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Diastereomeric excess upon cleavage and reformation of diastereomeric alkoxyamines † ‡

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The thermal reactions of several TEMPO and DEPN (*N*-(2-methylpropan-2-yl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-aminoxyl) based alkoxyamines were studied by means of ^{1}H and ^{31}P NMR spectroscopy aiming to distinguish the contributions of diastereoselective homolysis and coupling to the total equilibrium diastereomeric distribution. The TEMPO-based compounds reveal no diastereomeric excess while DEPN based compounds show a moderate excess both upon homolysis and coupling. The diastereomeric preference of homolysis for DEPN-(propionate-like) adducts does not depend on the ester group and it is mainly affected by the size of β-substituents. The diastereoselective coupling is sensitive to the total recombination rate constant k_c and diastereoselectivity increases with the decrease of k_c. Small diastereoselective coupling is found in the recombination of DEPN with *sec*-butyl isobutyrate radical, where no prochiral centers are formed upon cleavage of corresponding alkoxyamine.

Introduction

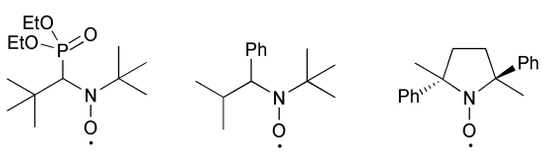
The recent use of alkoxyamines in nitroxide mediated free radical polymerization[1–3] (NMP) and tin-free radical chemistry[4] has attracted large attention to this class of compounds. The main features of the chemistry of alkoxyamines are relatively easy homolysis of the C–O bond and fast coupling of formed alkyl and nitroxyl radicals to regenerate the starting material [eqns. (1), (2)]. Self-termination of transient alkyl radicals [eqn. (3)] competes with the cross-coupling [eqn. (2)] at earlier times of reaction, then the formed excess of persistent nitroxyl radicals significantly suppresses the self-termination reaction (3) although it never removes it completely. This Persistent Radical Effect[5] enables high selectivity of reformation of the starting alkoxyamine and it became a key factor, which provided success in controlled free radical polymerization[1–3,5–7] and in synthetic applications.[4,5]

$$\mathrm{I} \longrightarrow \mathrm{R}^{\bullet} + \mathrm{Y}^{\bullet} \quad (1)$$

$$\mathrm{R}^{\bullet} + \mathrm{Y}^{\bullet} \longrightarrow \mathrm{I} \quad (2)$$

$$2\,\mathrm{R}^{\bullet} \longrightarrow 2\,\mathrm{P} \quad (3)$$

Some newly developed nitroxyl radicals for NMP have an asymmetrical center.[3] Two of such compounds (Scheme 1, DEPN[8] (called also SG1) and TIPNO[3,9]) are highly successful in the NMP of styrene, acrylates, and some others monomers.



DEPN TIPNO DPPO

Scheme 1

It is clear that coupling of the chiral nitroxyl radicals with alkyl radicals bearing prochiral carbon atoms can form two possible diastereomeric alkoxyamines with different rates.[10,11] On the other hand, the homolysis rates of such alkoxyamines can depend on the stereochemical configuration of the starting material.[12–15] Theoretically both factors might control stereochemistry in NMP and other applications; however, recent attempts[14,16] have not confirmed this expectation. It is clear, that there is a need to deeper understand the main factors governing the stereochemical preference in homolysis/reformation of alkoxyamines.

The main reasons of diastereoselectivity in coupling reactions between asymmetric nitroxyl (Scheme 1, DPPO) and prochiral carbon-centered radicals have been studied in recent work.[10] It has been shown that both electronic and steric factors can cause a diastereomeric preference in the radical recombination. However, diastereospecific homolysis of alkoxyamines has not been studied yet so intensely although some observations were reported.[12–17]

The interconversion of diastereomeric alkoxyamines can be described by the following elementary reactions:[15]

$$\mathrm{I}_1 \longrightarrow \mathrm{R}^{\bullet} + \mathrm{Y}^{\bullet} \quad (4)$$

$$\mathrm{I}_2 \longrightarrow \mathrm{R}^{\bullet} + \mathrm{Y}^{\bullet} \quad (5)$$

$$\mathrm{R}^{\bullet} + \mathrm{Y}^{\bullet} \longrightarrow \mathrm{I}_1 \quad (6)$$

$$\mathrm{R}^{\bullet} + \mathrm{Y}^{\bullet} \longrightarrow \mathrm{I}_2 \quad (7)$$

$$\mathrm{R}^{\bullet} + \mathrm{Y}^{\bullet} \longrightarrow \mathrm{R}(-\mathrm{H}) + \mathrm{YH} \quad (8)$$

Isomers I_1 and I_2 decompose into the corresponding alkyl ($\mathrm{R}^{\bullet}$) and nitroxyl ($\mathrm{Y}^{\bullet}$) radicals with the rate constants k_{d1} and k_{d2}, respectively. Transient alkyl radicals recombine with persistent nitroxyl radical to yield isomers I_1 and I_2 with the rate constants k_{c1} and k_{c2}, respectively. Side reactions such as disproportionation between alkyl and nitroxyl radicals [eqn. (8)] can be neglected as the first approximation.[18–22] Alkyl radicals also decay by self-termination reaction *via* recombination and/or disproportionation. For simplicity, only the second is considered [eqn. (3)].

