Supporting information for

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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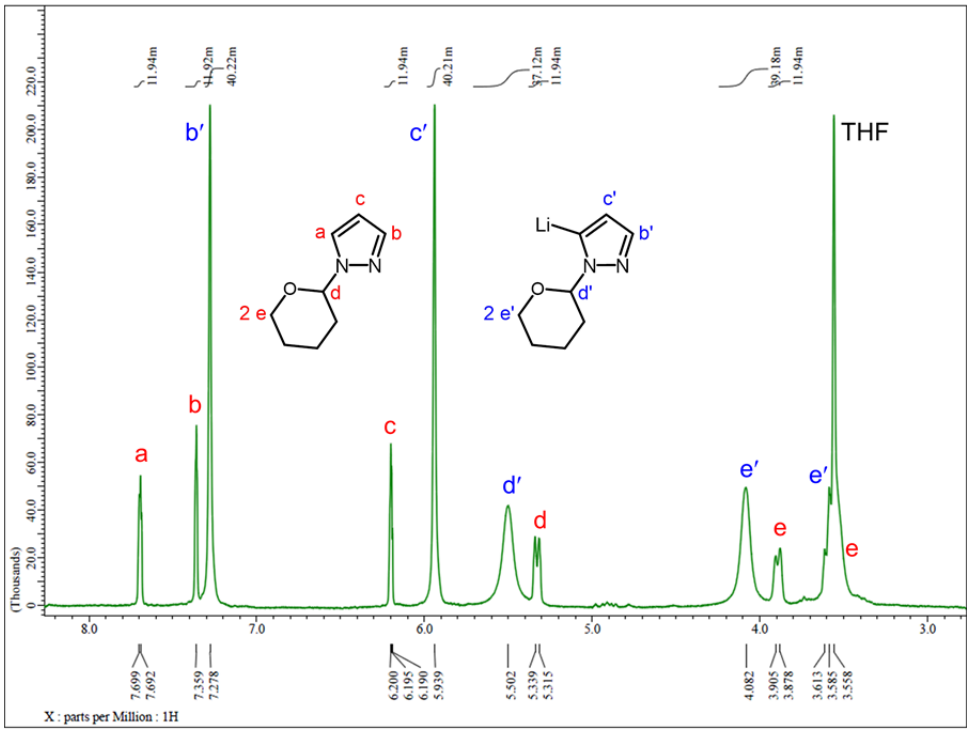

Figure S1. ^{1}H NMR spectrum of 1-(tetrahydropyran-2-yl)pyrazole in THF-d_8 at –55 °C, immediately after a substoichiometric amount of ^{n}BuLi (1.6 M in hexanes) was added. Peaks of both the protonated (red) and deprotonated (blue) species are observed. The spectrum is stable over time (1 hour).

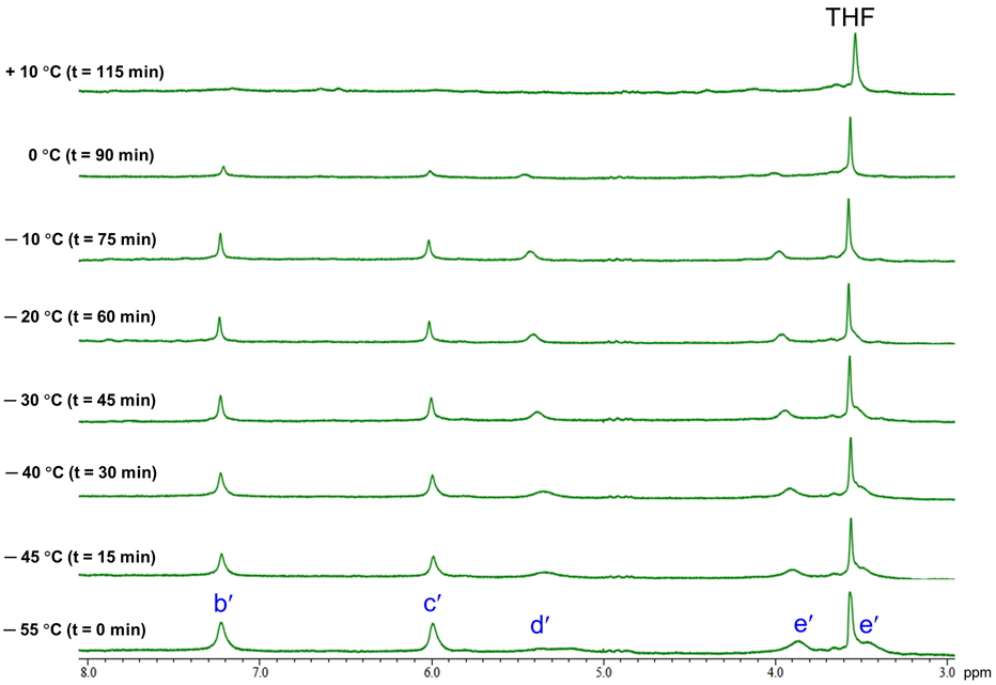

Figure S2. Variable-temperature ^{1}H NMR spectra of 1-(tetrahydropyran-2-yl)pyrazole in THF-d_8, with a slight excess of ^{n}BuLi (1.6 M in hexanes) added (t = 0 is immediately after addition of ^{n}BuLi). No shifts are observed as time passes or as the temperature increases; however, decomposition occurs above ~0 °C, and an off-white precipitate falls out of the solution.

