# 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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S Supporting Information

ABSTRACT: N-Protected 3-alkylpyrazoles are easily deprotonated by ^nBuLi at the 5-position of the aromatic ring, while the 5-alkyl isomers are completely unreactive under the same conditions. Using computational analysis, we reveal that electron pair repulsion within the deprotonated anion is not the reason behind the lack of reactivity of 5-alkylpyrazoles. 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 presented.
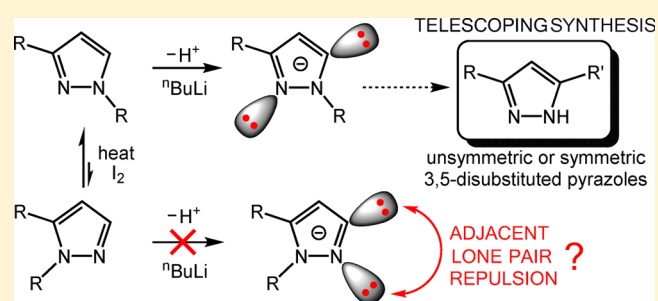
Pyrazole derivatives are employed in various applications, including a wide variety of pharmaceuticals, insecticides, fungicides, herbicides, and dyes.[1] Due to its ability to bridge metal centers together, the pyrazole moiety has also been exploited extensively for the construction of diverse multimetallic complexes such as macrocycles,[2] grids,[3] clusters,[4] nanocages,[5] and 3D frameworks.[6] Uses for 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 recently revealed that the preferred deprotonation of 3-methyl-1-R-pyrazole (R = N-protecting group) at an endocyclic carbon, rather than at the exocyclic methyl group, is due to a subtle combination of diminished π-conjugation, smaller bond angles, and strengthened induction of Csp^2 versus Csp^3. In comparison, the six-membered analogue, 3-methylpyridazine, 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 ^nBuLi at −78 °C, the 5-methyl-1-THP-pyrazole isomer is completely resistant to deprotonation under the same experimental conditions (Figure 1). Herein, we unveil that this intriguing property is not a result of the repulsion between the lone pairs of the deprotonated anion and the adjacent N atom as previously believed and commonly referred to as 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. Finally, we developed a convenient, one-pot, telescopic synthesis of unsymmetrical 3,5-dialkylpyrazoles.
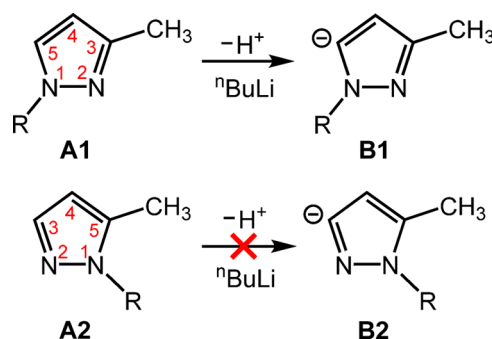
Figure 1. Deprotonation of 3-methyl-1-R-pyrazole (**A1**) and 5-methyl-1-R-pyrazole (**A2**) isomers. R = methyl (computations) or tetrahydropyran-2-yl (synthesis).

Because the aromatic rings of the 1,3-dimethylpyrazole (**A1**) and 1,5-dimethylpyrazole (**A2**) isomers, as well as those of their deprotonated products **B1** and **B2** (Figure 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.

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 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 decrease (2.2 kcal/mol) from the repulsion between the two lone pairs in **B2** to the repulsion between the single lone pair with the σ_{CN} bond in **B1** (Figure 2). This amount, however, is small and is correlated to the structural change, i.e., the CN bond in these two species.

$$RE = \left\langle \phi_i \phi_i \left| \frac{1}{r_1 - r_2} \right| \phi_j \phi_j \right\rangle \tag{1}$$
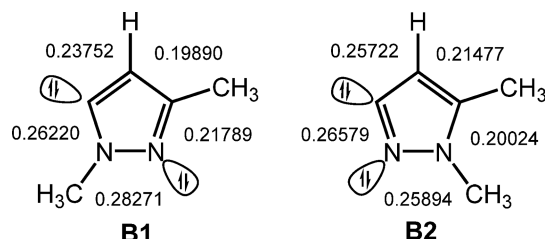
Figure 2. Adjacent pair−pair Coulomb interactions in **B1** and **B2** (a.u.).

