Note

Drastic deprotonation reactivity difference of 3- and 5-alkylpyrazole isomers, their I2-catalyzed thermal isomerization, and telescoping synthesis of 3,5-dialkylpyrazoles: the “adjacent lone pair effect” demystified

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Drastic deprotonation reactivity difference of 3- and 5-alkylpyrazole isomers, their I_2-catalyzed thermal isomerization, and telescoping synthesis of 3,5-dialkylpyrazoles: the "adjacent lone pair effect" demystified

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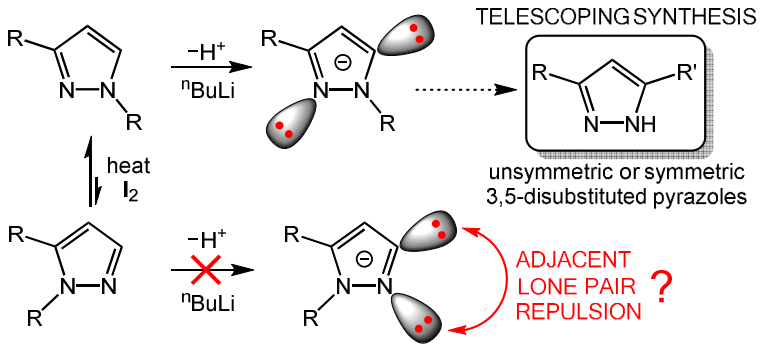

ABSTRACT

N-protected 3-alkyl-pyrazoles are easily deprotonated by ^{n}BuLi at the 5-position of the aromatic ring, while the 5-alkyl isomers are completely unreactive under the same conditions. We reveal, using computational analysis, that electron pair repulsion within the deprotonated anion is not the reason behind the lack of reactivity of 5-alkyl-pyrazoles. Instead, diminished π-resonance and attractive electrostatic interactions within the pyrazole ring are responsible for the observed effect. A greener, telescoping alternative to the synthesis of 3,5-dialkylpyrazoles is also presented.

Pyrazole derivatives are employed in various applications, including a wide variety of pharmaceuticals, insecticides, fungicides, herbicides and dyes.[1] Owing to its ability to bridge metal centers together, the pyrazole moiety has also been exploited extensively for the construction of diverse multi-metallic complexes, such as macrocycles,[2] grids,[3] clusters,[4] nanocages[5] and 3D-frameworks.[6] Uses of the resulting materials include H_2-storage, isomer separation, anion extraction and single-molecule magnets. Despite the broad interest and widespread use, certain intrinsic properties of the pyrazole ring are still not fully understood. For

instance, we have just recently revealed that the reason behind the preferred deprotonation of 3-methyl-1-R-pyrazole (R = *N*-protecting group) at an endocyclic carbon instead of the exocyclic methyl group is a subtle combination of diminished π-conjugation, smaller bond angles and strengthened induction of C_{sp^2} versus C_{sp^3}, as compared to the six-membered analog, 3-methylpyridazine, which is preferentially deprotonated at the exocyclic methyl group (known as the "benzylic" position).[7] Furthermore, while 3-methyl-1-THP-pyrazole (THP = tetrahydropyran-2-yl) is easily deprotonated by ^{n}BuLi at −78 °C, the 5-methyl-1-THP-pyrazole isomer is completely resistant to deprotonation under the same experimental conditions (Fig. 1). Herein we unveil that this intriguing property is not the result of the repulsion between the lone pairs of the deprotonated anion and the adjacent N-atom, as previously believed and referred to as to the "adjacent lone pair (ALP) effect".[8] We also discovered that the thermal isomerization of the 5-methyl- to the 3-methyl-1-THP-pyrazole isomer is catalyzed by trace amounts of iodine, and developed a convenient one-pot, telescopic synthesis of unsymmetrical 3,5-dialkylpyrazoles.