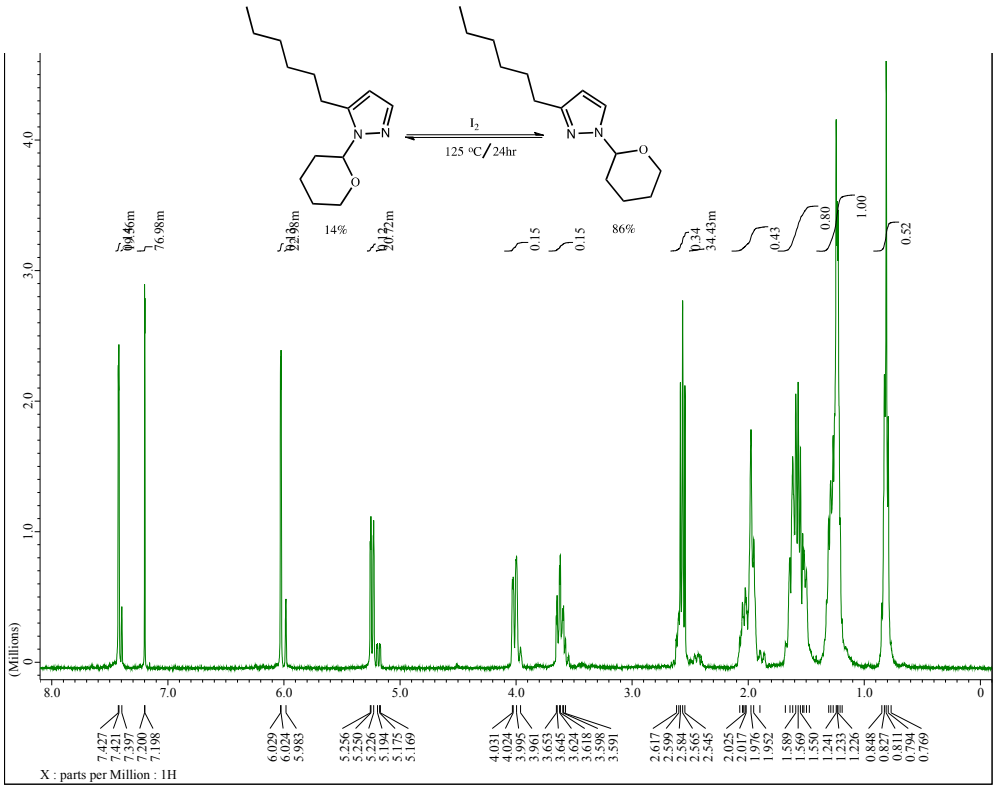

Figure S3. ^{1}H NMR spectrum of the isomer mixture at equilibrium, containing 5-hexyl-1-(tetrahydropyran-2-yl)pyrazole (15%) and 3-hexyl-1-(tetrahydropyran-2-yl)pyrazole (85%).

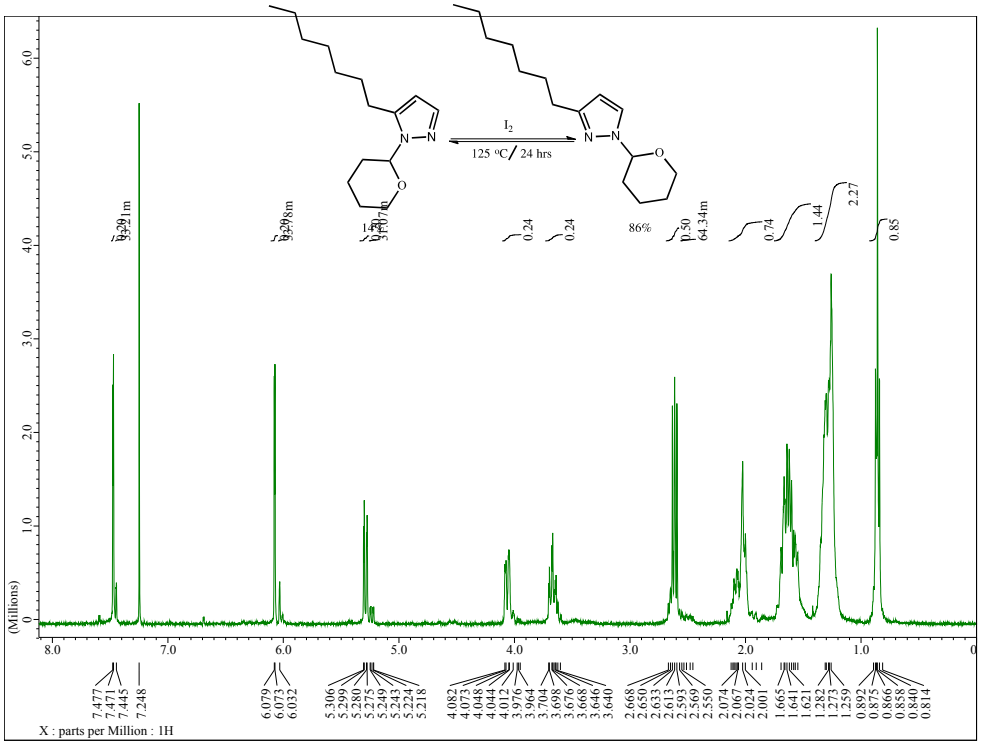

Figure S4. ^{1}H NMR spectrum of the isomer mixture at equilibrium, containing 5-heptyl-1-(tetrahydropyran-2-yl)pyrazole (15%) and 3-heptyl-1-(tetrahydropyran-2-yl)pyrazole (85%).

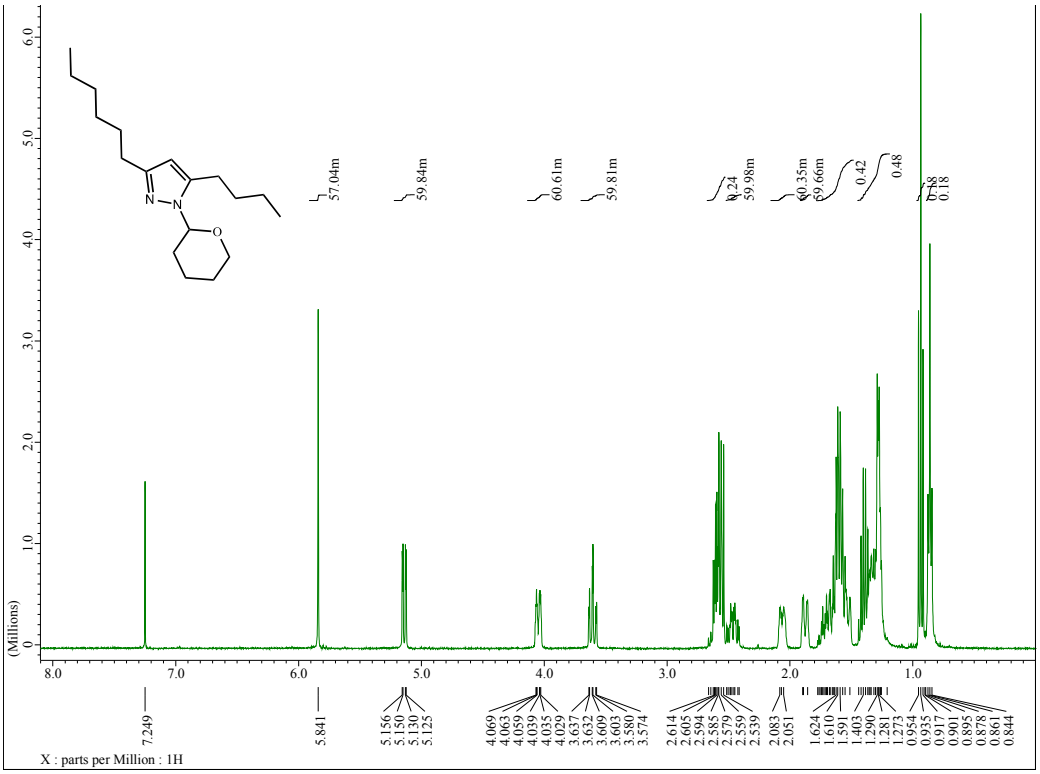

Figure S5. ^{1}H NMR spectrum of 5-butyl-3-hexyl-1-(tetrahydropyran-2-yl)pyrazole.