This result prompts further investigation into the electron delocalization effect in these systems.[9−12] Table 1 compiles the

Table 1. Relative Energies of A2 vs A1 and B2 vs B1 in Addition to Their Inherent Electron Delocalization Energies (DEs) for σ- and π-Electrons (kcal/mol)[a]

	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

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

major results, where DE(total) is the energy change between a fully delocalized and a fully localized Lewis state (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 there is little change from **A** to **B** 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 is an H nucleus and a CH_3 group around the negatively charged carbon in **B1** but only a single H nucleus in **B2** (Figure 2). To verify our hypothesis, we examined the model system methylamine in different conformations as shown in Figure 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 deprotonation energy higher than that of **A4**, the difference is
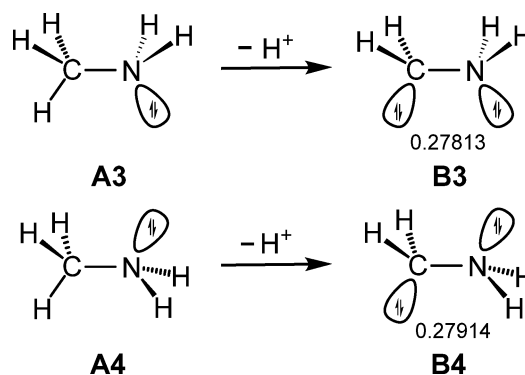

Figure 3. Deprotonation of eclipsed (**A3**) and staggered (**A4**) methylamine conformers with values of adjacent pair−pair Coulomb interactions shown for **B3** and **B4** (a.u.).

only 7.5 or 7.1 kcal/mol at the MP2 or HF level, 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 Figure 3), which was 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).

Because 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, due to the O atom's ability to 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 analogues that lack the stabilizing O atom (R = CH_3) also lead to the same conclusion. 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, which offers additional stability to the resulting anion **B1**.

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 (Figure 4). The solvent- and catalyst-free quantitative step of pyrazole protection and the solvent-free isomerization step of the unreactive 5-alkyl-1-THP-pyrazole to the reactive 3-alkyl-1-THP-pyrazole isomer are both crucial to the value of this method. 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). Because the one-pot method requires no purification of the intermediates, losses are eliminated and waste production is greatly diminished.

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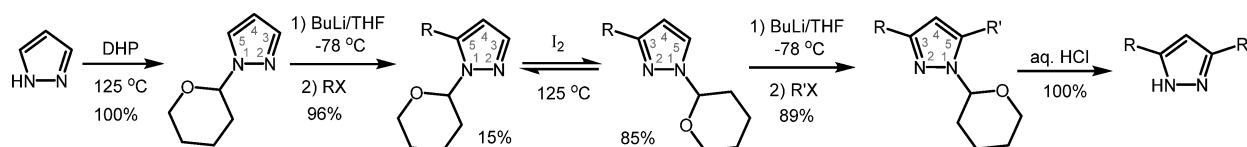
Figure 4. Telescoping synthesis of 3,5-dialkylpyrazoles from pyrazole (DHP = 3,4-dihydro-2H-pyran; R = n-hexyl or n-heptyl; R′ = n-butyl), with % conversions (based on ^{1}H NMR).

