The reactivity of 3,5-dimethylidene-2,2,6,6-tetramethyl-4-oxopiperidin-1-oxyl and its diamagnetic *N*-methyl analog in nucleophilic addition of amines and Diels—Alder dimerization

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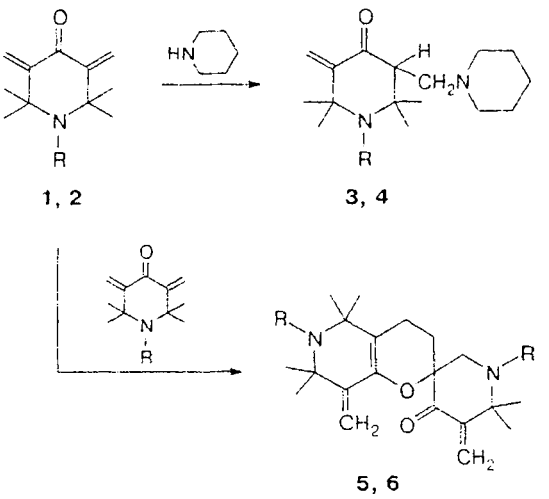
3,5-Dimethylidene-1,2,2,6,6-pentamethyl-4-oxopiperidine was shown by the kinetic method to be less reactive than 3,5-dimethylidene-2,2,6,6-tetramethyl-4-oxopiperidin-1-oxyl in the nucleophilic addition of secondary amines and Diels—Alder dimerization. According to the quantum-chemical AM1 calculations, this is due to the difference in the structures of the activated complexes (in the reactions with amines) and to the "press" effect created by the *N*-methyl group that impedes the necessary cycle flattening (in the Diels—Alder reaction).

Key words: nitroxyl radical, diamagnetic analog, piperidine, dimerization, kinetics, rate constants, "press" effect, AM1 method, quantum-chemical calculations.

The influence of the nitroxyl center on the reactivity of functional groups has previously been considered for imidazoline[1] and piperidine[2] nitroxyl radicals. In this work, we compared the reactivities of the nitroxyl radical 3,5-dimethylidene-2,2,6,6-tetramethyl-4-oxopiperidin-1-oxyl (**1**) and its diamagnetic analog 3,5-dimethylidene-1,2,2,6,6-pentamethyl-4-oxopiperidine (**2**) in reactions with secondary amines in an inert solvent (hexane) and in Diels—Alder dimerization (Scheme 1).

Scheme 1



It has previously been shown[3] that the ratio of the reaction rates of **1** and **2** with piperidine in a hexane solution is ~30. Approximately the same ratio of the rates was found for the addition of morpholine, piperazine, and *N*-methylpiperazine[4] to compounds **1** and **2**. Under comparable conditions, the Diels—Alder dimerization of **1** and **2** at 20 °C is more than 100-fold slower than the addition of piperazine. In addition, radical **1** is dimerized at room temperature, whereas the dimerization of molecule **2** occurs at temperatures >100 °C.

Three main factors can affect, most likely, the difference in the reactivities of compounds **1** and **2** in the nucleophilic addition of secondary amines and Diels—Alder dimerization. On the one hand, the replacement of the strong donor acceptor (O) in molecule **1** by the Me group, which possesses an electron-donor effect, decreases the polarization of the C=C bond in molecule **2**, which can decrease, as a result, the reaction rates. On the other hand, the decrease in the reactivity of molecule **2** can be due to a strong steric interaction of the relatively bulky N-methyl group with the α-methyl substituents (the so-called press effect[5]), capable of affecting, for example, the cycle conformation. In addition, compounds **1** and **2** can react with secondary amines *via* different mechanisms, for example, involving the NO group of radical **1** in the formation of hydrogen bonds.

To reveal the reasons for the different reactivities of compounds **1** and **2**, we used the kinetic method for the study of their reaction with piperidine and performed the quantum-chemical semiempirical AM1 calculations of

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the equilibrium structures and transition states of amine addition.