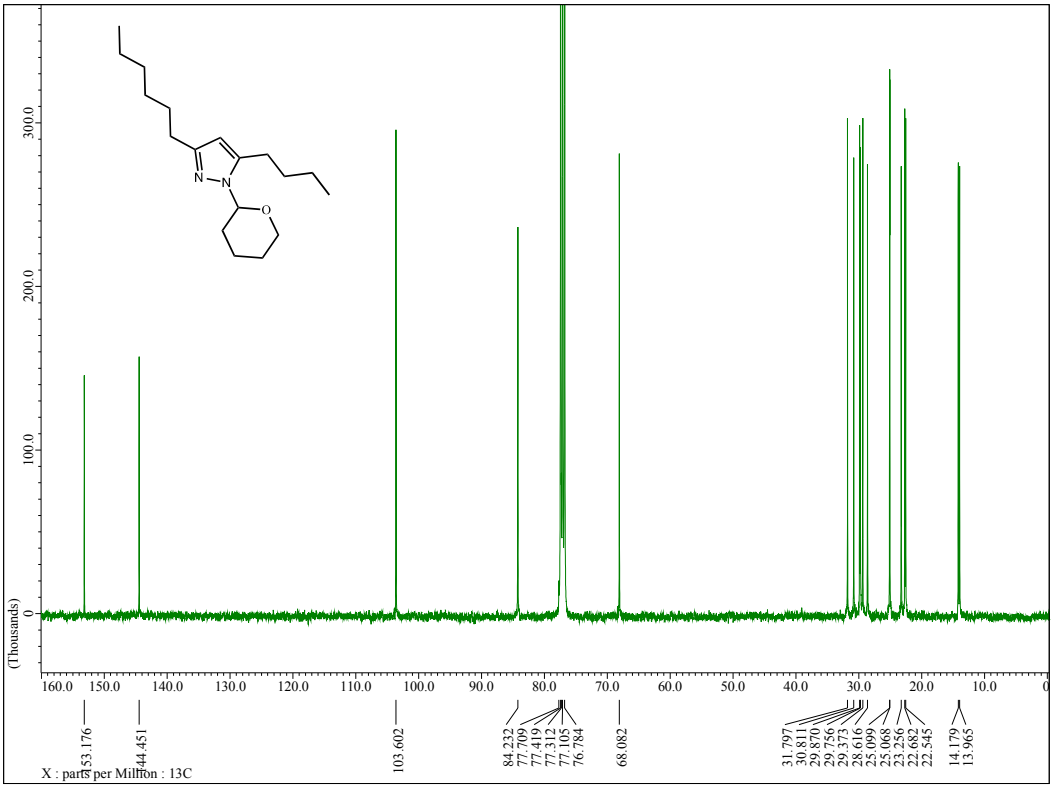

Figure S6. ^{13}C NMR spectrum of 5-butyl-3-hexyl-1-(tetrahydropyran-2-yl)pyrazole.

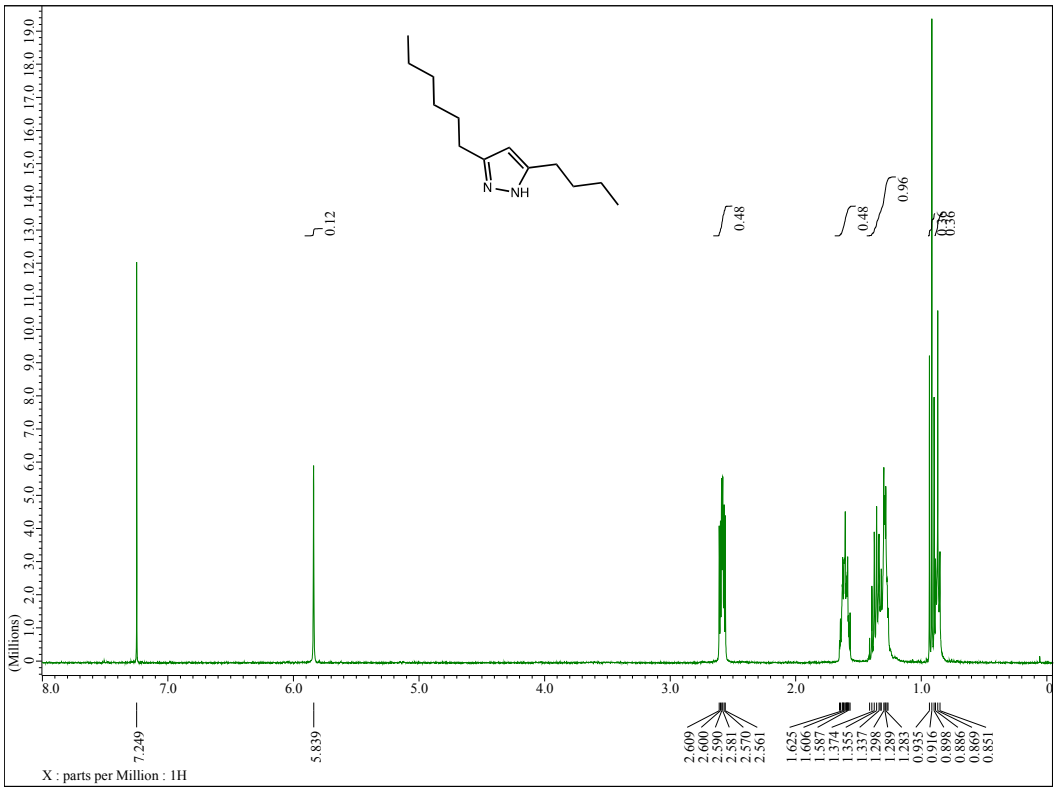

Figure S7. ^{1}H NMR spectrum of 3(5)-butyl-5(3)-hexylpyrazole.

