

Attractive Steric Interactions within Molecules. The Masking of Effects in *meta*-Disubstituted Benzenes by Buttressed Repulsive Interactions

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The attractive steric interaction between the groups in a sidechain to a benzene ring and a *meta*-substituent is usually more than offset by the repulsive interaction of the sidechain with the *ortho*-hydrogen atom which is buttressed by the *meta*-substituent.

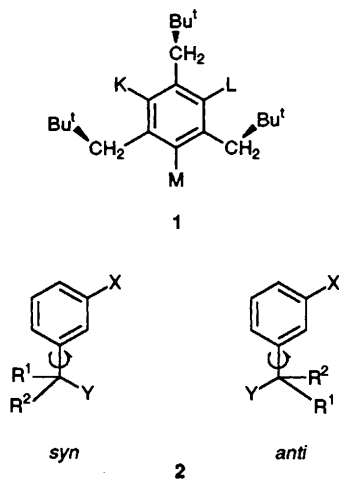
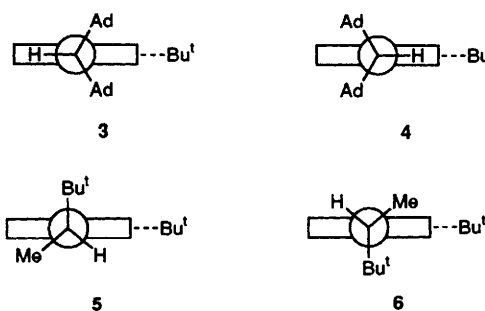
It is reasonable to hope to quantify van der Waals attractive forces within molecules by adapting the conformational equilibrium technique so widely used to study steric repulsions. A few such conformational equilibria have been convincingly shown¹⁻³ to be determined by attractive forces present in one conformation but much reduced in the other. For example, in trineopentylbenzene derivatives **1**, where sidechain rotation can be stopped on the NMR timescale,^{1a} the conformation shown, with three *tert*-butyl groups on the same side of the ring plane, is more stable than that with one group on the opposite side of the plane, reflecting the mutual attraction of these groups. Molecular mechanics calculations bear out these experimental observations.^{1b}

Other examples that exploit conformational equilibria, usually involving attraction between alkyl groups so as to minimise electrostatic effects, have been reviewed.³ Such studies assume that repulsive forces do not differ significantly between the two conformations; we now report an investigation that reveals shortcomings of this approach.

Rotation of a phenyl group about the sp²-sp³ bond to a sidechain has been studied in a considerable variety of phenyl alkanes and alkanols,⁴⁻⁶ since conformer interconversion is slow on the NMR timescale at easily accessible temperatures. If degeneracy is lifted by means of a *meta*-substituent (see **2**) then the compact *anti* conformation with more sidechain

atoms near the *meta*-substituent should be of lower energy, because the two groups *meta* to each other are in the region of van der Waals attraction. Thus for **2d** which is expected⁵ to adopt conformations with the benzylic hydrogen near the plane of the ring, **3** should be preferred over **4**. For **2h** which is expected⁴ to adopt conformations **5** and **6** with the *tert*-alkyl group nearly perpendicular to the ring plane, **6** ought to be the more stable.

These intuitive deductions are quantified (see Table 1) by molecular mechanics calculations for **2a-h** using two force fields MMP2⁷ and MM3,⁸ which differ in their treatment of van der Waals interactions.^{8b} The more compact *anti* conformation is invariably suggested to be the more stable, by up to several hundred J mol⁻¹ depending on the number of atoms.



- a** R¹ = R² = Ad Y = OH X = Me
b R¹ = R² = Ad Y = OH X = Bu^t
c R¹ = R² = Ad Y = H X = Me
d R¹ = R² = Ad Y = H X = Bu^t
e R¹, R² = *ax*Cx Y = H X = Bu^t
f R¹, R² = *ag*Cx Y = OH X = Bu^t
g R¹, R² = *ag*Cx Y = H X = Bu^t
h R¹ = Me R² = Bu^t, Me Y = H X = Bu^t

Ad = 1-adamantyl.
 Cx = *ag*2, *ag*6-dimethylcyclohexyl.
 Prefix to Cx indicates phenyl group orientation.