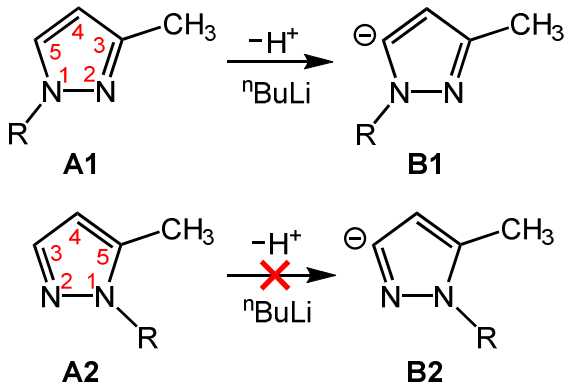

Figure 1. Deprotonation of 3-methyl-1-R-pyrazole (**A1**) and 5-methyl-1-R-pyrazole (**A2**) isomers. R = methyl (computations) or tetrahydropyran-2-yl (synthesis).

As the aromatic rings of the 1,3-dimethylpyrazole (**A1**) and 1,5-dimethylpyrazole (**A2**) isomers, as well as of their deprotonated products **B1** and **B2** (Fig. 1) are nearly but not perfectly planar, all aromatic rings were restrained to a plane in quantum mechanical computations to allow for the differentiation of σ and π interactions. Planarity requires an energy of less than 0.4 kcal/mol at the MP2/6-311+G(d,p) level.

Table 1. Relative energies of **A2** *vs.* **A1** and **B2** *vs.* **B1**, along with their inherent electron delocalization energies (DEs) for σ and π electrons (kcal/mol)*

	A1	**A2**	**B1**	**B2**
ΔE(MP2)	0.00	0.12	0.00	18.21
ΔE(HF)	0.00	0.82	0.00	21.53
DE(total)	140.37	139.70	141.87	128.93
DE(σ)	36.62	36.71	39.91	40.90
DE(π)	104.96	104.26	102.87	88.38

* Geometries are optimized at the MP2/6-311+G(d,p) level.

As expected, the 1,3-dimethylpyrazole (**A1**) and 1,5-dimethylpyrazole (**A2**) isomers are essentially isoenergetic at the HF or MP2 theoretical levels. However, their deprotonated products have very different energies: **B1** is much more stable than **B2**. The conventional explanation is the adjacent lone pair (ALP) effect, which suggests that the repulsion between the two lone pairs on the adjacent carbon and nitrogen atoms destabilizes **B2**.[8] Our calculations based on the pairwise Coulomb interaction (Eq. 1) show that there is indeed a slight increase (2.2 kcal/mol) from the repulsion between the two lone pairs in **B2** to the repulsion between one lone pair with the σ_{CN} bond in **B1** (Fig. 2). This amount, however, is small and is correlated to the structural change, i.e., the CN bond in these two species.

$$RE = \left\langle \phi_i \phi_i \left| \frac{1}{r_1 - r_2} \right| \phi_j \phi_j \right\rangle \qquad (1)$$

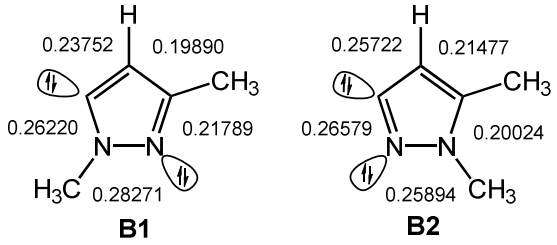

Figure 2. Adjacent pair-pair Coulomb interactions in **B1** and **B2** (a.u.).

This prompts further investigations of the electron delocalization effect in these systems.[9–12] Table 1 compiles the major results, where DE(total) is the energy change between a fully delocalized and a fully localized Lewis state (i.e., the most stable resonance structure), and

DE(π) and DE(σ) refer to the energy change by localizing π and σ electrons, respectively. The sum of DE(π) and DE(σ) is very close to DE(total), suggesting negligible coupling between the delocalizations of σ and π electrons.