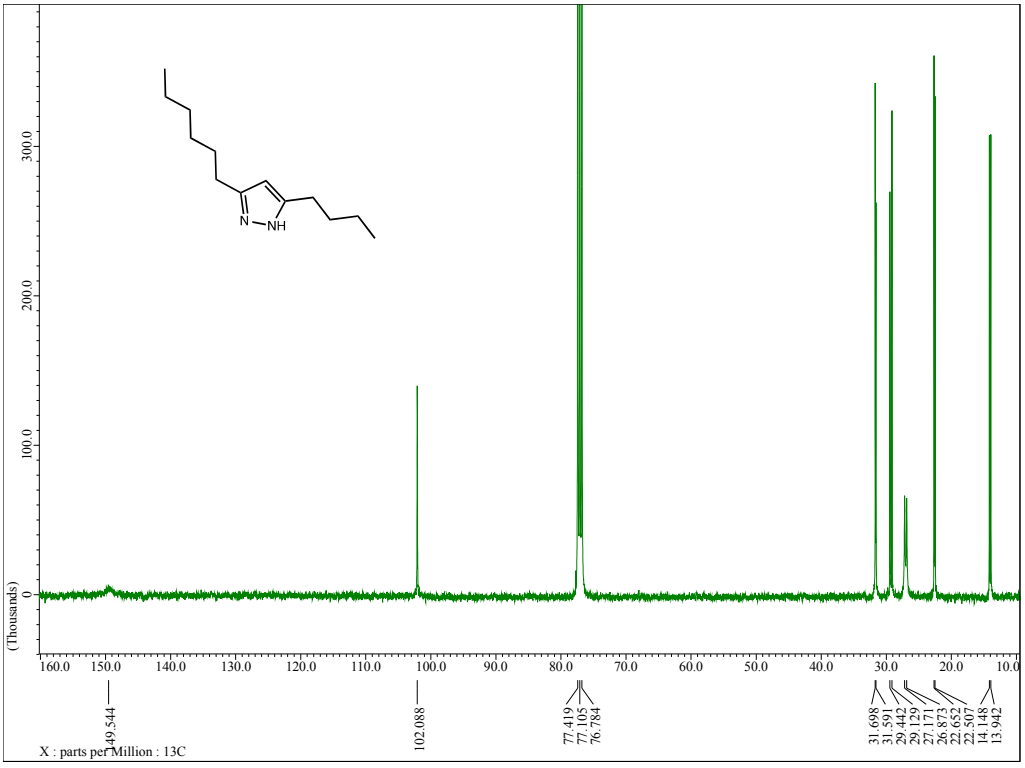

Figure S8. ^{13}C NMR spectrum of 3(5)-butyl-5(3)-hexylpyrazole.

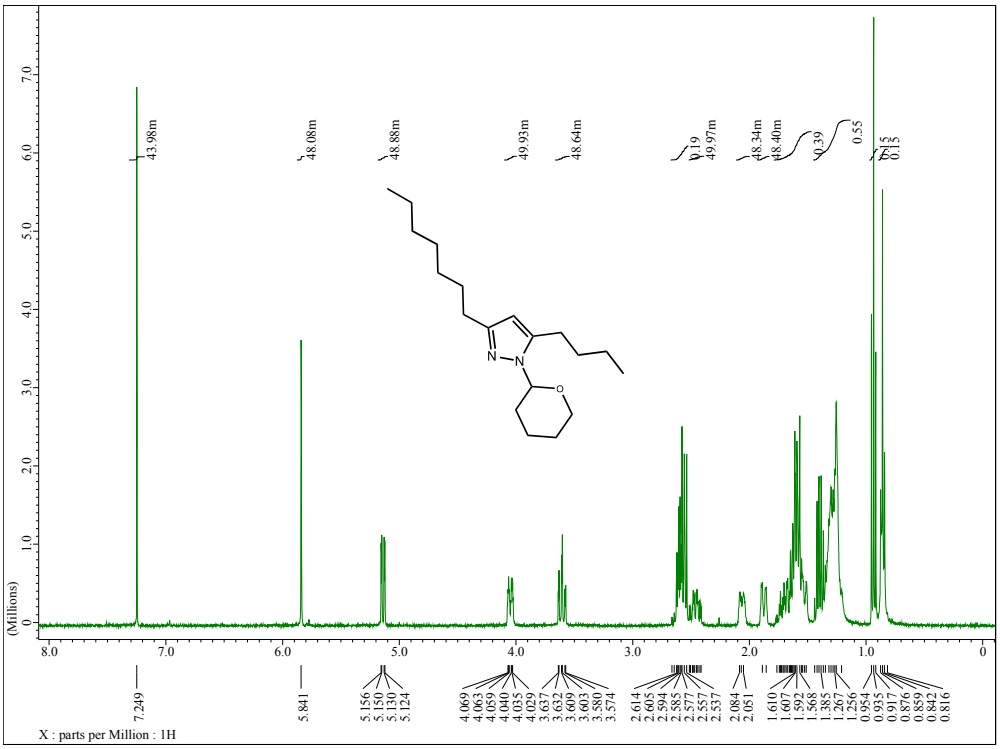

Figure S9. ^{1}H NMR spectrum of 5-butyl-3-heptyl-1-(tetrahydropyran-2-yl)pyrazole.

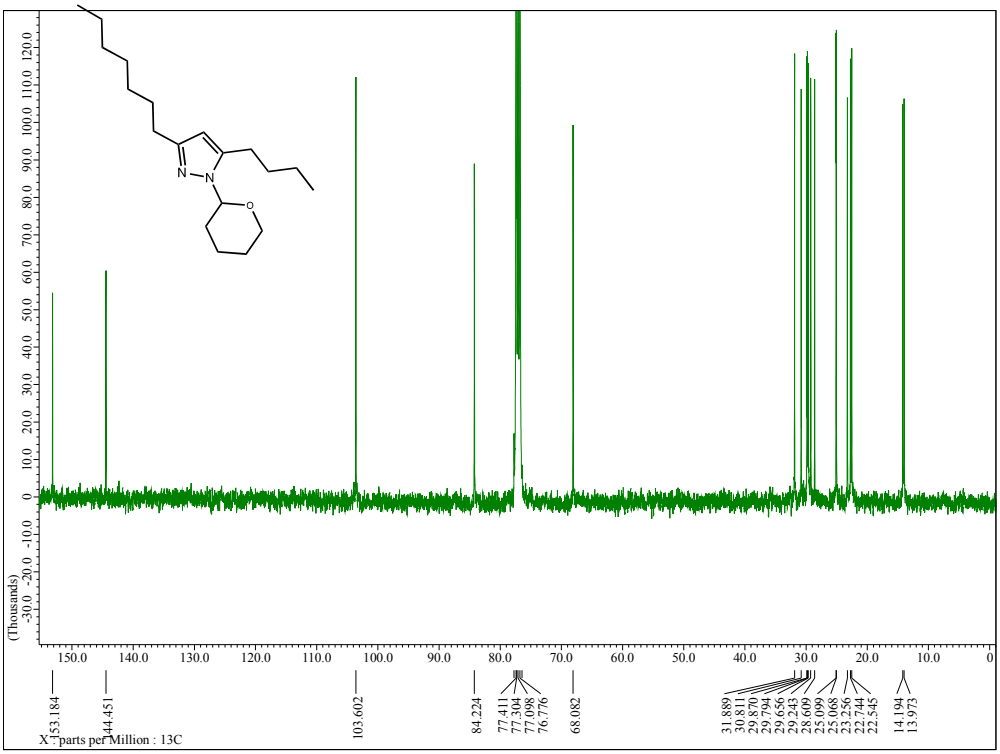

Figure S10. ^{13}C NMR spectrum of 5-butyl-3-hexyl-1-(tetrahydropyran-2-yl)pyrazole.

