed the preferred chairlike conformation **pAC** (Figure 1) for the nitroxide based on both EPR and kinetic experiments and subsequently the intermediate **5**. This chairlike conformation **pAC** exhibiting two bulky phenyl-1-methyl-2-propyl groups in pseudoaxial positions is unexpected from steric hindrance expectation in the chairlike system and led us to perform DFT calculations aiming to determine the stability of a few key conformations for *RS*/*SR* diastereoisomer of **3**. The extended conformation **E**, the chairlike conformation **pAC**, and the chairlike conformation **pEC** with the phenyl-1-methyl-2-propyl groups in pseudoequatorial positions (Figure 1) were calculated at the UB3LYP/6-31+G (d,p) level of theory.[2]

Calculations starting on conformer **E** showed that the conformation of the extended conformer **E′** did not differ much from that of **E**. On the other hand, calculations starting on conformers **pEC** and **pAC** led to dramatically different conformers **pEC′** and **pAC′**, respectively (Figure 2). In the case of **pEC**, the dihedral angle between two nitroxide moieties was set close to 180° whereas the energy minimization afforded conformer **pEC′**, for which the initial six-membered conformation unfolded, with the two nitroxide moieties exhibiting a dihedral angle of 118° (Figure 2). For **pAC′**, the unfolded conformation of **pAC**, minimization of energy afforded conformer exhibiting dihedral angle of 157° between the two nitroxide moieties. Noteworthy, all the nitroxides moieties of **E′** and **pEC′** exhibited the expected *anti* conformation between the $N-O^{\bullet}$ and $C-H\alpha$ bonds, whereas one of the nitroxide moieties of **pAC′** exhibited the more sterically demanding *syn* conformation. The differences of minimized energies (see Table 1SI) are of ca. 25 and 48 kJ/mol between **E′** and **pEC′** and between **E′** and **pAC′**, respectively. Such a difference in energy between **E′** and **pAC′** precludes the existence of conformer **pAC**, as proposed by Braslau and colleagues,[1] and subsequently the existence of the bulky alkoxyamine **5**.

Comments on EPR Experiments

The DFT results presented above agree nicely with the EPR data recorded at −143 °C by Braslau.[1] Indeed, the conformers **E′** and **pEC′** with distances d of 6.3 and 5.2 Å between the two nitroxide moieties correspond to species exhibiting the weak ($d \approx 9.8$ Å by EPR) and the strong ($d \approx 4.7-5.8$ Å by EPR) spin−spin interaction, respectively.[3] In general,[4] spin−spin interaction involves striking to dramatic changes on EPR signal at room temperature and higher. As EPR spectra of **3** have not been reported neither at room temperature nor at 80 °C,[1] one can assume that the conventional 6 lines signature[5] of **4** has been observed and consequently that no spin−spin interactions or very weak ones occurred at these temperatures. Therefore, it was very unlikely that the conformer **pAC** occurred at high temperature, and hence, conformer **5** as proposed by Braslau should be disregarded. Furthermore, it is also unlikely that the spin−spin interaction in **pEC′** plays a role in the stabilization of **3** as it cannot be observed at high temperatures.

Comments on the Arrhenius Parameters

Braslau[1] reported similar Arrhenius parameters for **1** and **2**. Surprisingly, although k_d values measured by Braslau[1] for **2** differed of less than 20% from our data reported in SI, the frequency factor A was 2 orders of magnitude smaller than the one previously reported.[6] In a recent review,[7] frequency factors A were critically analyzed and discussed about the possible bias which would lead to observe very low or very high A values. The main bias is due to the E_a-A compensation error effect,[8] which implies that several couples of (E_a, A) values afford the same k_d within a short range of temperature. To limit the effect of this bias, achieving accurate and reliable A values requires to measure k_d values over as wide a temperature range as possible, to measure several values on the steep part of the curve of the exponential plot, and to repeat experiments at a few critical temperatures. To highlight our comment, the Arrhenius parameters (frequency factor A and activation energy E_a in Table 1) for **2** were plotted and re-estimated combining Marque (see Supporting Information) with Braslau[1] data, using both exponential (Figure 3a, eq 1) and linear (Arrhenius plot, Figure 3b, eq 2) plots.

$$k_d = A \exp\left(-\frac{E_a}{RT}\right) \tag{1}$$

$$\log(k_d/\mathrm{s}^{-1}) = \log(A/\mathrm{s}^{-1}) - \frac{E_a}{2.302RT} \tag{2}$$