It is interesting that from **A** to **B**, there is little change for the σ electron delocalization in isomers (**A1** *vs.* **A2** and **B1** *vs.* **B2**). However, the π-conjugation in **B2** is less stabilizing than in **B1** by 13 kcal/mol, which accounts for 60% of the energy gap between **B1** and **B2**. With all electron pairs localized on either two atoms (bonds) or individual atoms (lone pairs), **B1** is still more stable than **B2** by 8 kcal/mol, which most likely is a consequence of electrostatic interactions: there are two H nuclei around the negatively charged carbon in **B1** but only one in **B2 (**Fig. 2). To verify our hypothesis, we examined the model system methylamine in different conformations, as shown in Fig. 3. The deprotonation of the eclipsed conformation (**A3**) results in two adjacent lone pairs, while the deprotonation of the staggered conformation (**A4**) does not. Although **A3** does have a higher deprotonation energy than **A4**, the difference is only 7.5 or 7.1 kcal/mol at the MP2 or HF levels, respectively (with geometries optimized at the MP2/6-311+G(d,p) level). This amount is in excellent agreement with the energy difference between electron-localized **B1** and **B2** (8 kcal/mol). Using Eq. 1, we also evaluated the repulsion between the lone pairs in **B3** (see Fig. 3), which turns out to be even less than the repulsion between the lone pair and the C−H bond in **B4**. Therefore, we conclude that it is not the repulsion between adjacent lone pairs of electrons (ALP effect) that leads to the drastic difference between the deprotonation energies of the two isomers, but rather reduced π-resonance (62% or 13 kcal/mol) and attractive electrostatic interactions (38% or 8 kcal/mol).

As the deprotonation of **A1** (R = THP) is an ortho-metalation reaction,[13] it can be argued that the tetrahydropyran-2-yl group promotes ortho-deprotonation, as its O-atom can potentially coordinate to the lithium countercation. While this scenario certainly contributes to the stability of anion **B1** compared to **B2** (R = THP) in practice, our gas-phase calculations on the analogs which lack the stabilizing O-atom (R = CH_3), also lead to the same conclusion that **B1** is much more stable than **B2**. Therefore, the computational results clearly establish that the metalation of the 5-position in **A1** is not directed, but rather assisted by the THP group in practice, which offers additional stability to the resulting anion **B1**.

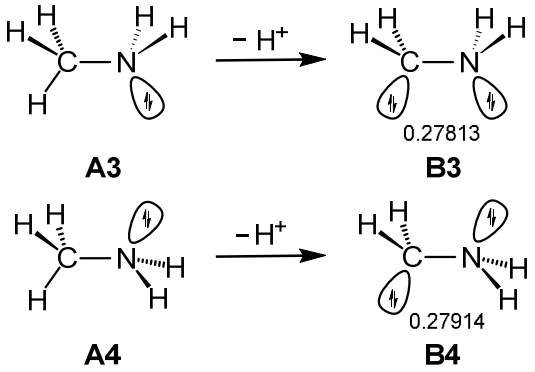

Figure 3. Deprotonation of eclipsed (**A3**) and staggered (**A4**) methylamine conformers, with values of adjacent pair-pair Coulomb interactions shown for **B3** and **B4** (a.u.).

Aiming at greener preparative methods, we developed a telescopic synthesis of 3,5-dialkylpyrazoles (53% overall yield based on 1*H*-pyrazole), by combining five synthetic steps into a one-pot method (Fig. 4). Crucial to the value of this method are the solvent- and catalyst-free, quantitative step of pyrazole protection, and the also solvent-free isomerization step of the unreactive 5-alkyl-1-THP-pyrazole to the reactive 3-alkyl-1-THP-pyrazole isomer. Such protective group switching is usually accomplished by an acid-catalyzed, sequential[14] or direct[15] deprotection-reprotection route. Our method significantly reduces the consumption of organic solvents and additional reagents, and eliminates the use of highly toxic or explosive starting materials and reagents (such as hydrazine, diazomethane and derivatives, often employed for the synthesis of pyrazole derivatives). As the one-pot method requires no purification of the intermediates, losses are eliminated and waste production is greatly diminished.