† *In memoriam* of Professor Aleksei Dneprovskii.

‡ Electronic supplementary information (ESI) available: Experimental procedures for the synthesis of **1a**–**b**, **2a**–**c** and **3**. See http://www.rsc.org/suppdata/ob/b3/b313990e/

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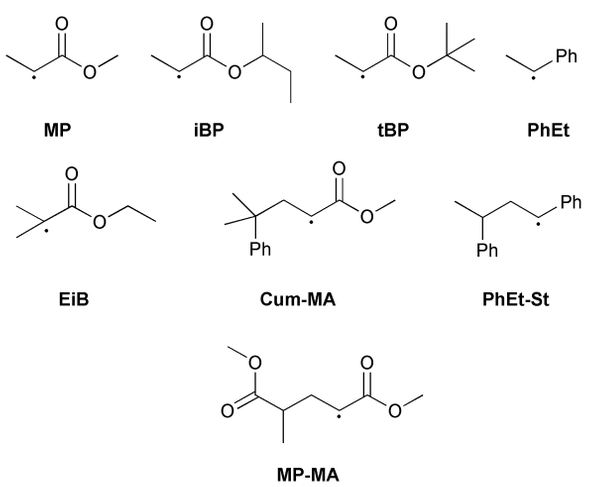
The detailed kinetic analysis of set of eqns (3), (4)–(7) was developed in ref. 15. Starting with one isomeric alkoxyamine, decomposition will result in the planar radical R$^{\bullet}$, which can recombine with a nitroxyl radical yielding two diastereomeric alkoxyamines I_1 and I_2. The same reaction will occur with the second isomer. Thus, after a certain time, an equilibrium between two isomers will be reached. The equilibrium constant and isomer ratio will depend only on the ratio of homolysis and coupling rate constants [eqn. (9)]:

$$\frac{[I_1]_\infty}{[I_2]_\infty} = \frac{k_{c1}}{k_{c2}}\frac{k_{d2}}{k_{d1}} \qquad (9)$$

Homolysis rate constants for each diastereomer can be easily measured using ESR or NMR techniques,[12,15,23] and comparison of k_{d2}/k_{d1} with the diastereomeric ratio in the equilibrium allows the diastereoselectivity of the coupling reaction to be derived. This approach has been already applied in the investigation of the diastereomeric excess upon homolysis/reformation of DEPN adduct with *tert*-butylpropionyl (tBP, see Scheme 2 for abbreviations of alkyl radicals) radical.[16]

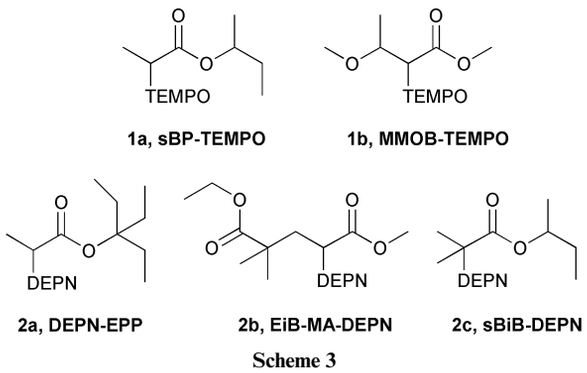


Scheme 2

It is useful to check the diastereomeric excess upon coupling (*i.e.* k_{c1}/k_{c2}) in independent experiments like generation of the corresponding alkyl radical by catalytic activation of halogenides[10,16] or other compounds[10] or by photolytic cleavage of corresponding ketones and using chemically induced dynamic nuclear polarization (CIDNP) monitoring of the coupling reaction.[15] However, all these methods have serious disadvantage since the temperatures[10,15,16] are usually different from those used for k_d determination.

It should be also noted that these experiments are very similar to those with enantiomeric compounds[24] but are much simpler because the diastereomers do not require separation and analysis of optically active species.

In the present paper, we report results of isomerization of the ester based alkoxyamines (Scheme 3) with various positions of asymmetrical atom. The simplest nitroxyl radical TEMPO (2,2,6,6-tetramethylpiperidinyl-*N*-oxyl) has been chosen for the models with both chiral centers at the alkyl moiety (compounds **1a** and **1b**, in Scheme 3). The structure of alkoxyamine **2a** is similar to that studied in recent papers[12,15,16] but the bulky 3-ethylpent-3-yl group has been chosen to check the dependence of diastereomeric ratio on the size of ester group.[17] The compound **2b** is an example of dimeric alkoxyamines, where the influence of bulky substituent at β-C atom on diastereomeric distribution has not been studied yet. Both chiral atoms of the compound **2c** do not change their configuration upon homolysis and it is interesting to compare the diastereomeric preferences during the cleavage of the C–O bond and during the recombination of radicals with different configurations.



Scheme 3

Results

TEMPO-based alkoxyamines

Compounds **1a** and **1b** were isolated as viscous oils; therefore the X-ray analysis was not performed. The assignments 'diastereomer 1' and 'diastereomer 2' are arbitrary and based only on different NMR spectra of compounds (*cf.* Supporting Information ‡).

