

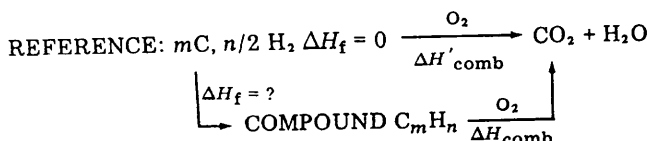
# The Evaluation of Strain and Stabilization in Molecules Using Isodesmic Reactions

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## Heats of Formation, $\Delta H_f(g)$ (1-3)

We commonly discuss the stability of compounds relative to the standard states of the component elements (graphite,  $H_2$ , etc., at 25°C, 1 atm pressure), which are arbitrarily assigned heats of formation of 0.0 kcal/mole.

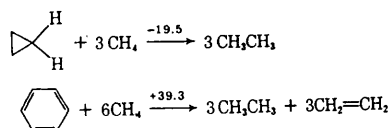


Since the compound can seldom be formed directly from the elements, the heat of formation is often determined from heats of combustion:  $\Delta H_f = \Delta H'_{comb} - \Delta H_{comb}$ . In combustion experiments the samples are usually liquids or solids. Since we are interested in intramolecular energies only, we must correct  $\Delta H_{comb}$  or  $\Delta H_f$  for the heat necessary to overcome intermolecular forces in the sample, which is the heat of vaporization (or sublimation):  $\Delta H_f(g) = \Delta H_f(l) + \Delta H_v$ .

$\Delta H_f(g)$  becomes more exothermic (negative) in homologous series as the number of bonds increases:  $CH_4$ , -17.8 kcal/mole;  $C_2H_6$ , -20.0;  $C_3H_8$ , -25.0, etc., yet the larger molecules are not less reactive. A similar problem exists with cyclopropane [ $\Delta H_f(g) = 12.7$ ] relative to benzene [ $\Delta H_f(g) = 19.8$  kcal/mole]. The less endothermic value does not reflect greater stability. This seems to imply that we can compare only isomeric compounds, but, in fact, we can consider non-isomers if we choose some other reference state. One could use values of C—C and C—H bond dissociation energies, and examine deviations of the compounds from bond additivity, but there are no unique values for BDE's, even in unstrained compounds. The energies of hypothetical models can be calculated, but the results depend on the assumptions made and the method (a few experimental thermochemical data for benzene have been interpreted as demonstrating stabilization of <20 to >40 kcal/mole).

## Isodesmic Reactions

These reactions, introduced by Pople (4), "are examples of (hypothetical) chemical changes in which there is retention of the number of bonds of a given formal type (C—H, C—C, C=C) but with a change in their formal relation to one another." The following are examples. For the reaction,  $\Delta H = \sum \Delta H_f(g)(\text{Products}) - \sum \Delta H_f(g)(\text{Reactants})$ .



Numerous quantum and thermochemical errors cancel, so "the energies of isodesmic reactions measure deviations from the additivity of bond energies." The enthalpies of reaction (calculated from independently measured heats of formation)

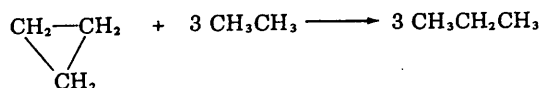
represent the strain in cyclopropane and the resonance stabilization of benzene. We can thus relate the energy of a molecule to the energies of a few simple reference molecules.

The choice of reference molecules is significant. Comparison of  $\Delta H_f(g)$  values for a series of methyl derivatives ( $CH_3X$ ,  $X = -NO_2, -OH, -NH_2, -OCH_3, -H, -CN, -CO-CH_3$ , and  $-COOH$ ) with the corresponding ethyl derivatives shows differences of 2.3–7.9 kcal/mole, whereas the primary alkyl derivatives beginning with ethyl have quite uniform methylene increments ( $CH_3CH_2X$  versus  $CH_3CH_2CH_2CH_2X$  differences are 4.7–5.3 kcal/mole/ $CH_2$ ) (2). Similarly,  $\Delta H_f(g)$  of *tert*-butyl and the isomeric 1-butyl derivatives differ by 1.9–10.9 kcal/mole. It is therefore desirable to include in isodesmic reactions reactants and products with alkyl groups of two carbon atoms or more, and to convert reactants with primary, secondary, or tertiary functional groups to products with the same structural features. Chlorocyclopropane and chloroethylene, for example, are secondary derivatives which should be converted into the simplest secondary chloroalkane, 2-chloropropane. (Note that C-1 of chloroethylene forms only one carbon-hydrogen bond, and two carbon-carbon bonds, and, in this sense, is a secondary carbon. Similarly, 1-chloro-1-methylcyclohexane, chlorobenzene, and chloroacetylene should give *tert*-butyl chloride as one of the products.)

Improved methods using these principles have been proposed by Bock (5) (homodesmotic reactions), and by Dill, Greenberg, and Liebman (6) (group separation reactions), and will be used in the following discussion. We will also illustrate a related method, metathetical isodesmic reactions.