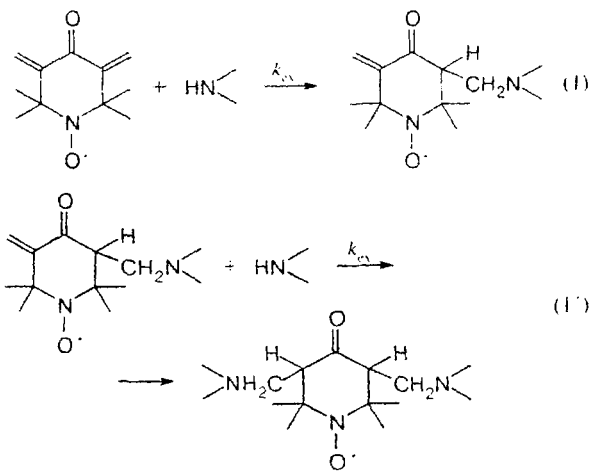
Experimental

Compounds **1** and **2** were synthesized by published procedures.[4,5] The reactions of the methylene groups in molecules **1** and **2** with piperidine were studied by the jet flow method in an *n*-hexane solution on a spectrophotometer (Durrum) at 20—50 °C and λ = 425 nm for **1** and λ = 250 and 400 nm for **2**. The initial concentrations of compounds **1** and **2** were 10^{-2}—10^{-3} mol L^{-1}, and the concentration of piperidine was 0.25 mol L^{-1}. The absorbance of the solution was measured over time, and the effective rate constant k_{ex} was found from the ratio $k_{ex} = 2.3/t \cdot \log(D_0 - D_\infty)/(D_0 - D)$, where D_0 and D are the initial and current absorbances of the solution, D_∞ is its absorbance at the end of the reaction, and t/s is the time. The error in the determination of k_{ex} did not exceed 10—15%. The addition products of piperidine to **1** and **2** (compounds **3** and **4**, identical to those of the Mannich reaction[6]) were isolated by distillation of the solvent *in vacuo* followed by recrystallization from hexane. Compounds **5** and **6** have been described previously.[5,7]

The equilibrium geometry of compounds **1** and **2** was calculated and the steric effects in these structures were examined by the semiempirical AM1 method using the GAMESS program.[8] The elementary acts of the reactions of these compounds with secondary amines (dimethylamine was chosen as the model) were also studied by this method. For each system considered, two minima corresponding to the starting reactants and final products and one stationary point attributed to the transition state (the Hessian matrix has only one negative eigenvalue) were found on the potential energy surface (PES). The activation energies of the reactions of compounds **1** and **2** with amine were found as the differences between the corresponding full energies of the transition states of the systems and initial reactants.

Results and Discussion

Compounds **1** and **2**, bearing two methylene groups, form with piperidine the mono- and bisaddition products (see, *e.g.*, for compound **1**, reactions (1) and (1′)).

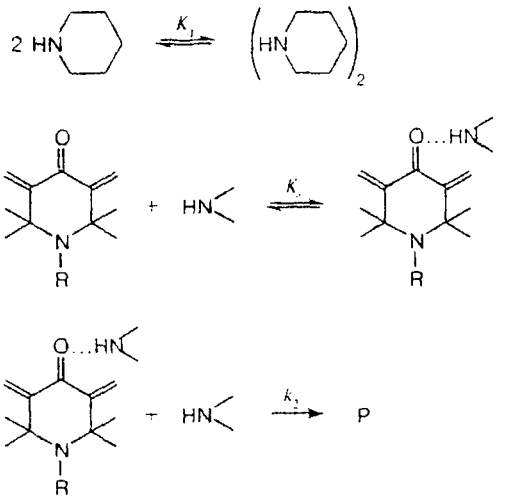


(1)

(1′)

In the case of piperidine, the ratio of the reaction rates (1) and (1′) is[3] $k_{ex}/k'_{ex} = 4 \cdot 10^3$, *i.e.*, they are distinctly separated in time, which allows these constants to be exactly measured. We studied reaction (1). The experiments showed that the formation rates of the monoderivatives in at least a tenfold amine excess with respect to compounds **1** and **2** obey the regularities of irreversible second-order reactions at amine concentration >0.1 mol L^{-1} until the complete transformation of **1** and **2** into the corresponding monoproducts occurred. These reactions with piperidine proceed in several stages[3] (Scheme 2).

Scheme 2



R = O, Me

P is final product

Here k_2 is the rate constant of the rate-determining stage, K_c is the formation constant of the H bond >C=O...HN<, and K_d is the constant of piperidine dimerization. The apparent rate constant k_{ex} is related to the kinetic and thermodynamic parameters of the reaction as follows:

$$k_{ex} = k_2 K_c B_m^2/(1 + K_c B_m), \qquad (2)$$

where B_m is the concentration of the monomeric form of piperidine.[3] Since the reaction was carried out in an inert solvent (*n*-hexane), we may exclude its participation in the formation of complexes with the reactants, which considerably facilitates the interpretation of the results.