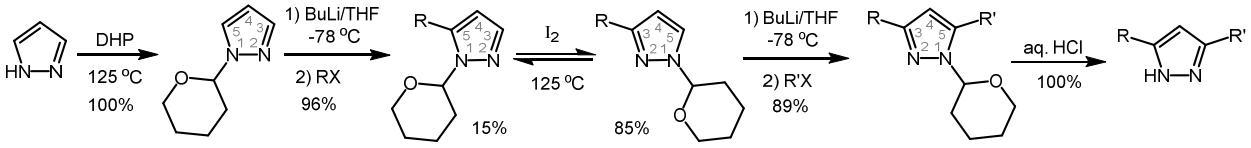

Figure 4. Telescoping synthesis of 3,5-dialkylpyrazoles from pyrazole (DHP = 3,4-dihydro-2H-pyran; R = *n*-hexyl or *n*-heptyl; R′ = *n*-butyl), with % conversions (based on ^{1}H-NMR) .

Although the isomerization step of 5-alkyl- to 3-alkyl-1-THP-pyrazole can be accomplished by simple heating,[16] a catalytic amount of iodine (I_2) greatly reduces the reaction time needed to reach equilibrium. This discovery is rooted in our observation that when 5-hexyl-

1-THP-pyrazole is prepared from 1-iodohexane, it undergoes isomerization much faster than when it is prepared from 1-bromohexane, under the same conditions. Indeed, addition of 0.08 mol% I_2 to 5-hexyl-1-THP-pyrazole prepared from 1-bromohexane reduces the isomerization time at 125 °C from 8 days to 24 hours, confirming our hypothesis that trace amounts of iodine originating from 1-iodohexane catalyze the isomerization. The mechanism of isomerization is likely similar to the one proposed for the 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) catalyzed SEM group transposition in SEM-protected pyrazoles,[17] as well as the N,N-dimethylaminosulfonyl (DMAS), benzyl (Bn), methoxymethyl (MOM) and SEM protecting group switching in N-protected imidazoles catalyzed by DMAS-Cl, BnBr, MOM-Cl or SEM-Cl, respectively.[18] All the above protecting agents are alkylating agents, which, upon alkylation of the free N2-atom of the N1-protected diazole, induce the elimination of the protecting group and render the N1-atom free. The liberated protecting group alkylates the next substrate and propagates the reaction. In our case (Figure 5), the alkylating agent is presumed to be 2-iodotetrahydropyran,[19] which initially forms from the reaction of 3,4-dihydro-2H-pyran (formed in trace amounts as a result of partial deprotection of the substrate upon heating[16]) with HI (formed from the reaction of I_2 with the pyrazole ring, leading to 4-iodopyrazole[20]). Alternatively, I_2 can react directly with 3,4-dihydro-2H-pyran to produce 2,3-diiodotetrahydropyran, which can react similarly to 2-iodotetrahydropyran as the initial alkylating agent.