Table 1 Calculation (molecular mechanics steric energies) and direct NMR measurement of the energy differences [kcal mol⁻¹ (1 cal = 4.184 J)] for conformational equilibria *2-anti* ⇌ *2-syn*^a

Compound	Force Field	<i>anti</i>	<i>syn</i>	Difference ^a
2a	MMP2	54.98	55.17	0.19
	MM3	71.86	71.95	0.09
2b	Experimental	(85–150 °C)		-0.20
	MMP2	58.60	59.74	1.14
2c	MM3	73.29	73.97	0.68
	Experimental	(85–150 °C)		0.33
2d	MMP2	45.47	45.62	0.15
	MM3	64.10	64.22	0.12
2e	Experimental	(100–130 °C)		-0.15
	MMP2	49.31	50.06	0.75
2f	MM3	65.63	66.04	0.41
	Experimental	(100–150 °C)		0.16
2g	MMP2	14.14	14.67	0.53
	MM3	22.12	22.43	0.31
2h	Experimental	(-100 °C)		-0.12
	MMP2	14.47	14.69	0.22
2i	MM3	21.81	21.99	0.18
	Experimental	(-40 °C)		-0.15
2j	MMP2	9.89	10.03	0.14
	MM3	17.15	17.25	0.10
2k	Experimental	(-50 °C)		-0.12
	MMP2	9.12	9.27	0.15
2l	MM3	16.26	16.37	0.11
	Experimental	(-110 °C)		-0.20

^a +ve means that *2-anti*, with α-H or α-OH *anti* to the *meta* substituent, is favoured.

Compounds **2a-h** have been synthesised.^{4,5,9-11} Compounds **2a-d** were equilibrated in CDCl₃ solution at temperatures around 100 °C then quenched to room temp. for ¹H NMR measurements.¹¹ For the other compounds rotation was slow on the NMR timescale at the low temperatures indicated, when separate signals the intensities of which could be measured directly were obtained. Signal assignment is based on known substitution effects on chemical shift or on observation of NOE effects at *ortho*-protons when the benzylic proton is irradiated.¹¹

In all but two instances it is found that in the more stable rotamer, the bulk of the sidechain CR¹R²Y is distant from the attracting *meta* substituent, and even when, for **2b** and **2d**, the compact conformation is more stable, the preference is smaller than calculated.

These observations cast doubt on the assumption that repulsive interactions are the same on both sides of the conformational equilibrium. Groups R are most obviously repelled by the two *ortho* hydrogen atoms, and one of these is buttressed by the *meta*-substituent. This effect disfavors the compact conformations **4** and **6**, and the present results imply that buttressing more than compensates for attractive interactions in all but two cases **2b** and **2d**.

This result contrasts with the earlier success in finding equilibria predicted and experimentally shown to be determined by attractive forces,¹⁻³ but in all previous cases the two attracting groups were separated by clear space. Here, the intervening hydrogen at position 2 of the benzene ring, serving as a relay, appears to produce a repulsion between groups known to be attracting. To have this effect the hydrogen must necessarily repel both groups. Buttressing is not a new phenomenon,¹² but we show here its consequences in a relatively new kind of conformational investigation. Thus, when weak attractive forces between two groups potentially determine the position of an equilibrium, weak buttressing interactions that would normally be deemed insignificant may countervail.

The present failure of molecular mechanics calculations, albeit small in absolute magnitude, shows either that both force fields overestimate attractive interactions or that they underestimate the buttressing, due possibly to small errors in parametrisation of benzene ring distortion. It is noteworthy that MM3 performs better than MMP2 particularly when the *meta*-substituent is *tert*-butyl. Any experimental observations which set two small effects against each other are a substantial

test for parametrisation derived from rather stronger steric interactions. A larger set of experimental results highlighting such a conflict of attractive and buttressing interactions may lead to a judicious modification of force fields.

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