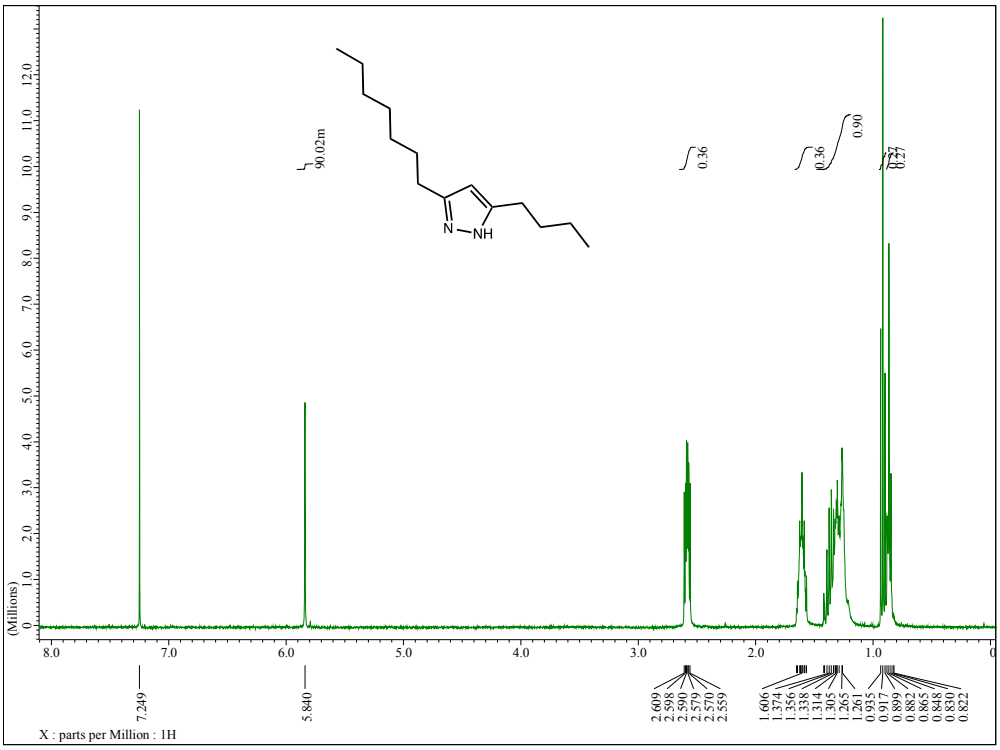

Figure S11. ^{1}H NMR spectrum of 3(5)-butyl-5(3)-heptylpyrazole.

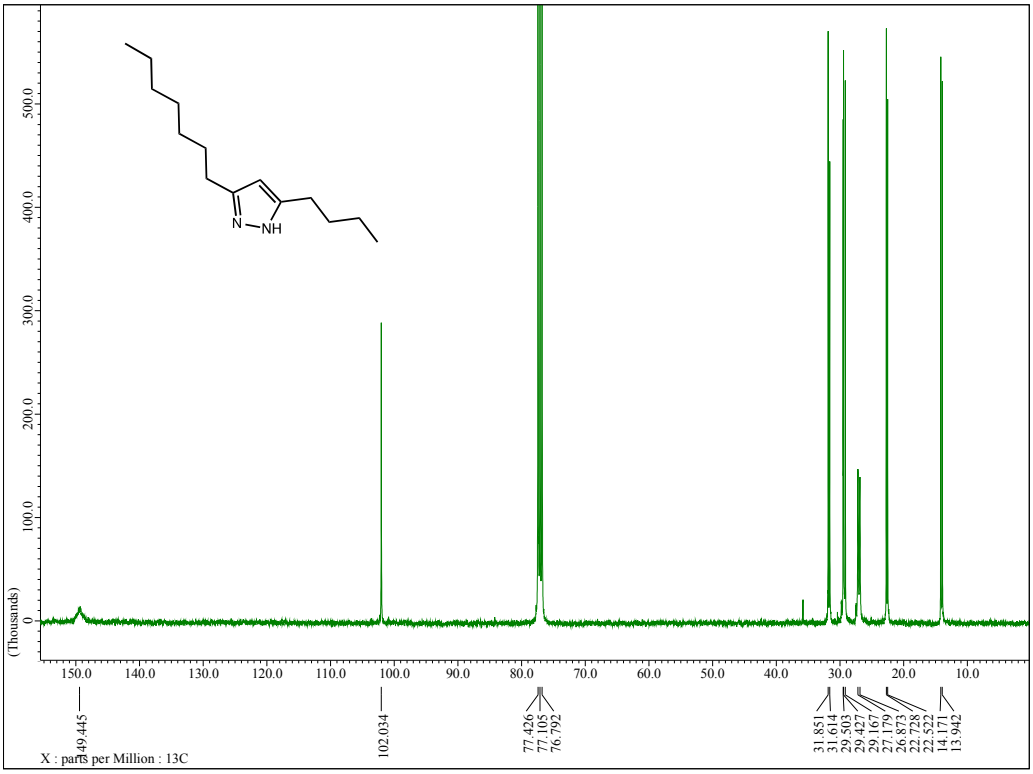

Figure S12. ^{13}C NMR spectrum of 3(5)-butyl-5(3)-heptylpyrazole.