Fig. 1 shows kinetic curves obtained upon thermolysis of **1a** at 120 °C in chlorobenzene-d_5 solution. Due to difficulties in resolving the ^{1}H NMR signals of individual diastereomers we analyzed intensities at the maximum (but no integrals) of each signal of CH-O group quartet (see inset on Fig. 1).§

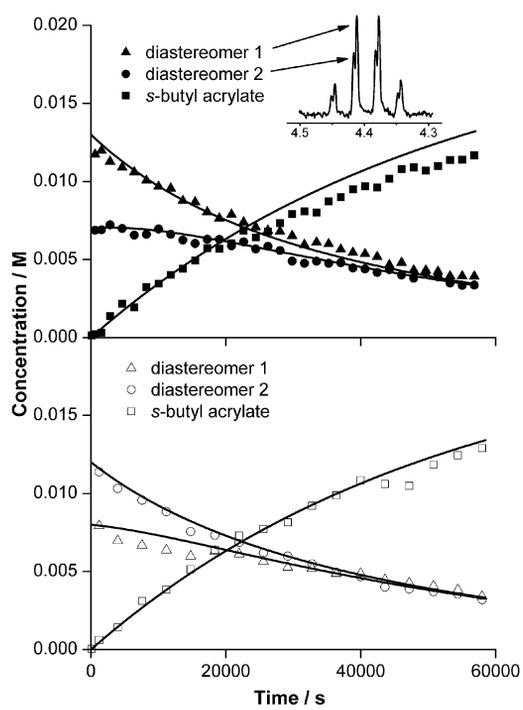


Fig. 1 Time dependence of concentrations during the thermolysis of **1a** at 120 °C in chlorobenzene-d_5. Top: starting from the mixture enriched with diastereomer 1; bottom: starting from the mixture enriched with diastereomer 2. Inset: ^{1}H NMR signal of starting compound. Lines calculated with numerical solution of the kinetics from reactions 3, 4–8 using parameters for tBP-TEMPO.[20]

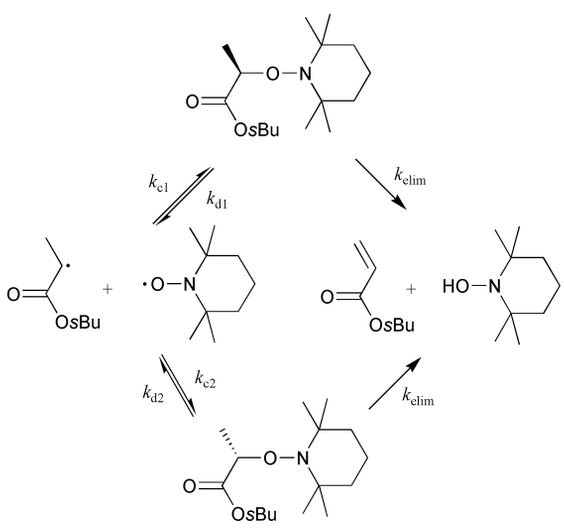
§ This is accurate approach if the magnetic field homogeneity of the NMR magnet is not markedly changed in the course of reaction. We used intensity of residual protons of the solvent to control the homogeneity, which proved to be unstable only in the first *ca.* 5 min of the reaction run. So, the first data points in these kinetic curves were neglected.

Table 1 Kinetic parameters of isomerization of alkoxyamines

Compound	Solvent	T [°C]	$I_{1\infty}/I_{2\infty}$	k_{d1}; k_{d2} [s^{-1}][a]	k_{d2}/k_{d1}[c]	k_{c1}/k_{c2}[c]
1a	C_6D_5Cl	120	1.0	5.2×10^{-5}[b]	*1*	*1*
1b	$C_6D_4Cl_2$	135	1.02	1.4×10^{-4}	*1*	1.0
MP-DEPN[15]	C_6D_5Cl	100	2.8	1.3×10^{-4} 3.8×10^{-4}	2.9	1.0 (*0.96*)
2a	C_6D_5Cl	100	2.6	2.6×10^{-5} 7.8×10^{-5}	3.0	0.87
2b	C_6D_5Cl	100	6.0	9.5×10^{-4} 4.0×10^{-3}	4.2	*1.4*
2c	toluene	60	1.2	1.2×10^{-3} 1.2×10^{-3}	1.0	*1.2*

[a] ±10%; for **2b**: ±15%. [b] $k_{elim} = 1.8 \times 10^{-5}$ s^{-1}.[20] [c] estimated values [eqn. (9)] are given in *italic*.

One can see from Fig. 1 that along with isomerization a dramatic decay of both isomers occurs and accumulation of *sec*-butyl acrylate is simultaneously observed. *sec*-Butyl acrylate and hydroxylamine TEMPO-H (not shown on Fig. 1) are products of hydroxylamine elimination (Scheme 4), which has been already discussed in ref. 20. The observed total decay of both isomers due to this reaction is equal to the decay of tBP-TEMPO.[20] One can also see that there is no diastereomeric excess within experimental error. For theoretical treatment of experimental data we used parameters derived for tBP-TEMPO from previous work[20] (see also Table 1). The agreement between calculated curves and experimental kinetics is reasonable.