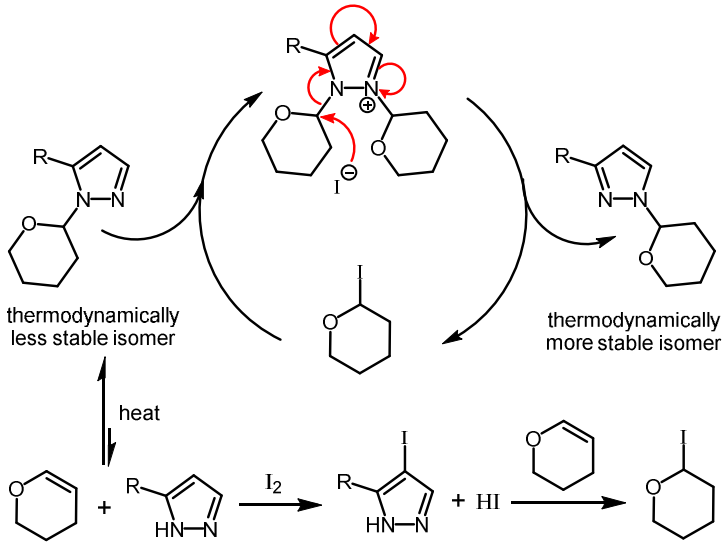

Figure 5. Proposed mechanism of the I_2-catalyzed thermal isomerization of 5-alkyl- to 3-alkyl-1-THP-pyrazoles (R = alkyl).

Improved overall yields of 3,5-dialkylpyrazoles (60% based on 1*H*-pyrazole) are obtained if the THP-protected 3,5-dialkylpyrazoles are purified before deprotection, as column chromatographic separation is more efficient on the protected pyrazoles than the deprotected products. Pure 3,5-dialkylpyrazoles are obtained after deprotection with HCl and removal of the solvent in vacuum.

In summary, we have shown that the drastic deprotonation reactivity difference between N-protected 3-alkyl- and 5-alkylpyrazole isomers is not the result of repulsion between adjacent lone pairs (ALP effect), as previously thought, but is rather due to reduced π-resonance and weaker stabilizing attractive electrostatic interactions within the 5-alkylpyrazole isomer. The thermal isomerization of the unreactive 5-methyl- to the reactive 3-methyl-1-THP-pyrazole isomer is greatly accelerated by small amounts of elemental iodine. By combining five synthetic steps into one pot, we developed a greener, telescoping synthesis of 3,5-dialkylpyrazoles. This new methodology could also be applied for the synthesis of various other 3,5-disubstituted pyrazoles (e.g., alkyl, halogen, hydroxyl, amino, azido, carbonyl, organo-element substituents), both symmetrical and unsymmetrical, by employing the appropriate electrophiles.

EXPERIMENTAL SECTION

General methods. Tetrahydrofuran is dried with Na/benzophenone and freshly distilled under nitrogen prior to use. All other commercial reagents and solvents are used as received. ^{1}H and ^{13}C NMR spectra are recorded at room temperature, and peak assignments are confirmed by ^{1}H–^{1}H COSY experiments. High-resolution mass spectra are obtained using an electrospray ionization source (negative mode for pyrazoles, positive mode for THP-protected pyrazoles).

Telescopic synthesis of 3(5)-butyl-5(3)-hexylpyrazole. The following steps are carried out in a 500 mL pressure flask (one-pot). The contents are protected from atmospheric moisture between steps by using an N_2 blanket.

a) Protection of 1*H*-pyrazole. THP-protection of 1*H*-pyrazole is accomplished according to our green method described previously,[15] by heating 1.200 g (17.62 mmol) 1*H*-pyrazole and 2.00 mL (1.85 g, 22.0 mmol) of 3,4-dihydro-2*H*-pyran for 24 h at 125 °C. After removing the slight excess of DHP in vacuum, 2.68 g (100 %) pure 1-(tetrahydropyran-2-yl)pyrazole is obtained.

b) Synthesis of 5-hexyl-1-(tetrahydropyran-2-yl)pyrazole. The flask containing the THP-protected pyrazole is evacuated and purged with N_2, then anhydrous THF (40 mL) is added via N_2-purged syringe. The solution is chilled to −78 °C, stirred for 30 minutes, then ^{n}BuLi solution (1.6 M in hexanes, 11.0 mL, 17.6 mmol) is added dropwise over 10 minutes. After stirring at −78 °C for 30 minutes, 1-bromohexane (2.72 mL, 3.20 g, 19.3 mmol) is added, the solution is stirred at −78 °C for 90 minutes, then it is left to warm up to room temperature overnight under stirring. The flask is then connected to vacuum (0.005 mmHg) and the excess bromohexane and unreacted 1-THP-pyrazole are both removed by gently heating in a water bath at 55 °C. ^{1}H NMR shows a 96% conversion.