As shown by the Arrhenius plot (inset in Figure 3b), no differences were observed between the Braslau[1]and our data, and the log A obtained by combining both sets of data is close to the one reported.[6] Furthermore, the Arrhenius plots (Figure 3b) show how difficult it is to achieve reliable and accurate A values, as the difference between the two slopes is small although 2 orders of magnitude are observed for the A values (Table 1). On the other hand, the exponential plots show that

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Table 1. Arrhenius Parameters of 2 (Figure 1) for the Two Sets of Data and Their Combination, Estimated with Eqs 1 and 2

			eq *1*		eq *2*			
	T (K)[a]	N[b]	A (s^{-1})	E_a (kJ mol^{-1})	log A	A (s^{-1})	E_a (kJ mol^{-1})	R^{2c}
this work[d]	333−404	10	5.7×10^{14}	129.7	14.3	1.8×10^{14}	126.1	0.996
Braslau[e]	358−378	5	8.7×10^{10}	102.3	12.7	4.6×10^{12}	114.6	0.991
combination[f]	333−404	15	5.5×10^{14}	129.5	14.2	1.5×10^{14}	125.3	0.996

[a] Error of ±1 K. [b] Number of data. [c] Square of the linear regression coefficient. [d] See Supporting Information. [e] See ref 1. [f] Combination of the data given in Supporting Information and ref 1.

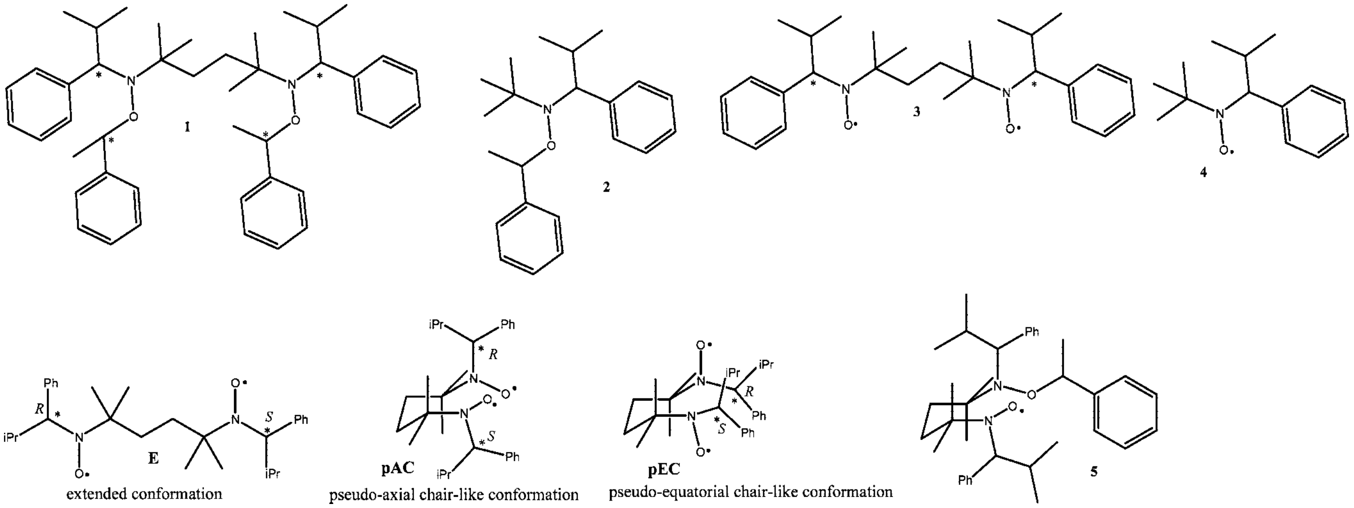

Figure 1. Structures and conformations for nitroxides and alkoxyamines studied and discussed in this work.