The equilibrium constant of piperidine dimerization is known[9] only for 20 °C. Therefore, we could not calculate the concentrations of its monomeric form and determine k_2 by Eq. (2) for **1** and **2** in the studied temperature interval. In this work, we found the ratio of the pre-exponential factors A_1/A_2 and the difference of the activation energies $E_1 - E_2$, which allowed us to evaluate the preferential influence of either steric hindrances or the inductive factor on the reactions of

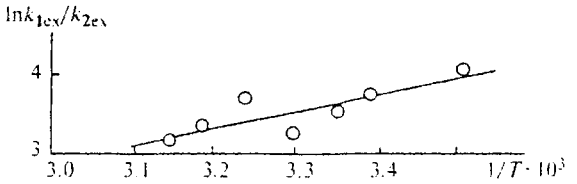


Fig. 1. The ratio of the rate constants (k_{ex}) of the reaction of molecules **1** and **2** with piperidine as a logarithmic function of $1/T$.

Table 1. Charges on the atoms in molecules **1** and **2** according to the AM1 data

Atom	1	2	Atom	1	2
O(1)	−0.28	−0.29	C(5)	−0.18	−0.16
N(1)	0.06	−0.27	C(6)	0.06	0.10
C(2)	0.06	0.10	C(9)	−0.14	−0.16
C(3)	−0.18	−0.16	C(10)	−0.14	−0.16
C(4)	0.30	0.31			

compounds **1** and **2** with piperidine. The ratio k_{1ex}/k_{2ex} in the specified temperature (T) interval can be reduced to the corresponding ratios of the kinetic ($k_2 = A \cdot e^{-E/RT}$) and thermodynamic ($K_e = C \cdot e^{\Delta H/RT}$) parameters of these reactions (C and ΔH are the pre-exponential factor and the enthalpy of formation of the H bond >C=O...HN<, respectively) using Eq. (2) and neglecting the concentration function. Then we obtain

$$\ln(k_{1ex}/k_{2ex}) = \ln(A_1 e^{-E_1/RT} \cdot C_1 e^{\Delta H_1/RT})/(A_2 e^{-E_2/RT} \cdot C_2 e^{\Delta H_2/RT}).$$

The plot of $\ln(k_{1ex}/k_{2ex})$ *vs* $1/T$ is presented in Fig. 1 and shows that $\ln(A_1 \cdot C_1/A_2 \cdot C_2) = -5.9$, *i.e.*, $(A_1 \cdot C_1/A_2 \cdot C_2) < 1$ (0.25), and $(E_2 - E_1) + (\Delta H_1 - \Delta H_2) = (5.5 \pm 2)$ kcal mol^{-1}. At first sight, we may assume that the induction factor prevails in the reactions. However, calculations in the AM1 approximation showed that the charges on the C atoms of the cycle and exocyclic double bonds in molecules **1** and **2** are almost equal (Table 1), *i.e.*, the induction factor barely affects the reaction course. A deeper analysis of the reactivity requires data on the equilibrium geometry of structures **1** and **2** and the corresponding transition states of amine addition.

According to the AM1 calculations (Fig. 2, *a*, *b*), the six-membered cycle in molecules **1** and **2** has a boat conformation. The deviations of the N(1) and C(4) atoms from the plane of other atoms of the cycle are 0.40, 0.44 and 0.45, 0.49 Å in molecules **1** and **2**, respectively. The exocyclic double bonds and the carbonyl group do not lie in the same plane (the torsion angle O(1)—C(4)—C(3)—C(9) is equal to 30.9° in molecule **1** and 35.0° in molecule **2**, and the O(1)—C(4)—C(5)—C(10) angle is −33.7° in **1** and −37.6° in **2**). In addition, the C(3) and C(5) atoms deviate from the plane that passes through the O(1), C(9), and C(10) atoms by 0.79, 0.80 and 0.80, 0.83 Å, respectively.

The Me group at the N atom in molecule **2** is in the equatorial position (the torsion angle C(13)—N(1)—C(6)—C(5) is equal to 178.8°). The presence of this group results in a noticeable steric repulsion of its H atoms and the H atoms of the methyl groups at the C(2) and C(6) atoms, which stipulates the appearance of the next shortened intramolecular contacts: H(C(7))...H(C(13)) 2.09 Å, H(C(8))...H(C(13)) 2.06 Å, H(C(13))...H(C(11)) 2.22 Å, and H(C(12))...H(C(13)) 2.01 Å (the sum of the van der Waals radii is[10] 2.32 Å). The existence of these contacts confirms the "press" effect[5] of the N—Me group, but its influence on the equilibrium conformation of the cycle in molecule **2** is insignificant.