Scheme 4

Fig. 2 shows the isomerization kinetics obtained during the thermolysis of **1b** in *o*-dichlorobenzene-d_4 at 135 °C. No elimination or disproportionation between alkyl and TEMPO, as well as no diastereomeric excess at the equilibrium are observed. The absence of diastereomeric excess could be due to $k_{d1} = k_{d2}$ and $k_{c1} = k_{c2}$ or due to a compensation $k_{d2}/k_{d1} = k_{c1}/k_{c2}$. The last seems to be less probable but nevertheless it was checked by a trapping experiment (*cf.* Experimental section). In this experiment, MMOB radicals were generated from the corresponding bromide by reaction with CuBr/PMDETA complex in dichlorobenzene and trapped by TEMPO at 90 °C. The activation of methyl 2-bromo-3-methoxybutyrate by Cu complex at this temperature is expected to be sufficiently fast[13,25] and therefore, the homolysis rate of formed **1b** is negligible. The diastereomeric ratio should be equal to k_{c1}/k_{c2}. Fig. 2 (inset) shows C*H*-ON NMR signals of **1b** formed at these conditions. The diastereomeric excess is negligible within the accuracy of integration, so extrapolation to 135 °C gives $k_{d2}/k_{d1} = k_{c1}/k_{c2}$ and the exponential fit of experimental curves gives k_d as $k_{d1} = k_{d2} = 1.4 \times 10^{-4}$ s^{-1}.

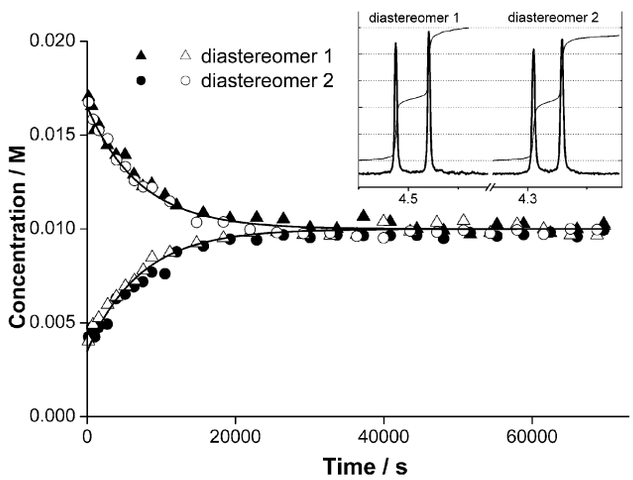


Fig. 2 Time dependence of concentrations during the thermolysis of **1b** at 135 °C in *o*-dichlorobenzene-d_4. Solid symbols: initial mixture enriched in diastereomer 1; open symbols: initial mixture enriched in diastereomer 2. Lines calculated with eqns. 11 and 12 of ref. 15. Inset: C*H*-ON ^{1}H NMR signals of **1b** obtained in a trapping experiment (see Experimental section).

DEPN-based alkoxyamines

For the compounds **2a** and **2b**, the diastereomer assignments can be easily made on ^{31}P-NMR chemical shifts by comparison with experimental data of similar substances,[15–17,23] where (*R*,*R*)/(*S*,*S*) diastereomer ('diastereomer 1') has always downfield shifted $\delta(^{31}P)$ values in comparison with (*R*,*S*)/(*S*,*R*) one ('diastereomer 2') (*cf.* Supporting Information ‡). The X-ray analysis of **2c** was difficult due to instability of the compound; therefore the assignments 'diastereomer 1' and 'diastereomer 2' for **2c** are arbitrary (*cf.* Supporting Information ‡).

Fig. 3 shows kinetic curves obtained during the isomerization of **2a** (Fig. 3a) and **2b** (Fig. 3b) in chlorobenzene-d_5 at 100 °C. The isomerization rate of **2b** is markedly faster than that of **2a** and the ratio of diastereomers at the equilibrium is greater for **2b** (Table 1). No decay of both diastereomers at longer times of reaction is observed. This allows the disproportionation/elimination to be neglected, as well as the estimation of the lower limit[15] for the total coupling rate constant as $k_c = k_{c1} + k_{c2} > \sim 10^7$ M^{-1} s^{-1}. In order to check the contribution of k_{d2}/k_{d1} and k_{c1}/k_{c2} to the total diastereomer distribution we measured homolysis rate constants of both alkoxyamines by means of NMR monitoring of the decay of each isomer during thermolysis of diastereomeric mixture in the presence of equimolar amounts of TEMPO. TEMPO was chosen as the trap due to its expected[26] faster coupling rate constant with the transient EPP and EiB-MA radicals ($k_{cT} >> k_{c1,2}$, Scheme 5) and also the expected[12] greater stability of the resulting alkoxyamine ($k_{dT} << k_{d1,2}$, Scheme 5).

Since the minor (second) diastereomer of **2b** has not been isolated, we isomerized the first diastereomer prior to measur-