c) Isomerization to 3-hexyl-1-(tetrahydropyran-2-yl)pyrazole. To the 5-hexyl-1-THP-pyrazole obtained from 1-bromohexane is added a solution of I_2 (7.0 mg, 28 μmol) in DHP (2 ml) under an N_2 atmosphere. The flask is closed and set in an oven at 125 °C for 24 hours. After cooling to room temperature, ^{1}H NMR of the product shows an isomeric mixture of 85% 3-hexyl-1-THP-pyrazole and 15% 5-hexyl-1-THP-pyrazole. In the absence of I_2, it takes 8 days to reach the 85/15 equilibrium mixture of isomers at 125 °C. If 5-hexyl-1-THP-pyrazole is prepared using 1-iodohexane instead of 1-bromohexane, traces of residual iodine in the product have the same catalytic effect.

d) Synthesis of 5-butyl-3-hexyl-1-(tetrahydropyran-2-yl)pyrazole. The flask containing the mixture described above, is evacuated and purged with N_2. Anhydrous THF (70 mL) is added and the mixture is chilled to −78 °C for 30 minutes. ^{n}BuLi (1.6 M in hexanes, 10.0 mL, 16.0 mmol) is added dropwise over 10 minutes and is stirred for 30 minutes, then 1-bromobutane (1.90 mL, 2.42 g, 17.6 mmol) is added. After stirring for 3 hours at −78 °C, the solution is left to warm up to room temperature overnight under stirring, 1 mL water is added and the THF is removed under vacuum. ^{1}H-NMR shows an 89% conversion of 3-hexyl-1-(tetrahydropyran-2-yl)pyrazole to 5-butyl-3-hexyl-1-THP-pyrazole, along with traces of unreacted 5-hexyl- and 3-hexyl-1-THP-pyrazole.

e) Deprotection to 3(5)-butyl-5(3)-hexylpyrazole. To the material obtained above is added 200 mL ethanol and 50 mL HCl (37% in H_2O). After stirring for 8 hours (^{1}H NMR shows complete deprotection), the solvent is removed under vacuum. 5 mL of water is added to the residue, and the pH is adjusted to 8 with a saturated $NaHCO_3$ solution. The mixture is extracted with diethyl ether (3 × 80 mL) and the combined organic layers are dried over $MgSO_4$ overnight. The solid

material is filtered out and the solvent is removed under vacuum to give crude 3(5)-butyl-5(3)-hexylpyrazole (3.760 g) as dark red-brown oil. ^{1}H NMR shows a small amount of 3(5)-hexyl-1*H*-pyrazole impurity. If 1-iodobutane is used instead of 1-bromobutane in the previous step, 3(5)-butyl-5(3)-hexyl-4-iodopyrazole byproduct is also identified by ESI-MS.

f) Purification of 3(5)-butyl-5(3)-hexylpyrazole. The crude material is purified by column chromatography using hexane:ethyl acetate (2:1) as eluent. The main product, 3(5)-butyl-5(3)-hexylpyrazole is obtained as a yellow oil (1.941 g, 53% overall yield based on 1*H*-pyrazole) with R_f = 45%. If 1-iodobutane is used instead of 1-bromobutane in step d), the yield of the product drops to 46% (1.671 g), and 0.649 g of 3(5)-butyl-5(3)-hexyl-4-iodopyrazole is also isolated as a byproduct.