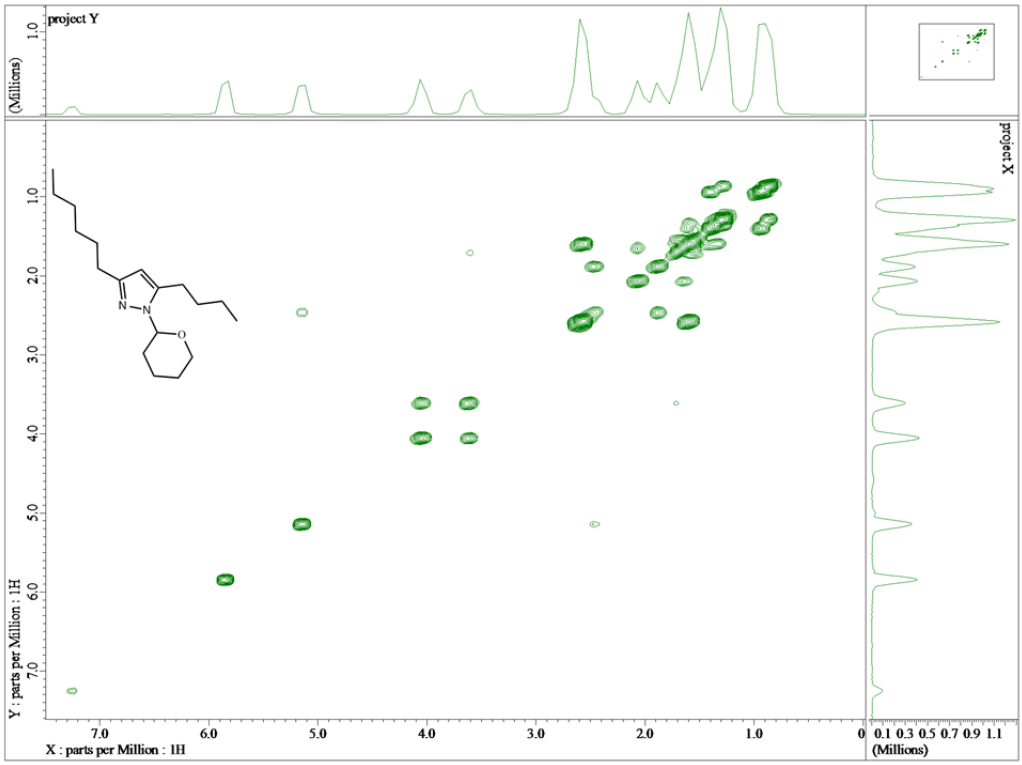

Figure S13. $^{1}H-^{1}H$ COSY spectrum of 5-butyl-3-hexyl-1-(tetrahydropyran-2-yl)pyrazole.

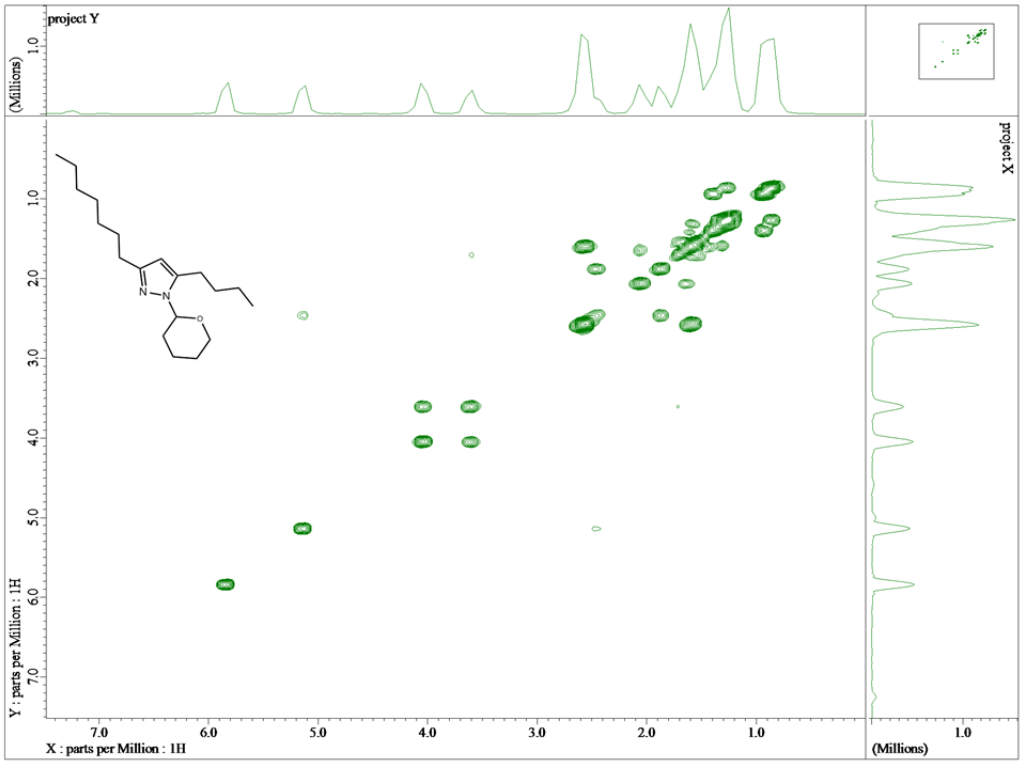

Figure S14. $^{1}H-^{1}H$ COSY spectrum of 5-butyl-3-heptyl-1-(tetrahydropyran-2-yl)pyrazole.

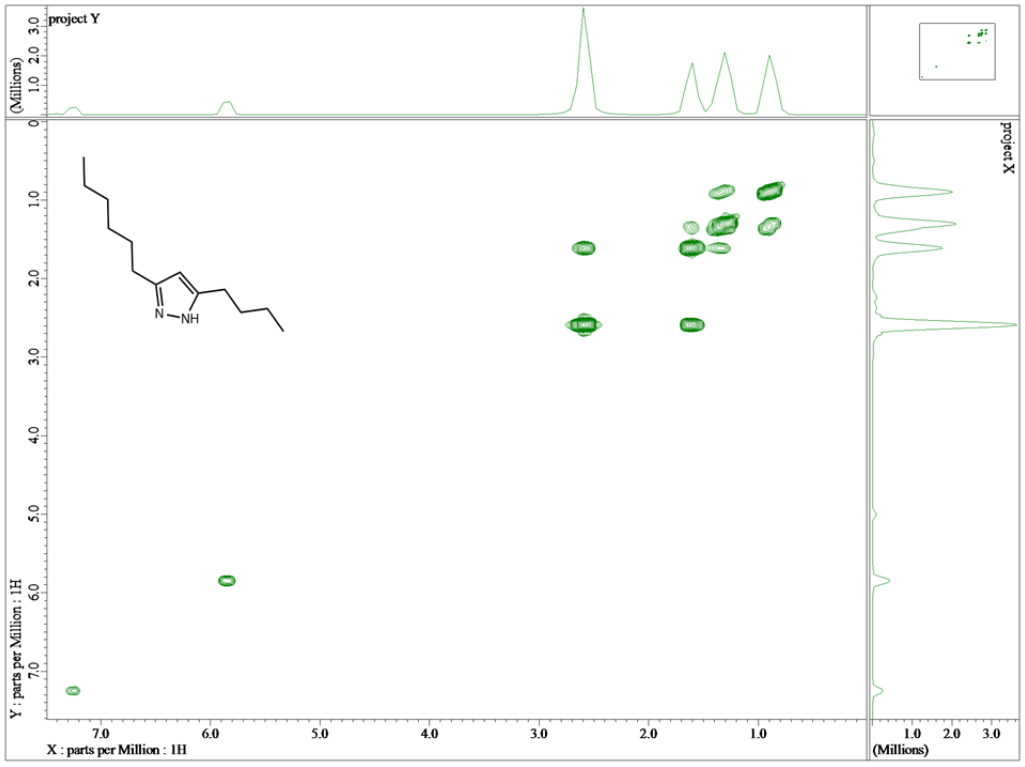

Figure S15. $^{1}H-^{1}H$ COSY spectrum of 3(5)-butyl-5(3)-hexylpyrazole.