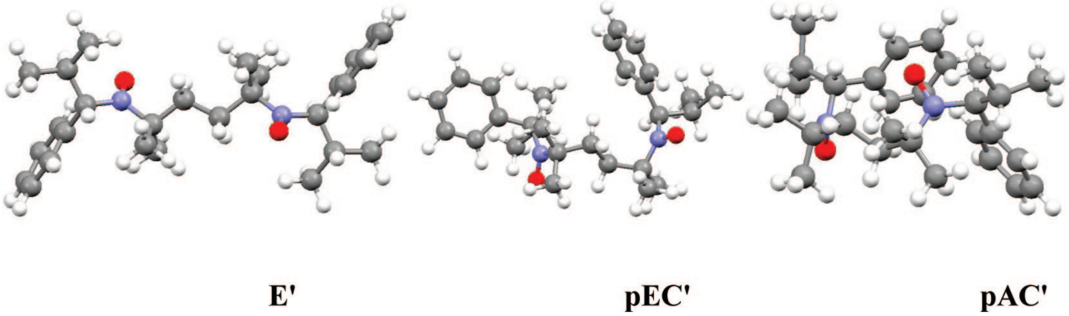

Figure 2. Conformers **E′**, **pEC′**, and **pAC′** obtained by UB3LYP/6-31+G (d,p) calculations on conformers **E**, **pEC**, and **pAC**, respectively.

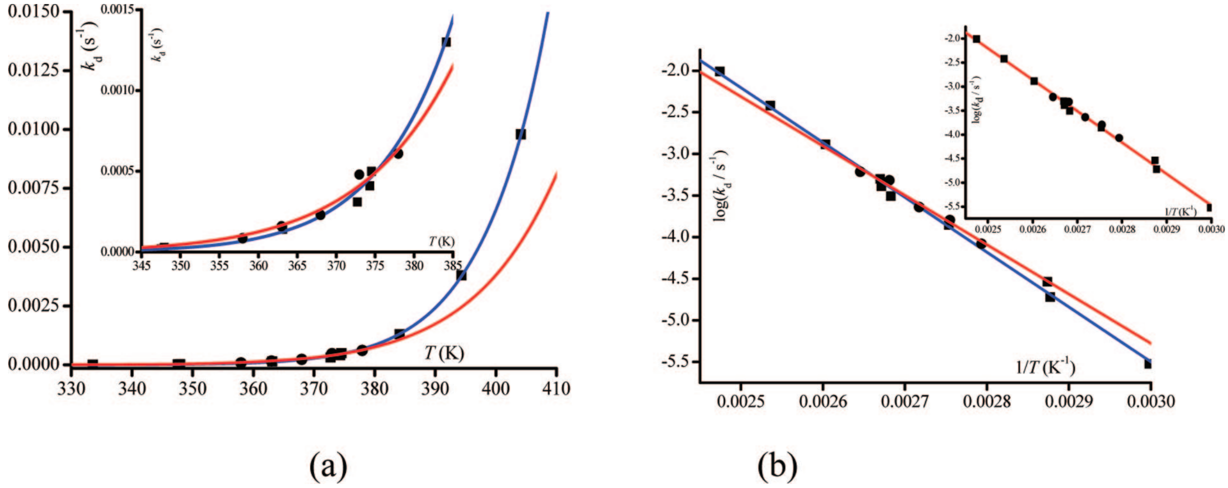

Figure 3. (a) Exponential plots $k_d = f(T)$ and (b) Arrhenius plots for **2**, data from ref 1 and Supporting Information. Red and blue curves are for data from ref 1 and Supporting Information fitted with (a) eq 1 and (b) eq 2. (●) for data given in ref 1 and (■) for data given in Supporting Information. For (a), inset shows the two sets of data for the same temperature range. For (b), inset shows the Arrhenius plot for the combination of the two sets of data.

the Braslau[1] data set does not differ from our data set (see Supporting Information)[6] for temperatures below 380 K, although above 390 K—that is, outside of the temperature range studied[1]—a clear difference could have been observed between the two data sets. Moreover, as expected, the combination of the two sets of data produced Arrhenius parameters (Table 1) that were close to those published.[6]

Thus, the experimental inaccuracies—temperature range, number of data, technique, or setup—can result in *A* values for the homolysis of alkoxyamines much smaller than 10^{14} s^{-1}. Consequently, a great care must be given to the discussion on Arrhenius parameters for such kind of reaction.

In his landmark book, Benson[9] showed that typical *A* values should be observed for a family of reactions. In the case of homolysis, *A* values are expected in the range $10^{13}-10^{14}$ s^{-1} [10] and for large molecules in the range $10^{15}-10^{16}$ s^{-1}. Therefore, dramatically low values should be questioned with respect to the items mentioned above.