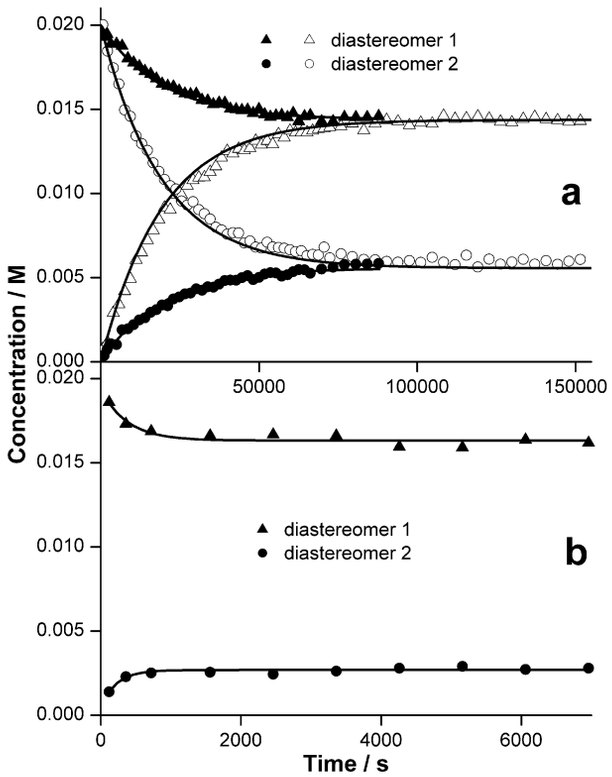


Fig. 3 Time dependence of concentrations during the thermolysis of **2a** (a) and **2b** (b) at 100 °C in C_6D_5Cl. Solid symbols: initial diastereomer 1, *i.e.* (*R*,*R*)/(*S*,*S*); open symbols: initial diastereomer 2, *i.e.* (*R*,*S*)/(*S*,*R*). Lines calculated with eqns. 11 and 12 of ref. 15.

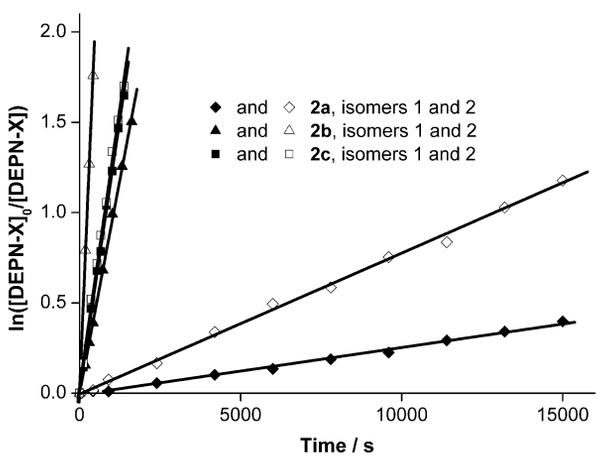
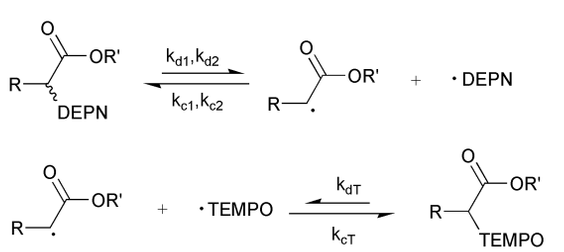


Fig. 4 Kinetics of decomposition of DEPN-based alkoxyamines: **2a** and **2b** at 100 °C in C_6D_5Cl; **2c** at 60 °C in toluene-d_8.



Scheme 5

ing k_d and the homolysis rate constants were measured in the mixture of diastereomers, 6/1. Fig. 4 shows decomposition kinetics of **2a**, **2b** as well as **2c** obtained during NMR monitoring of the decays of corresponding alkoxyamines.

The ratio k_{d2}/k_{d1} for **2a** is slightly different from the diastereomeric ratio at the equilibrium (3.0 *vs.* 2.6, Table 1), which can be explained by $k_{c1} \neq k_{c2}$. Therefore, by analogy with **1b**, we measured diastereoselectivity of the coupling of EPP and DEPN radicals by independent generation of the EPP radicals from the corresponding bromide *via* reaction with CuBr/PMDETA complex in chlorobenzene. Fig. 5a shows the ^{31}P NMR spectrum obtained immediately after the initial synthesis of the **2a** adduct (*cf.* Experimental section) after the $CuBr_2$/PMDETA complex had been removed by passing through a small layer of alumina. The diastereomeric ratio between the two isomeric alkoxyamines is 0.87. This indicates diastereoselectivity in the coupling process. After the reaction mixture was passed through alumina again to completely remove traces of the Cu^{II} complex, the mixture was degassed and heated to 100 °C for 18 h. Fig. 5b shows the ^{31}P NMR spectrum of the final mixture. The ratio of the integrals of the two signals is now 2.6, quite different from the original 0.87 and close, as expected, to 3.0 derived from Fig. 3a. Further heating of the mixture did not change the diastereomeric ratio.

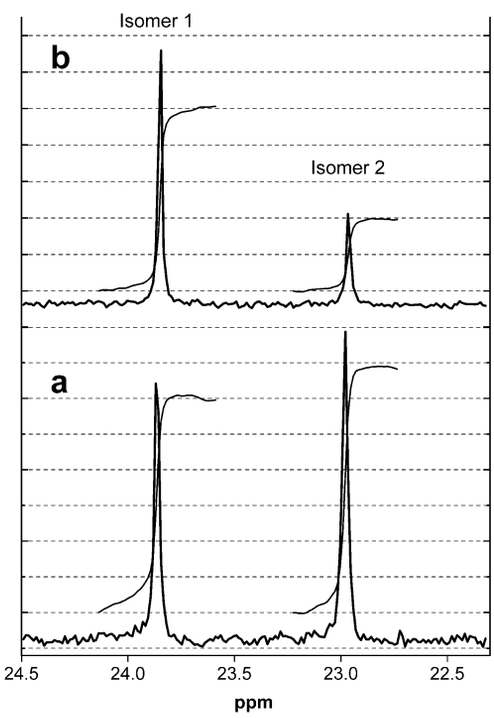


Fig. 5 ^{31}P NMR spectra of reaction mixture of (triethylmethyl)bromopropionate/CuBr/PMDETA/DEPN in chlorobenzene: (a) After 1.5 h of the reaction at room temperature, integrated ratio of diastereomers is 0.87 ± 0.05; (b) After stirring overnight at 100 °C; integrated ratio of diastereomers is 2.6 ± 0.1.