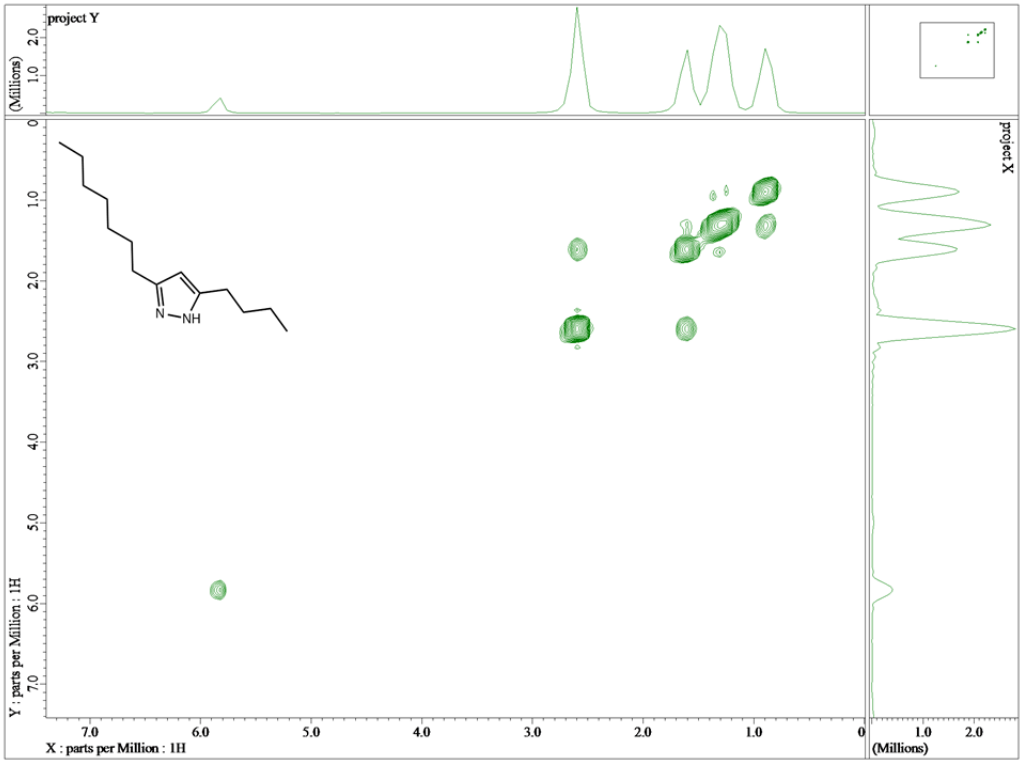

Figure S16. $^{1}H-^{1}H$ COSY spectrum of 3(5)-butyl-5(3)-heptylpyrazole.

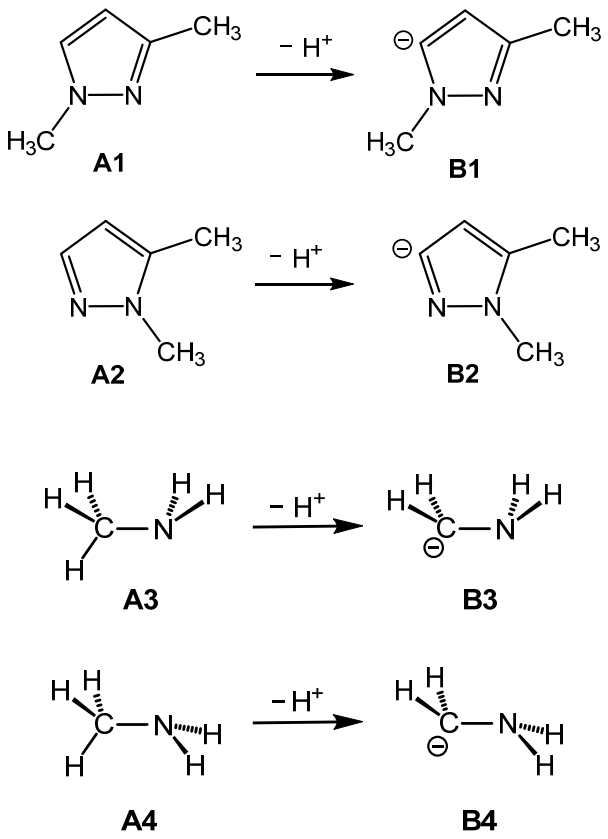

Table S1. Energies at different levels and the 6-311+G** basis set used in all calculations.[a]

	A1	**A2**	**B1**	**B2**
E(MP2)(a.u.)	-304.018015	-304.017822	-303.390466	-303.361447
E(HF)(a.u.)	-302.940334	-302.939024	-302.304423	-302.270113
$E_{\text{localized orbitals}}$(a.u.)	-302.716636	-302.716400	-302.078343	-302.064645
DE(total) (kcal/mol)	140.37	139.70	141.87	128.93
$E_{\text{only localized } \sigma \text{ orbitals}}$ (a.u.)	-302.881972	-302.880529	-302.240829	-302.204932
DE(σ) (kcal/mol)	36.62	36.71	39.91	40.90
$E_{\text{only localized } \pi\text{-orbitals}}$ (a.u.)	-302.773068	-302.772879	-302.140491	-302.129268
DE(π)(kcal/mol)	104.96	104.26	102.87	88.38

a. $DE(\text{total}) = E_{\text{localized orbitals}} - E(HF)$
$DE(\sigma) = E_{\text{only localized } \sigma \text{ orbitals}} - E(HF)$
$DE(\pi) = E_{\text{only localized } \pi\text{-orbitals}} - E(HF)$

	A3	B3	A4	B4
E(MP2)(a.u.)	-95.59350	-94.90120	-95.58843	-94.90814
E(HF)(a.u.)	-95.24218	-94.53641	-95.23805	-94.54357
$E_{\text{localized orbitals}}$(a.u.)	-95.21299	-94.49886	-95.20852	-94.50196
DE(total) (kcal/mol)	18.32	23.56	18.53	26.11

Cartesian Coordinates for A1−B4, where the aromatic rings in **A1**, **A2**, **B1** and **B2** were restrained to a plane