Comments on the Experimental Conditions

Polymerization experiments as well as the measurement of k_d of **1** have been performed with a mixture of four diastereoisomers.[1,11] Some years earlier,[6] it was shown that diasteroisomers may exhibit different k_d values. In Braslau's work,[1] the decomposition of each diasteroisomer of **1** afforded the mixture of bisnitroxide **3** exhibiting the same EPR signal, and thus, the measurement of k_d for each diastereoisomers requires a tedious work of purification. Thus, when the initial slope method is applied to diasteroisomers mixture, it affords the k_d values for the diastereoismer exhibiting the fastest homolysis.[12] *Consequently, under the experimental conditions reported by Braslau,*[1] *one cannot discard the possibility that the 2 times faster* k_d *for* **1** *than for the model alkoxyamine* **2** *is likely due to the measurement of the fastest decaying isomer.*

As conclusion, we would like to stress that calculations are of great help to unveil the effects underlying to the stability of alkoxyamine and that how the choice of the method for measuring k_d is important and can lead to contradictory analysis of the results. Our comments cast a clear doubt on the proposal of Braslau.[1] However, it still leaves a question unanswered: why would diastereoisomers exhibit different values of k_d? For ester-based alkoxyamines,[13] we showed that the small difference (2−3-fold) of k_d for each diastereoisomers was due to the interaction between the C−ON antibonding orbital σ^* and one of the oxygen lone pairs of the ester group. Importantly, this interaction depends both on the structure of the nitroxide and the alkyl fragments.[6,14] One possibility to account for small difference of k_d between **1** and **2** would be that such kind of interaction occurred between the C−ON antibonding orbital σ^* and the π-system of the phenyl group, which would be due to some specific conformation controlled by a remote steric effect.[7,12,15]

Supporting Information Available: Homolysis rate constants k_d for **2** in the temperature range 60−131 °C, minimized electronic energies *E* for **E′**, **pEC′**, and **pAC′**, and PDB files of calculated conformers **E′**, **pEC′**, and **pAC′**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Ruehl, J.; Hill, N. L.; Walter, E. D.; Millhauser, G.; Braslau, R. *Macromolecules* **2008**, *41*, 1972–1982.

(2) Geometries were optimized without constraints with the Gaussian G03 D02 software: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Wallingford, CT, 2004.

(3) In general, spin−spin interactions depend on both the distance *d* and the dihedral angle between the nitroxide moieties.

(4) See examples in: *Landolt-Börnstein*, Group II; Springer-Verlag: Berlin, 1980; Vol. *9d2*.

(5) Hyperfine coupling constants between N ($I = 1$) and the unpaired electron and between H ($I = 1/2$) at the position β and the unpaired electron, a_N and $a_{H,\beta}$, respectively.

(6) Marque, S.; Le Mercier, C.; Tordo, P.; Fischer, H. *Macromolecules* **2000**, *33*, 4403–4410.

(7) Bertin, D.; Gigmes, D.; Marque, S. R. A. *Recent Res. Dev. Org. Chem.* **2006**, *10*, 63–121, and references cited therein.

(8) Héberger, K.; Kemény, S.; Vidoczy, T. *Int. J. Chem. Kinet.* **1987**, *19*, 171–181.

(9) Benson, S. W. In *Thermochemical Kinetics*, 1st ed.; Wiley: New York, 1968; 2nd ed., 1976.

(10) Walsh, R. *Chem. Soc. Rev.* **2008**, *37*, 686–698.

(11) The preparation of **1** and its purification was described as an admixture of four diastereoisomers. Hill, N. L.; Braslau, R. *Macromolecules* **2005**, *38*, 2233–2235.

(12) Bertin, D.; Dufils, P.-E.; Durand, I.; Gigmes, D.; Giovanetti, B.; Guillaneuf, Y.; Marque, S. R. A.; Phan, T.; Tordo, P. *Macromol. Chem. Phys.* **2008**, *209*, 220–224.

(13) $(((EtO)_2(O)P)$ *i*PrCH)tBuNOCHMeCOOR ester-based alkoxyamines. Beaudoin, E.; Bertin, D.; Gigmes, D.; Marque, S. R. A.; Siri, D.; Tordo, P. *Eur. J. Org. Chem.* **2006**, *7*, 1755–1768.

(14) Bertin, D.; Gigmes, D.; Marque, S.; Tordo, P. *e-Polym.* **2003**, 000. paper no. 2.

(15) Calculations and X-ray studies are underway on models reported in ref 6. However, X-ray structures of several compounds show that the phenyl rings adopt very different conformations depending on the nitroxide fragments. Personal communication of the authors.

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