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 h, 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, and SEM-Cl, respectively.[18] The protecting agents listed above 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
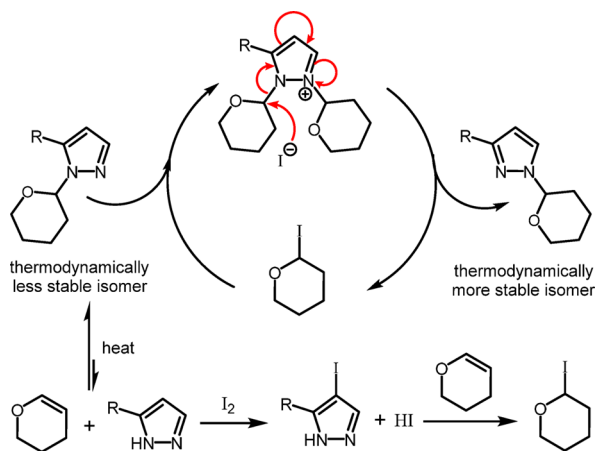
Figure 5. Proposed mechanism of the I$_2$-catalyzed thermal isomerization of 5-alkyl- to 3-alkyl-1-THP-pyrazoles (R = alkyl).

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.

Improved overall yields of 3,5-dialkylpyrazoles (60% based on 1H-pyrazole) are obtained if the THP-protected 3,5-dialkylpyrazoles are purified before deprotection, as column chromatographic separation on the protected pyrazoles is more efficient than on 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 rather the 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 to 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 and 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 1H-Pyrazole. THP protection of 1H-pyrazole is accomplished according to our green method previously described[16] by heating 1.200 g (17.62 mmol) of 1H-pyrazole and 2.00 mL (1.85 g, 22.0 mmol) of 3,4-dihydro-2H-pyran for 24 h at 125 °C. After removal of the slight excess of DHP in vacuum, 2.68 g (100%) of 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$_2$, and then anhydrous THF (40 mL) is added via an N$_2$-purged syringe. The solution is chilled to −78 °C and stirred for 30 min, and then the ^{n}BuLi solution (1.6 M in hexanes, 11.0 mL, 17.6 mmol) is added dropwise over 10 min. After the mixture is stirred at −78 °C for 30 min, 1-bromohexane (2.72 mL, 3.20 g, 19.3 mmol) is added, and the solution is stirred at −78 °C for 90 min and then allowed to warm to room temperature overnight under stirring. The flask is then connected to a vacuum (0.005 mmHg), and both the excess bromohexane and unreacted 1-THP-pyrazole are removed by gently heating the flask 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 h. After the mixture is cooled to room temperature, ^{1}H NMR of the product shows an isomeric mixture of 85 mol % 3-hexyl-1-THP-pyrazole and 15 mol % 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 min. nBuLi (1.6 M in hexanes, 10.0 mL, 16.0 mmol) is added dropwise over 10 min and stirred for 30 min, and then 1-bromobutane (1.90 mL, 2.42 g, 17.6 mmol) is added. After being stirred for 3 h at −78 °C, the solution is allowed to warm to room temperature overnight under stirring. One milliliter of 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 are added 200 mL of ethanol and 50 mL of HCl (37% in H_2O). After the mixture is stirred for 8 h (^{1}H NMR shows complete deprotection) the solvent is removed under vacuum. Five milliliters 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−d). The protected 3,5-dialkylpyrazoles are extracted from the crude residues obtained after quenching with water and removal of the THF (d), using 4 mL of water and three portions of 4 mL of diethyl ether (per millimole of substrate). The combined organic layers are washed with 60 mL of 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$_2$pyrazole, 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$_3$): δ 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*$_2$O−THP), 3.57−3.63 (m, 1H, *CH*$_2$O−THP), 2.53−2.67 (m, 4H, *CH*$_2$(CH$_2$)$_4$CH$_3$ and *CH*$_2$(CH$_2$)$_2$CH$_3$), 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$_2$*CH*$_2$(CH$_2$)$_3$CH$_3$ and *CH*$_2$CH$_2$CH$_2$CH$_3$), 1.20−1.44 (m, 8H, (CH$_2$)$_2$(*CH*$_2$)$_3$CH$_3$ and (CH$_2$)$_2$*CH*$_2$CH$_3$), 0.93 (t, 3H, ^2J = 7.32 Hz (CH$_2$)$_3$*CH*$_3$), 0.86 (t, 3H, ^2J = 6.6 Hz (CH$_2$)$_5$*CH*$_3$). ^{13}C NMR (101 MHz, CDCl$_3$): δ 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, 14.0. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for C$_{18}$H$_{32}$N$_2$NaO 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 (400 MHz, CDCl$_3$): δ 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*$_2$O−THP), 3.57−3.63 (m, 1H, *CH*$_2$O−THP), 2.53−2.67 (m, 4H, *CH*$_2$(CH$_2$)$_5$CH$_3$ and *CH*$_2$(CH$_2$)$_2$CH$_3$), 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$_2$*CH*$_2$(CH$_2$)$_4$CH$_3$