Therefore, the difference in the reactivities of compounds **1** and **2** in amine addition is most likely related

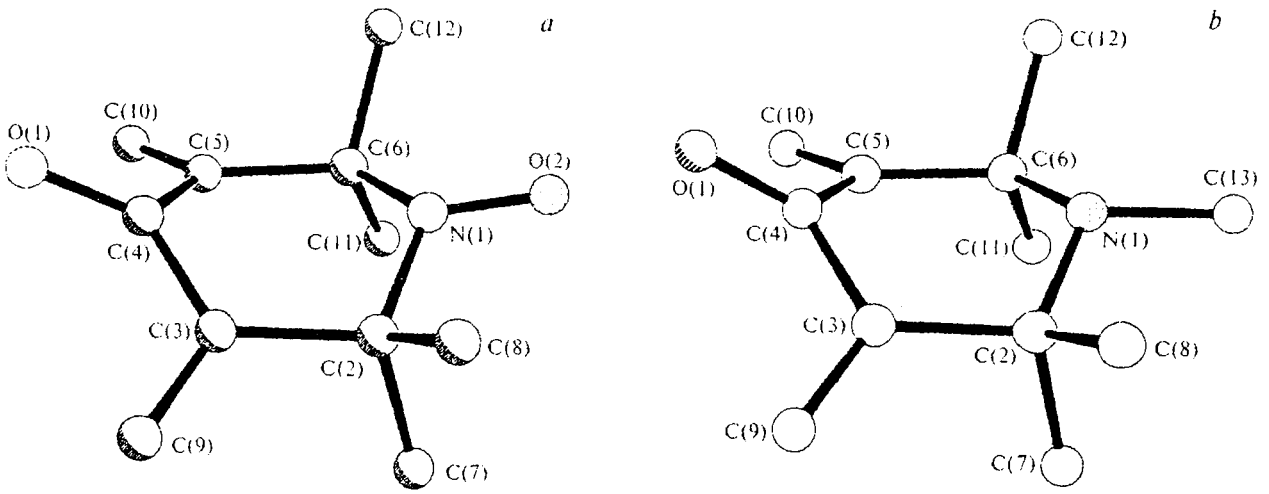


Fig. 2. General view of radical **1** (*a*) and molecule **2** (*b*) according to the AM1 data.

Table 2. Geometric parameters of the hydrogen bonds X—H...O (X = N, C) in the activated complexes **1**—2[NHMe$_2$] and **2**—2[NHMe$_2$]

H bond	d/Å			φ/deg
	X—H	H...O	X...O	X—H...O
		1—2[NHMe$_2$]		
N(2′)—H(2′)...O(1)	1.007	2.164	3.165	172.5
C(2′)—H(C(2′))...O(2)	1.126	2.387	3.500	169.5
		2—2[NHMe$_2$]		
N(2′)—H(2′)...O(1)	1.007	2.150	3.152	173.2

to different structures of the activated complexes in these reactions. According to the kinetic data, the addition of secondary amine to the exocyclic double C=C bond is the rate-determining stage of these reactions. This process, as has been already mentioned, has the

