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Establishment of Steric Substituent Constants in the Adamantane System by ab Initio Calculations

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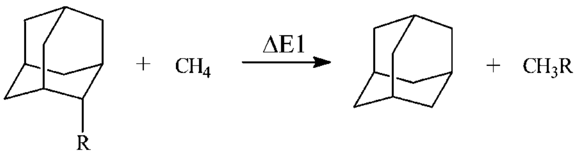
ABSTRACT



Steric substituent constants, S_A, of both alkyl and aryl substituents were calculated in the adamantane system by both isodesmic reactions and ab initio calculations. The method provides an easy and reliable way to quantify the substituent steric effects.

In addition to field, electronegativity, resonance, and polarization effects, the steric effect is very important in both chemistry and biology.[1] It plays an important role not only in conformation, stability, and reactivity of molecules but also in stereoselectivity and regioselectivity of many reactions.[1] In addition to the large amount of work on field, electronegativity, resonance, and polarization effects,[2] research on the steric effect has also been growing.[3]

Taft defined E_s, a steric substituent constant, as $E_s = \log(k/k_0)_A$, on the basis of acid-catalyzed hydrolysis of aliphatic esters with k_0 for a methyl substituent.[3a] However, E_s (-2.55) of phenyl is much bigger than that (-1.54) of *tert*-butyl, and Taft has suggested that the E_s values of α,β-unsaturated substituents such as phenyl and vinyl include an appreciable resonance effect.[3b] The same phenomena have also been found in Charton's υ steric constants.[3c] Conformational free-energy differences (*A* values) between axial and equatorial conformations of monosubstituted cyclohexanes were taken as measurements of the substituent steric effects, but the conformational free-energy difference of the Cl substituent is bigger than those of Br and I substituents.[3d] In addition to involvement of nonchair conformations for the axially substituted cyclohexane,[1] it was suggested that the larger van der Waals radii of Br and I relative to that of Cl are compensated for by the greater C−I and C−Br bond lengths.[1] Tolman's ligand cone angles θ were used to measure ligand steric effects,[3e] but only limited ligands can be examined in the system. Solid angles were calculated in various ways to quantify the substituent steric effects,[3f,g] but, as Coville[3g] said, the advantages of solid angles in steric size measurements

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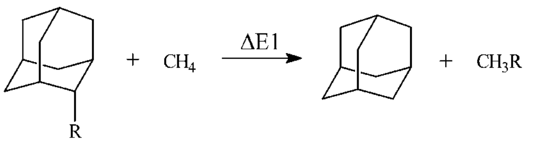
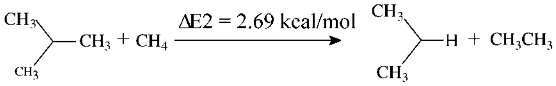
have not been fully recognized and the uses were inadequately explored. Molecular mechanics approaches have been used to measure the substituent steric effects,[3h,i] and the substituent steric effects were correlated with rates of acid-catalyzed hydrolysis.[3j] However, the molecular mechanics approaches handle the effects of electrons too simply by including nonbonding repulsion terms[3h,i] and they are economical at the expense of accuracy.[4] Recently, a few steric substituent constants were obtained experimentally by ^{13}C NMR of the substituents in an adamantane system,[3k] but syntheses of the adamantane system with a variety of substituents are a big job.

It is clear that an easy, reliable, and popular way to quantify substituent steric effects is lacking. We have endeavored to find an easy and reliable method to quantify the steric effects of substituents. We put a substituent at an axial position in an adamantane system to measure nonbonding interactions of the substituent. The advantage of the adamantane system is that no bulky axial substituents twist the six-membered ring at all in order to reduce the large nonbonding interactions. It is clear that resonance effect between the axial substituent and the adamantane is very small and that the whole system is not stabilized by the resonance effect. Since a polar (field) effect is caused by dipole−dipole interactions and the adamantane does not have a permanent dipole, there is very small polar effect between the axial substituent and the adamantane. Therefore, in the absence of both polar and resonance effects, all the nonbonding interactions caused by the axial substituent in the adamantane system can be used to measure the substituent steric effects.