A1

N	0.024280	-0.885970	0.000000
N	-1.047906	-0.077087	0.000000
C	-2.378002	-0.657569	0.000000
H	-2.515787	-1.263886	-0.897325
H	-2.506521	-1.280877	0.886878
H	-3.107263	0.153966	0.011552
C	-0.713043	1.243353	0.000000
H	-1.468543	2.016788	0.000000
C	0.676792	1.292783	0.000000
H	1.295678	2.178924	0.000000
C	1.092719	-0.055907	0.000000
C	2.481243	-0.617257	0.000000
H	3.098476	-0.133009	-0.762287
H	2.968606	-0.474527	0.969848
H	2.442476	-1.688397	-0.210995

B1

N	-0.009388	-0.871732	0.000000
N	-1.061024	-0.003400	0.000000
C	-2.382785	-0.586920	0.000000
H	-2.536394	-1.201754	-0.895566
H	-2.527050	-1.218309	0.885568
H	-3.095534	0.238228	0.011130
C	-0.784131	1.351414	0.000000
C	0.636424	1.303533	0.000000
H	1.293837	2.169208	0.000000
C	1.062405	-0.044648	0.000000

C	2.451970	-0.616913	0.000000
H	3.151764	0.073962	-0.484821
H	2.826791	-0.806367	1.015875
H	2.476168	-1.567838	-0.544062

A2

N	-0.127034	0.649912	0.000000
C	-1.181678	1.647413	0.000000
H	-1.949452	1.373442	-0.726507
H	-1.633073	1.738065	0.992905
H	-0.726741	2.595845	-0.282484
N	1.160197	1.044747	0.000000
C	1.862504	-0.107653	0.000000
H	2.943225	-0.066362	0.000000
C	1.013343	-1.229886	0.000000
H	1.285191	-2.276056	0.000000
C	-0.279233	-0.708490	0.000000
C	-1.622158	-1.365877	0.000000
H	-1.496758	-2.446619	0.094836
H	-2.239476	-1.023314	0.837416
H	-2.171724	-1.170661	-0.927697

B2

N	-0.067086	0.650425	0.000000
C	-1.068297	1.682810	0.000000
H	-1.709414	1.630648	-0.891597
H	-1.708441	1.631712	0.892372
H	-0.530773	2.633709	-0.000851
N	1.279995	0.973880	0.000000
C	1.999590	-0.191496	0.000000
C	1.018359	-1.250518	0.000000
H	1.223675	-2.318629	0.000000
C	-0.266808	-0.700979	0.000000
C	-1.640886	-1.297091	0.000000
H	-1.563680	-2.389340	-0.000332
H	-2.226627	-1.007565	0.885279
H	-2.226853	-1.007027	-0.884948

A3

C	0.00694806	0.00000000	-0.00120308
H	-0.37413559	0.00000000	1.02353927
H	-0.39741627	-0.88106330	-0.50727818

H	-0.39741627	0.88106330	-0.50727818
N	1.47821411	0.00000000	0.00091898
H	1.84523633	-0.81346517	-0.47575394
H	1.84523633	0.81346517	-0.47575394

B3

C	-0.73709148	0.01079310	0.00000000
H	-1.14667164	-0.48505563	0.89988094
H	-1.14667164	-0.48505563	-0.89988094
N	0.73038365	-0.01893540	0.00000000
H	1.29991836	-0.85550478	0.00000000
H	1.24325419	0.84176438	0.00000000
H	1.24627503	0.85339743	0.00000000

A4

C	-0.71254270	-0.00344398	0.00000000
H	-1.06335420	1.03064667	0.00000000
H	-1.13557121	-0.48929203	0.88787920
H	-1.13557121	-0.48929203	-0.88787920
N	0.72884633	-0.00248868	0.00000000
H	1.24691795	-0.85952738	0.00000000
H	1.24627503	0.85339743	0.00000000

B4

C	0.00000000	-0.04038983	0.04853971
H	-0.88473638	-0.38501139	-0.52700808
H	0.88473638	-0.38501139	-0.52700808
N	0.00000000	1.49936547	0.04297616
H	-0.79950845	1.83719025	-0.49455721
H	0.79950845	1.83719025	-0.49455721

Cartesian Coordinates for A1−B2, where the aromatic rings were NOT restrained to a plane

A1

N	-0.024738	-0.886590	-0.017514
N	1.047798	-0.077870	-0.048878
C	2.376392	-0.656684	0.029655
H	2.589827	-0.985912	1.049639
H	2.425335	-1.509620	-0.647935
H	3.103188	0.098710	-0.273874
C	0.714206	1.242555	-0.014861

H	1.470303	2.015450	-0.021845
C	-0.675219	1.292523	0.019967
H	-1.294002	2.178666	0.035539
C	-1.091959	-0.055925	0.017183
C	-2.480984	-0.615528	0.002348
H	-3.134048	-0.054366	0.676668
H	-2.915293	-0.573489	-1.001811
H	-0.024738	-0.886590	-0.017514

B1

N	-0.008595	-0.872181	0.009211
N	-1.060564	-0.004215	0.046681
C	-2.381140	-0.586582	-0.022483
H	-2.583785	-0.991697	-1.022757
H	-2.471802	-1.398198	0.708294
H	-3.096428	0.206163	0.199570
C	-0.784781	1.350703	0.018003
C	0.635064	1.303797	-0.016292
H	1.291774	2.169781	-0.038224
C	1.061895	-0.044450	-0.026207
C	2.451141	-0.615775	0.003390
H	3.154552	0.051713	-0.509012
H	2.819544	-0.758109	1.028705
H	2.477177	-1.591040	-0.496291

A2

N	0.122520	0.651012	-0.046912
C	1.163484	1.659363	0.031568
H	1.492069	1.798932	1.065756
H	2.013004	1.358240	-0.584729
H	0.744423	2.590660	-0.347989
N	-1.167835	1.035215	-0.022978
C	-1.860254	-0.122358	0.010678
H	-2.941320	-0.090328	0.016185
C	-1.001398	-1.237429	0.024326
H	-1.264230	-2.285722	0.043792
C	0.286511	-0.705716	-0.002998
C	1.633313	-1.355542	-0.009334
H	1.513376	-2.436593	0.089224
H	2.175168	-1.160772	-0.941438
H	2.254777	-1.007914	0.822984

B2

N	0.028800	0.653416	-0.142878
C	0.940937	1.742815	0.091584
H	1.175632	1.858072	1.160972
H	1.877321	1.591204	-0.458856
H	0.455996	2.656161	-0.260787
N	-1.336779	0.890955	-0.066752
C	-1.979282	-0.312287	0.033833
C	-0.927998	-1.306155	0.075607
H	-1.063556	-2.383342	0.143211
C	0.315382	-0.679023	-0.006670
C	1.721809	-1.195033	-0.029868
H	1.710106	-2.284753	0.076912
H	2.241437	-0.960786	-0.970356
H	2.333827	-0.789050	0.789397