A similar observation can be also made for **2b** (Table 1). While k_{d2}/k_{d1} = 4.2, the diastereomeric ratio is 6.0, *i.e.* the first isomer decomposes slower and is formed faster than the second one.

We were unable to separate (or enrich) the isomers of **2c**, so we measured the homolysis rate constants of the diastereomeric mixture in the presence of TEMPO as well as the diastereomeric ratio at the equilibrium. Surprisingly, there is small isomeric preference, which is mainly defined by coupling reaction (Table 1). We do not have X-ray data of this compound at present, so it is difficult to say which isomer is preferred, *i.e.* (*R*,*S*)/(*S*,*R*) over (*R*,*R*)/(*S*,*S*) or *vice versa*.

Discussion

Homolysis rate constants k_d and side reactions

Table 1 summarizes the kinetic data for all studied compounds.

The total decay of both isomers of **1a** is equal to that found for the corresponding *tert*-butyl ester[20] within experimental

error. Therefore, one can assume that both homolysis rate constant k_d and the competitive channel of hydroxylamine elimination k_{elim} in the compound **1a** are equal to those found for corresponding *tert*-butyl ester.[20]

The compound **1b** has only one β-hydrogen atom which can be abstracted in disproportionation or elimination. Therefore, in comparison to **1a**, the rates of these processes are smaller, and the low probability of H-abstraction is not compensated by possible formation of the conjugated chain O–C=C–C=O in the product of the hydroxylamine elimination. Moreover, methyl and methoxy groups in the alkoxyamine cumber to reach the right conformation required for the intramolecular elimination reaction. The strong conformational requirements generally agree with the recent observations of the elimination reaction occurring for simple alkyl-TEMPO adducts.[27] We were unable to reach the equilibrium between two diastereomers during isomerization of **1b** at 120 °C within a reasonable time. This certainly shows that the homolysis rate constant k_d of **1b** is smaller at that temperature than k_d of **1a** or similar compounds.[12,20] One of the possible reasons is destabilization of the corresponding transition state and of the formed MMOB radical in comparison to the propionyl one due to withdrawing effect of methoxy group.[28] Additional stabilization of the alkoxyamine due to stereoelectronic effects cannot be completely ruled out, as well.

The k_d values for DEPN-based alkoxyamines are usually larger than those for TEMPO-based alkoxyamines of similar structures[12] and disproportionation and/or elimination of hydroxylamine are negligible.[15] This is also observed here for three DEPN derivatives by comparison with the data published in ref. 11. It is interesting to compare these three compounds with other DEPN derivatives.[12,15–17,29] Replacement of $OCMe_3$ by $OCEt_3$ slightly lowers the averaged homolysis rate constant of the corresponding propionates.[16,17] This decrease of k_d is caused by an increase of the free energy $\Delta G^{\neq}$ of the transition state (TS). In the series of propionate based DEPN alkoxyamines,[12,15–17,29] the strength of the C–O bond is unlikely to be affected by the changes in the ester moiety. Therefore, the increase of $\Delta G^{\neq}$ from OCH_3 to $OCEt_3$ can be explained by two reasons: *i*) more degrees of freedom have to be frozen in the TS with larger R and/or *ii*) the molecule is locked in a preferred conformation in the ground state, which is different from that in the TS. The first factor is entropy governed. Thus, the expected value of the entropy parameter $-T\Delta S$ for **2a** should be *ca.* 3 kJ mol^{-1} larger than that for MP-DEPN, in order to achieve *ca.* 5 times smaller k_d for **2a** at 100 °C. On the other hand, the homolysis is an enthalpy controlled reaction and there is no evidence that the entropy plays an important role here,[26] so the second reason seems to be more likely (Fig. 6) and it generally agrees with the Curtin–Hammett principle, *i.e.* the most stable conformer is not the most reactive one.

Compound **2b** is one example of a dimeric nitroxyl based initiator.[20,30] An initiator containing a penultimate unit is expected to have a larger homolysis rate constant than one without such a group. The increase in k_d is *ca.* by factor of 4 for two similar units like in PhEt-St-TEMPO[30], or even by factor of 10 if the first unit is more bulky group like in Cum-MA-TEMPO.[20] Similar observation has been also made for dimeric initiators of atom transfer radical polymerization[31] (ATRP), where activation rate increased from 1.1 times (*i.e.* no changes, MP-Br *vs.* MP-MA-Br) to 5.1 times (MP-Br *vs.* EiB-MA-Br). For the case of **2b** *vs.* MP-DEPN[15], the increase of the average k_d is by a factor of 10 and can be explained by higher steric demands of both the penultimate unit (β-substituent) and leaving DEPN.[32] To summarize known data[20,25,30,31] about changes of k_d in NMP or k_a in ATRP with increasing initiator chain length, one can conclude that k_d (k_{act}) is very sensitive to the bulkiness of the penultimate unit. It is almost unchanged by substituents with low steric demands and increases more than 10 times for very bulky units. Extrapolation of these