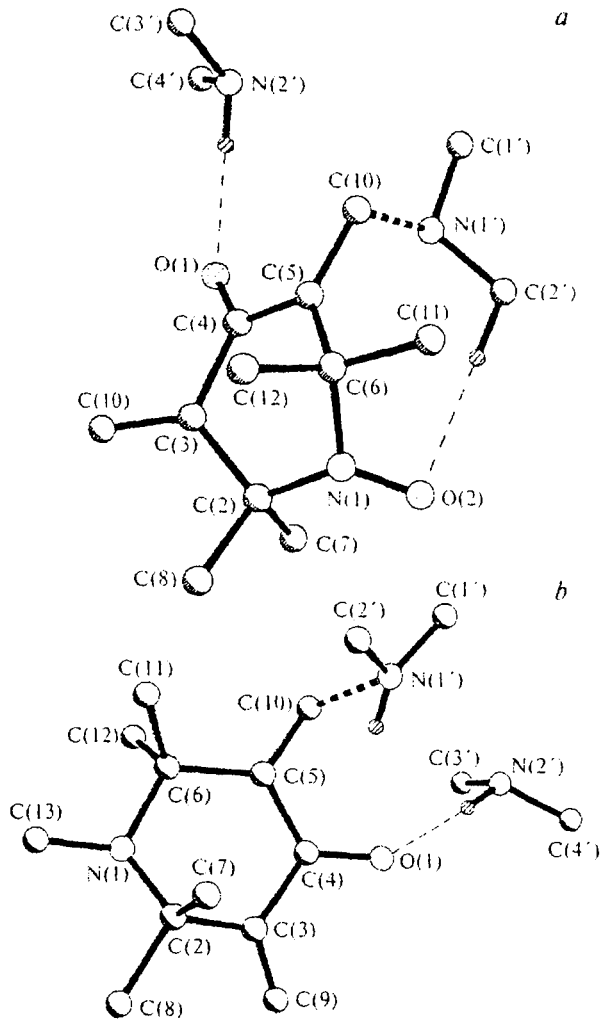


Fig. 3. General view of the activated complexes of the reaction of dimethylamine with molecules **1** (*a*) and **2** (*b*) according to the AM1 data.

first order with respect to the amine concentration, and the second amine molecule is bound to the substrate by the hydrogen N—H...O bond between the H atoms of the NH group of the amine and the O atom of the carbonyl group in compound **1** or **2** (Table 2, Fig. 3, *a*, *b*).

The structure of the **1**—2[NHMe$_2$] complex differs from that with molecule **2** by the C—H...O bond between the O atom of the nitroxyl group and the H atom of the methyl group of dimethylamine, chosen as the model reactant (see Table 2, Fig. 3, *a*). (Probably, a similar bond also appears with piperidine.) The H...O distance usually ranges[11,12] from 2.0 to 2.8 Å, and C...O ranges from 3.30 to 3.80 Å. The determining influence of these C—H...O contacts, for example, on the motive of crystal packing or on the molecular organization in the liquid phase is well known.[13—15] The double C(5)—C(10) bond in the transition state is elongated to 1.39 Å as compared to 1.34 Å in the starting molecules **1** and **2**. The interatomic C—N distance is 1.877 Å for **1**—2[NHMe$_2$] and 1.855 Å for **2**—2[NHMe$_2$].

It is of interest that the shape of the six-membered cycle strongly changes when the activated complex **1**—2[NHMe$_2$] is formed, which favors the formation of the C—H...O bond. This cycle gains the conformation of a nonsymmetrically flattened boat, and the deviations of the N(1) and C(6) atoms from the plane of the other atoms are 0.39 and 0.61 Å, respectively. This change in the conformation corresponds to a very smooth minimum on PES for both **1** and **2**, which is related to the existence of the saturated ring and exocyclic double bonds. For example, according to the AM1 calculations, the deviation of the torsion angle C(2)—N(1)—C(6)—C(5) from the equilibrium value by ±30° increases the energy of **1** by less than 0.4 kcal mol^{-1}.

The formation of the C—H...O bond in the transition state of **1**—2[NHMe$_2$] should enhance its stability as compared to the analog **2**—2[NHMe$_2$] and decrease the corresponding activation energy. The calculations in the AM1 approximation showed that the activation energy of the addition of amine to radical **1** amounts to 23.3 kcal mol^{-1}, and that to molecule **2** is 25.3 kcal mol^{-1}, *i.e.*, the difference is equal to 2 kcal mol^{-1}. According to the kinetic data, this difference is 5 kcal mol^{-1}. This deviation is appropriate if we take into account the assumptions used in the calculations ($\ln k_{1ex}/k_{2ex}$ is independent of the concentration of the monomeric form of amine, $\Delta H_1^{\neq} \approx \Delta H_2^{\neq}$, and the use of a model amine instead of piperidine).

We did not calculate the transition state for the Diels—Alder dimerization. However, it is known[16] that the formation of the endodimer during heterodiene synthesis requires planar arrangement of the corresponding fragments in the reactant molecules. For compounds **1** and **2**, this requirement is fulfilled when the exocyclic double bonds and the carbonyl group lie in the same plane. Despite the smooth character of the minimum on PES for the system involving compounds **1** and **2**, the

formation of this conformation requires appreciable energy. According to our calculations, the energy of this conformation is higher than that of the equilibrium conformation by ~2 kcal mol^{-1} for molecule **1** and by ~3 kcal mol^{-1} for **2**. This indicates that the formation of the planar conformation for the Diels–Alder dimerization is more difficult for molecule **2** as compared to that for radical **1**. This can be related to the "press" effect of the N–Me group mentioned above.

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