Alternative general method of preparation of 3,5-dialkyl-1-(tetrahydropyran-2-yl)pyrazoles. 1-THP-pyrazole, 5-alkyl-1-THP-pyrazoles and 3,5-dialkyl-1-THP-pyrazoles are prepared as described above (steps *a* through *d*). The protected 3,5-dialkyl-pyrazoles are extracted from the crude residues obtained after quenching with water and removal of the THF (*d*), using 4 mL water and three portions of 4 mL diethyl ether (per mmol of substrate). The combined organic layers are washed with 60 mL brine and dried over $MgSO_4$. After evaporation of the solvent, the crude products are purified by column chromatography using dichloromethane:ethyl acetate (4:1) as eluent, and are obtained pure (by ^{1}H NMR, ^{13}C NMR and ESI-MS) as yellow oils (R_f = 87% for 3(5)-R_1-5(3)-R_2pyrazole, where R_1 = *n*-butyl and R_2 = *n*-hexyl or *n*-heptyl).

5-butyl-3-hexyl-1-(tetrahydropyran-2-yl)pyrazole. Yield: 1.515 g (61% based on 1*H*-pyrazole). ^{1}H NMR (400 MHz, $CDCl_3$): 5.84 (s, 1H, 4-*H*-pz), 5.14 (dd, 1H, ^3J = 10.4 Hz, ^3J = 2.4 Hz, *CH*–THP), 4.02–4.06 (m, 1H, CH_2O–THP), 3.57–3.63 (m, 1H, CH_2O–THP), 2.53–2.67 (m, 4H, $CH_2(CH_2)_4CH_3$ and $CH_2(CH_2)_2CH_3$), 2.41–2.52 (m, 1H, CH_2–THP), 2.05–2.08 (m, 1H, CH_2–THP), 1.84–1.91 (m, 1H, CH_2–THP), 1.50–1.8 (m, 7H, CH_2–THP, $CH_2CH_2(CH_2)_3CH_3$ and $CH_2CH_2CH_2CH_3$), 1.20–1.44 (m, 8H, $(CH_2)_2(CH_2)_3CH_3$ and $(CH_2)_2CH_2CH_3$), 0.93 (t, 3H, ^2J = 7.32 Hz $(CH_2)_3CH_3$), 0.86 (t, 3H, ^2J = 6.6 Hz $(CH_2)_5CH_3$). ^{13}C-NMR (101 MHz, $CDCl_3$): 153.2, 144.5, 103.6, 84.2, 68.1, 31.8, 30.8, 29.9, 29.8, 29.4, 28.6, 25.10, 25.06, 23.3, 22.7, 22.5, 14.2 and 14.0. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{18}H_{32}N_2NaO$ 315.2412; found 315.2415.

5-butyl-3-heptyl-1-(tetrahydropyran-2-yl)pyrazole. Yield: 3.137 g (62% based on 1*H*-pyrazole). ^{1}H-NMR (400MHz, $CDCl_3$): 5.84 (s, 1H, 4-*H*-pz), 5.14 (dd, 1H, ^{3}J = 10.4 Hz, ^{3}J = 2.4 Hz, *CH*–THP), 4.02–4.06 (m, 1H, CH_2O–THP), 3.57–3.63 (m, 1H, CH_2O–THP), 2.53–2.67 (m, 4H, $CH_2(CH_2)_5CH_3$ and $CH_2(CH_2)_2CH_3$), 2.41–2.51 (m, 1H, CH_2–THP), 2.05–2.08 (m, 1H, CH_2–THP), 1.85–1.89 (m, 1H, CH_2–THP), 1.51–1.77 (m, 7H, CH_2–THP, $CH_2CH_2(CH_2)_4CH_3$ and $CH_2CH_2CH_2CH_3$), 1.21–1.44 (m, 10H, $(CH_2)_2(CH_2)_4CH_3$ and $(CH_2)_2CH_2CH_3$), 0.93 (t, 3H, ^{2}J = 7.6 Hz $(CH_2)_3CH_3$), 0.85 (t, 3H, ^{2}J = 6.8 Hz $(CH_2)_5CH_3$). ^{13}C-NMR (101 MHz, $CDCl_3$): 153.2, 144.5, 103.6, 84.2, 68.1, 31.9, 30.8, 29.9, 29.8, 29.7, 29.2, 28.6, 25.09, 25.06, 23.3, 22.7, 22.5, 14.2 and 14.0. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{19}H_{34}N_2NaO$ 329.2568; found 329.2559.