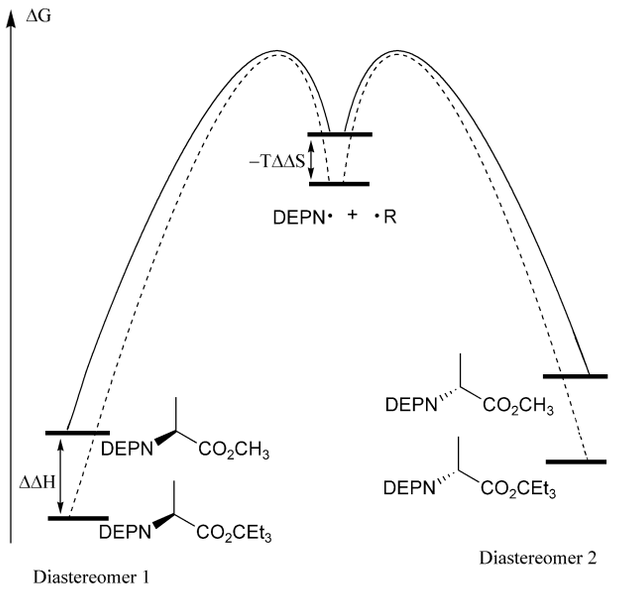
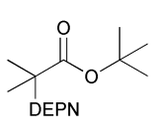


Fig. 6 Reaction diagram for homolysis and radical recombination of DEPN-propionate adducts.

observations to polymeric alkoxyamines allows the prediction that homolysis rate constants of polyacrylates or polystyrene based alkoxyamines will not be dramatically different from those known for short chain initiators. This has been already observed in recent works,[33,34] where the changes in k_d were from 1 to 2–3 times.

Compound **2c** exhibits a slightly larger homolysis rate constant ($k_d = 1.2 \times 10^{-3}$ s^{-1}) than it was predicted[12] ($k_d = 9.4 \times 10^{-4}$ s^{-1}) but this difference is not significant if one takes the accuracy of the experiment and the error of the estimation[12] into account.

In order to check the sensitivity of homolysis rate constants of DEPN-isobutyrate alkoxyamines to the bulkiness of ester group and to compare with the corresponding propionate derivatives, we synthesized tBiB-DEPN adduct (Scheme 6). The obtained ratio k_d(**2c**)/k_d(**3**) ≈ 2 (k_d(**3**) = 5.8×10^{-4} s^{-1} at 60 °C) proved to be very close to the ratio (2.0) of the corresponding DEPN-propionate systems.[17] Therefore, the effects observed in propionate series can be also expected for isobutyrate derivatives (more examples are given in ref. 17) and certainly for acetate derivatives. However, such fast homolysis rate constants involve drastic conditions to prepare and isolate diastereoisomer (*cf.* Supporting Information‡). On the other hand, k_d(**1a**)/k_d(**tBP-TEMPO**)[20] ≈ 1, so one can assume that dependence of k_d on the size of ester group is much weaker for TEMPO-derivatives.



3, tBiB-DEPN

Scheme 6

Diastereomeric excess

Analysis of the data shown in Table 1 reveals that differences in homolysis rate constants k_d are the main (but not only) reason for the diastereomeric excess in the quasi-equilibrium for all studied ester-based alkoxyamines (except of **2c**) including those of previous investigations.[12,15,16] The diastereomeric excess for TEMPO and DPPO[10] based alkoxyamines is usually smaller than that for DEPN. The full analysis of k_{d2}/k_{d1} dependence on the nature of DEPN-based alkoxyamine is complicated and it requires additional systematic investigation. However, some observations can be made. First of all, k_{d2}/k_{d1} does not depend

on the ester substituent in propionate radicals (Table 1). Bulky groups at the β-carbon from the chiral center seem to increase the ratio, for example, from 2.9 in DEPN-MP[15] to 4.2 in **2b**. One can predict that $k_{d2}/k_{d1} \longrightarrow 1$ with increase of the temperature, however this is hardly measurable at very low and very high temperatures. There is no significant diastereomeric preference in the homolysis of **2c** (Table 1) or PhEt-DEPN.[15,35] Analysis of known kinetic data for DEPN based alkoxyamines[12,15–17,23,29] allows us to conclude that probably only the DEPN-propionate (-propionitrile and -propionic acid, as well) system possess this feature as relatively large k_{d2}/k_{d1} ratio. Moreover, the (*R*,*R*)/(*S*,*S*) diastereomer always possess a smaller k_d value than the (*R*,*S*)/(*S*,*R*) one.

Coupling of propionate-like radicals and DEPN, as well as TEMPO and DPPO[10] reveals less diastereomeric preference than homolysis of corresponding alkoxyamines. However, a very interesting observation can be made for the propionate + DEPN coupling reaction by variation of the ester group. Increasing the bulkiness of the alkyl substituent leads to the appearance of a small diastereomeric excess on coupling. This agrees with a similar observation made for propionate + DPPO recombination although the effect with DPPO was larger.[10] One can expect a decrease in the rate constant k_c with increasing steric demand of the ester moiety, *i.e.* entropy control of the reaction would be increased. Systems reach a later transition state (Fig. 6) where the propionyl radical must not be planar. The larger the $\Delta G^{\#}$ of the coupling process the larger the diastereoselectivity upon recombination may take place. This can be seen in the reactions of DEPN with the following radicals: MP $k_{c1}/k_{c2} = 1$[15]; tBP $k_{c1}/k_{c2} \sim 1$[16]; EPP $k_{c1}/k_{c2} = 0.87$; EiB-MA $k_{c1}/k_{c2} = 1.4$; PhEt $k_{c1}/k_{c2} = 1.73$.[15] In this row, the total coupling rate constant is expected to decrease due to an increase of the size or electronic stabilization of the corresponding alkyl radical. Benzyl-type radicals are generally more stabilized than propionate radicals, so the diastereomeric excess upon coupling can be larger. This agrees with the results obtained in reactions with DPPO radicals.[10]

The appearance of diastereomeric preference upon coupling of DEPN with sBiB is an astonishing observation, which we cannot explain at present and this requires additional investigation.