and CH$_2$*CH*$_2$CH$_2$CH$_3$), 1.21−1.44 (m, 10H, (CH$_2$)$_2$(*CH*$_2$)$_4$CH$_3$ and (CH$_2$)$_2$*CH*$_2$CH$_3$), 0.93 (t, 3H, ^2J = 7.6 Hz (CH$_2$)$_3$*CH*$_3$), 0.85 (t, 3H, ^2J = 6.8 Hz, (CH$_2$)$_5$*CH*$_3$). ^{13}C NMR (101 MHz, CDCl$_3$): δ 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, 14.0. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for C$_{19}$H$_{34}$N$_2$NaO 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 of ethanol and 2 mL of HCl (37% in H_2O) per mmol of substrate for 8 h. After removal of the solvent, addition of 0.4 mL of H_2O, neutralization and extraction with 3 × 6 mL of diethyl ether (per millimole of 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 (400 MHz, CDCl$_3$): δ 5.83 (s, 1H, 4-*H*-pz), 2.56−2.60 (m, 4H, *CH*$_2$(CH$_2$)$_4$CH$_3$ and *CH*$_2$(CH$_2$)$_2$CH$_3$), 1.56−1.65 (m, 4H, *CH*$_2$CH$_2$(CH$_2$)$_3$CH$_3$ and *CH*$_2$CH$_2$CH$_2$CH$_3$), 1.26−1.41 (m, 8H, (CH$_2$)$_2$(*CH*$_2$)$_3$CH$_3$ and (CH$_2$)$_2$*CH*$_2$CH$_3$), 0.91 (t, 3H, ^2J = 7.60 Hz, (CH$_2$)$_3$*CH*$_3$), 0.86 (t, 3H, ^2J = 6.8 Hz, (CH$_2$)$_5$*CH*$_3$). ^{13}C NMR (101 MHz, CDCl$_3$): δ 149.5, 102.1, 31.7, 31.6, 29.4, 29.1, 27.2, 26.8, 22.7, 22.5, 14.1, 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 (400 MHz, CDCl$_3$): δ 5.84 (s, 1H, 4-*H*-pz), 2.55−2.60 (m, 4H, *CH*$_2$(CH$_2$)$_5$CH$_3$ and *CH*$_2$(CH$_2$)$_2$CH$_3$), 1.56−1.65 (m, 4H, *CH*$_2$CH$_2$(CH$_2$)$_3$CH$_3$ and *CH*$_2$CH$_2$CH$_2$CH$_3$), 1.26−1.42 (m, 10H, (CH$_2$)$_2$(*CH*$_2$)$_4$CH$_3$ and (CH$_2$)$_2$*CH*$_2$CH$_3$), 0.91 (t, 3H, ^2J = 7.20 Hz, (CH$_2$)$_3$*CH*$_3$), 0.86 (t, 3H, ^2J = 6.8 Hz, (CH$_2$)$_5$*CH*$_3$). ^{13}C NMR (101 MHz, CDCl$_3$): δ 149.4, 102.0, 31.9, 31.6, 29.5, 29.4, 29.2, 27.2, 26.9, 22.7, 22.5, 14.2, 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 wave function (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 nonorthogonal, 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/acs.joc.5b02746.

^{1}H, ^{13}C, and ^{1}H−^{1}H COSY NMR spectra of all new compounds and computational data (PDF)

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Notes
The authors declare no competing financial interest.

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■ REFERENCES

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