(Eq 1)



$$(CH_3)_2CH{-}CH_3 + CH_4 \xrightarrow{\Delta E2 = 2.69\ \mathrm{kcal/mol}} (CH_3)_2CH{-}H + CH_3CH_3$$

(Eq 2)

To measure all the nonbonding interactions caused by the axial substituent in the adamantane system, we designed an isodesmic reaction[4,6] (eq 1), which eliminates the strain of both the adamantane and the substituent itself. All the molecules were optimized at the level of B3LYP/6-311+G(2d,p)//HF/6-31G* by Gaussian98,[5] and the conformation with the lowest energy was chosen for each of the molecules. The ΔE_1 of the isodesmic reaction represents all the nonbonding interactions caused by the axial substituent in the adamantane system. As shown in Table 1, the $-(\Delta E_1)$ increases as the substituent R gets bulkier, except for the H substituent. The reason for this is that R is located at a tertiary carbon and H is located at a methyl carbon on the reactant side, while H is located at a secondary carbon and R is located at a methyl carbon on the product side. Branched alkanes are more stable than linear isomeric alkanes.[1d] Therefore, the stabilization caused by R on the reactant side is slightly higher than that on the product side, and this electronic effect can be estimated as ΔE_2 by an isodesmic reaction (eq 2). Subtraction of ΔE_2 from ΔE_1 should be a measurement of the substituent steric effect for all the alkyl and aryl substituents except hydrogen. Therefore, we name the substituent steric effect in the adamantane system as S_A, which is equal to $(\Delta E_1 - \Delta E_2)$.

Table 1. ΔE_1 of the Isodesmic Reaction (Eq 1) and the Steric Substituent Constants of S_A, E_s, A, and Ω_s (0.9,0.5)[a]

R	ΔE_1	S_A	E_s	A	Ω_s (0.9,0.5)
H	0.00	0.00		0.0	0.0967
Me	0.67	−2.02	0.00	1.8	0.2081
Et	−0.25	−2.94	−0.07	1.8	0.2585
n-Pr	−0.29	−2.99	−0.36		0.2730
i-Pr	−2.59	−5.28	−0.47	2.1	0.3128
c-Pr	1.27	−1.42			
$(Et)_2CH$	−5.15	−7.84			0.3842
$(i\text{-}Pr)_2CH$	−9.78	−12.47			
t-Bu	−9.76	−12.45	−1.54	5.4	0.3668
Ph	−2.41	−5.10	−2.55	2.9	

[a] E_s: Taft's substituent steric constants (ref 3a). $A = -\Delta G°$ for axial and equatorial conformations of monosubstituted cyclohexanes (refs 1d and 3l). Ω_s (0.9,0.5): Hirota's solid angles (ref 3f). Units of ΔE_1, S_A, and A are all kcal/mol.

The substituent steric interactions for systems of both Taft's E_s and Hirota's solid angles Ω_s (0.9,0.5)[3f] come from reactions in which an external reagent approaches the substituted molecule. The former is experimental data, while the latter is theoretical data. On the other hand, the substituent steric interactions for systems of both the S_A and the A values[1d,3l] mainly come from 1,3-diaxial and "butane-gauche" nonbonding interactions between the substituent and the six-membered ring. The S_A correlates with the E_s, including Me, Et, n-Pr, i-Pr, and t-Bu substituents, very well with a correlation coefficient of 0.97, even though they both are completely different systems to be examined for the substituent steric effect. Correlation of the S_A with the A values is also good with a correlation coefficient of 0.95. Although they both are similar systems, nonchair conformations of the axially substituted cyclohexanes may not make the A values satisfactorily reflect the substituent steric effect. To improve the deficiency, the S_A was investigated in the adamantane system. On the other hand, the S_A correlates with the Hirota's

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Ω_s (0.9,0.5) poorly with a correlation coefficient of 0.74, indicating that the latter is less reliable.

The steric effect of the i-Pr group is much bigger than that of the n-Pr group, because the former has more "butane-gauche" nonbonding interactions with the adamantane system. On the other hand, the steric effect of the n-Pr group is twice that of the c-Pr group, because the dihedral angle between the substituent and the adamantane is 66.6° for the n-Pr group and 82.5° for the c-Pr group, indicating that the former suffers more "butane-gauche" nonbonding interactions with the adamantane system than the latter. More interesting is that the steric effect of the c-Pr is even smaller than that of methyl group. However, on the basis of Charton's υ steric constants, the steric effect (1.06) of the c-Pr is bigger than that (0.76) of the i-Pr, and Charton has suggested that the unreliable data is due to an appreciable resonance effect caused by the c-Pr.[3c] The order of the substituent steric effects, $(\text{i-Pr})_2\text{CH} > (\text{Et})_2\text{CH} > \text{i-Pr}$, indicates that branching on the terminal carbons of the i-Pr group increases the steric effect significantly. The phenyl group has a slightly smaller steric effect than the i-Pr group. The steric substituent constants, S_A, of a variety of other substituents are under investigation now.

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Supporting Information Available: Computational details, single-point energies, and Cartesian coordinates of the molecules discussed in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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