Concluding remarks

The diastereomeric excess upon homolysis and reformation of the diastereoisomeric alkoxyamines depends strongly on the structure of both nitroxyl and released alkyl part. For propionate-like radicals, the diastereoselectivity of the cleavage generally prevails over that in the coupling reaction. The diastereoselectivity of the coupling can become comparable with that of the cleavage with decrease of k_c, so both bulky ester and β-substituents will favour the diastereoselective coupling. Both homolysis and coupling are expected to be diastereoselective with increase of bulkiness of a leaving radical (DEPN, DPPO). The (*R*,*R*)/(*S*,*S*)-diastereomers of DEPN-based alkoxyamine have always smaller homolysis rate constant than (*R*,*S*)/(*S*,*R*)-diastereomers. The increase of the size of ester group affects only the total homolysis rate constant but not the diastereomeric preference upon homolysis. Our results allow the assumption that the homolysis does not occur *via* a single step but rather by a two-step pathway and that the difference of k_d for diastereoisomers is certainly due to an enthalpy difference in ground state. However, better and deeper understanding of the homolysis pathway requires more structural studies and high-level calculations.

One can predict that some stereocontrol in the NMP processes can be achieved for special polymerizing systems, which can combine relatively fast homolysis and slow coupling and have bulky substituents. It is better to run the reaction at temperatures close to ambient. If these conditions are fulfilled, the transient propagating radical may not be a planar and may give one preferable isomer upon coupling. These qualitative requirements can restrict general kinetic criteria of NMP,[36] so it is not so easy to find appropriate model monomer and nitroxyl radical to verify these predictions. Recently, some livingness/polydispersity control in DEPN mediated polymerization of methyl methacrylate has been achieved[37] at relatively low temperatures, so the systems based on DEPN/(bulky)alkyl methacrylate[38] combination is very promising for achieving stereocontrol, as well.

It is logical to assume that similar predictions can be made for ATRP. Despite the unsuccessful first attempts,[39] the recent experiments with methacrylate systems and chiral catalysts[40] showed some progress in enantiomeric control in ATRP.

However, at the present stage of our knowledge about NMP and ATRP, any kind of the stereocontrol in these polymerizations cannot be significant and the utilization of auxiliary compounds (like Lewis acids[41]) is more promising.

Experimental

All chemicals were purchased from Aldrich, Fluka, or Acros and were used without purification. *N*-(2-Methylpropan-2-yl)-*N*-(1-diethylphosphophono-2,2-dimethylpropyl)aminoxyl (DEPN, 89%) was provided by Atofina. The NMR spectra were registered on Bruker DPX 200, DRX 300 and DRX 600 NMR spectrometers. The ^{1}H and ^{31}P NMR procedures for kinetic measurements have been described previously.[15,23] Concentrations presented on the Figures above are accurate to about ±10%.

The synthesis and spectral data of compounds **1a**,**b**, **2a**–**c** and **3** (Schemes 3 and 6) are described in the Supporting Information. ‡

Trapping of MMOB radical by TEMPO

A solution of 0.693 g (4 mmol) of PMDETA in 15 ml of *o*-dichlorobenzene was bubbled by Ar within 30 min and transferred by syringe to a flask containing 0.574 g (4 mmol) of CuBr and purged by Ar. After the Cu complex was formed and the solution became homogeneous, a degassed mixture of 0.105 g (0.5 mmol) of methyl 2-bromo-3-methoxybutyrate, 0.078 g (0.5 mmol) of TEMPO in 3 ml of *o*-dichlorobenzene was added. The mixture was stirred for 15 min in Ar atmosphere at 90 °C. Thereafter, the mixture was exposed to open air for 30 min, filtered through a small pad of alumina. *o*-Dichlorobenzene was evaporated in high vacuum at room temperature. The residue was dissolved in $CDCl_3$ and analysed by NMR.

Trapping of EPP radicals by DEPN

A solution of 18.0 mg (0.006 mmol) of DEPN and 1.6 mg (0.009 mmol) of PMDETA in 1.0 mL of chlorobenzene was degassed using three freeze–pump–thaw cycles and transferred by syringe to a flask purged with nitrogen and containing 1.3 mg (0.009 mmol) of CuBr. After the Cu(I) complex was formed, 1.4 mg (0.006 mmol) of 3-ethylpent-3-yl 2-bromopropionate was added, and the mixture was stirred at 50 °C for 1.5 h. After exposing the mixture to air for 5 min, it was filtered through a small pad of alumina into an NMR sample tube to remove Cu(II) complex. The first NMR spectrum was measured after *ca.* 10 min. Then, the solution was degassed again and stirred in an oil bath heated at 100 °C for 18 h. After cooling to room temperature, the second NMR spectrum was measured.

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