Alternative general method of preparation of 3,5-dialkylpyrazoles. 3,5-Dialkyl-1-(tetrahydropyran-2-yl)pyrazoles are deprotected as described above (*e*), using 8 mL ethanol and 2 mL HCl (37% in H_2O) per mmol of substrate for 8 hours. After removal of the solvent, addition of 0.4 ml H_2O, neutralization and extraction with 3 × 6 mL diethyl ether (per mmol substrate), followed by drying with $MgSO_4$ and removal of the solvent in high vacuum, pure products are obtained (based on ^{1}H NMR, ^{13}C NMR and ESI-MS).

3(5)-butyl-5(3)-hexylpyrazole. Yield: 1.061 g (99% based on 3(5)-butyl-5(3)-hexyl-1-THP-pyrazole). ^{1}H-NMR (400MHz, $CDCl_3$): 5.83 (s, 1H, 4-*H*-pz), 2.56–2.60 (m, 4H, $CH_2(CH_2)_4CH_3$ and $CH_2(CH_2)_2CH_3$), 1.56–1.65 (m, 4H, CH_2CH_2 $(CH_2)_3CH_3$ and $CH_2CH_2CH_2CH_3$), 1.26–1.41 (m, 8H, $(CH_2)_2(CH_2)_3CH_3$ and $(CH_2)_2CH_2CH_3$), 0.91 (t, 3H, ^{2}J = 7.60 Hz $(CH_2)_3CH_3$), 0.86 (t, 3H, ^{2}J = 6.8 Hz $(CH_2)_5CH_3$). ^{13}C-NMR (101 MHz, $CDCl_3$): 149.5, 102.1, 31.7, 31.6, 29.4, 29.1, 27.2, 26.8, 22.7, 22.5, 14.1 and 13.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{25}N_2$ 209.2017; found 209.2023.

3(5)-butyl-5(3)-heptylpyrazole. Yield: 2.133 g (94% based on 3(5)-butyl-5(3)-heptyl-1-THP-pyrazole). ^{1}H-NMR (400MHz, $CDCl_3$): 5.84 (s, 1H, 4-*H*-pz), 2.55–2.60 (m, 4H, $CH_2(CH_2)_5CH_3$ and $CH_2(CH_2)_2CH_3$), 1.56–1.65 (m, 4H, $CH_2CH_2(CH_2)_3CH_3$ and $CH_2CH_2CH_2CH_3$), 1.26–1.42 (m, 10H, $(CH_2)_2(CH_2)_4CH_3$ and $(CH_2)_2CH_2CH_3$), 0.91 (t, 3H, ^{2}J = 7.20 Hz $(CH_2)_3CH_3$), 0.86 (t, 3H, ^{2}J = 6.8 Hz $(CH_2)_5CH_3$). ^{13}C-NMR (101 MHz, $CDCl_3$): 149.4, 102.0, 31.9, 31.6, 29.5, 29.4, 29.2, 27.2, 26.9, 22.7, 22.5, 14.2 and 13.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{27}N_2$ 223.2174; found 223.2197.

Computational method. The computations of resonance energies were performed with the general block-localized wavefunction (BLW) method, which is the simplest variant of ab initio valence bond (VB) theory.[9−12] In the BLW method, each block-localized orbital is expanded only in a subgroup of basis functions and orbitals of different blocks are non-orthogonal, and the wave function is expressed with a Slater determinant composed of doubly occupied orbitals.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/xxxxxx. ^{1}H, ^{13}C and ^{1}H−^{1}H COSY NMR spectra of all new compounds, computational data (PDF).

AUTHOR INFORMATION

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