## Strain Energies of Cycloalkanes

Cyclopropane consists of three methylene groups ( $-CH_2-$ ) in a strained ring. In a hypothetical reaction with ethane the methylene groups will be transferred to propane:



$$\Delta H_f(g) = 12.7 \pm 0.1 (3) \quad 3(-20.1 \pm 0.05) \quad 3(-25.0 \pm 0.1)$$

$$\Delta H(\text{reaction}) = 3(-25.0) - 12.7 - 3(-20.1) = -27.4 \text{ kcal/mole}$$

Since the reaction is exothermic we are converting a strained reactant to an unstrained one. The strain energy is  $-\Delta H(27.4 \pm 0.3 \text{ kcal/mol})$ . The "conventional ring strain energy" (CRSE) derived from bond energy additivity schemes (2) is 27.5 kcal/mole.

Other cycloalkanes can be involved in similar reactions:

Ring	$\Delta H(\text{Group Separation})$	CRSE
c-C <sub>3</sub> H <sub>6</sub>	-27.4 ± 0.3 kcal/mole	27.5
c-C <sub>4</sub> H <sub>8</sub>	-26.4 ± 0.4	26.5
c-C <sub>5</sub> H <sub>10</sub>	-5.8 ± 0.5	6.2
c-C <sub>6</sub> H <sub>12</sub>	0.1 ± 0.5	0.0
c-C <sub>7</sub> H <sub>14</sub>	-6.0 ± 0.6	6.2
c-C <sub>10</sub> H <sub>20</sub>	-12.1 ± 0.9	12.3
c-C <sub>15</sub> H <sub>30</sub>	-1.5 ± 1.2	1.8
c-C <sub>16</sub> H <sub>32</sub>	-1.5 ± 1.3	1.8

In all cases  $-\Delta H$  and the CRSE are in excellent agreement.

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## Alkenes

Energies of cycloalkenes or branched alkenes can be related to simple alkanes and alkenes (5), or to alkanes only (6). In the latter (group separation) method  $\text{=CH}_2$  or  $\text{—CH}_2\text{—}$  of an alkene is changed to propane,  $\text{—CH=}$  becomes isobutane, and



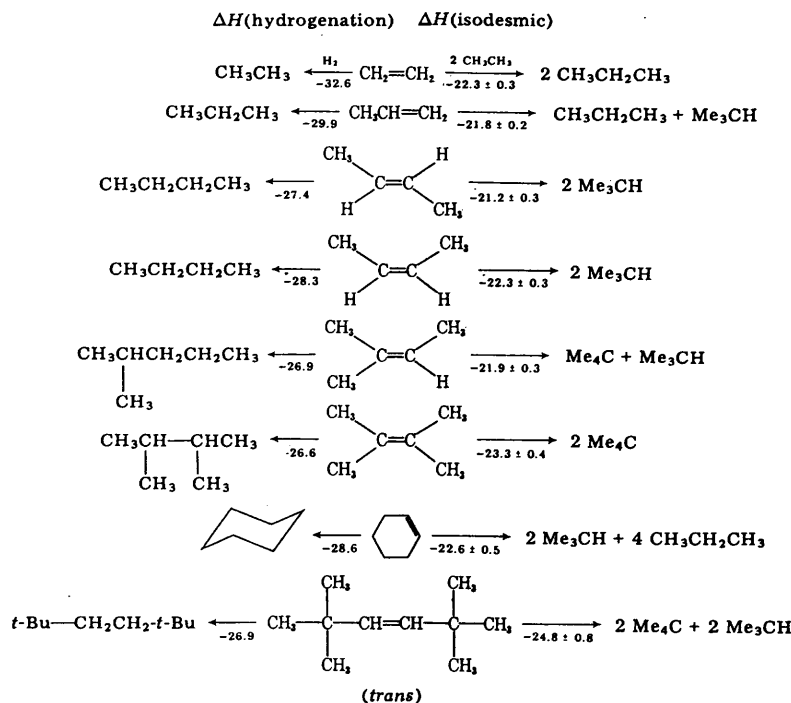
becomes neopentane. The number of hydrogen atoms attached to a carbon atom remains unchanged. Aromatic C—H groups are similarly converted to isobutane, and substituted aromatic carbon atoms (C—X) become *tert*-butyl-X, by reaction with ethane.

A traditional view of alkene stability is based on heats of hydrogenation (7, 8).

carbon atom of ethylene has two carbon-carbon bonds, and two C—H bonds). But even in the alkanes this would be a  $-7.1$  kcal/mole transformation. The *unique* stabilizing effects of a methyl group attached to ethylenic carbon (whether hyperconjugation or other factors) is *not*  $7.7 - 5 = 2.7$  kcal/mole, but rather,  $7.7 - 7.1 = 0.6$  kcal/mole, and this is the quantity that isodesmic reactions evaluate. The remaining 2.1 kcal/mole of stabilizing effect is common to alkanes and other homologous series, and cannot result from a "special" electronic interaction of the methyl group and  $\pi$  electron system.

## Aromatic Compounds

Resonance and hyperconjugative interactions of substituents with aromatic rings is an old concept of organic chemistry (9, 10) which is more readily demonstrated for charged and



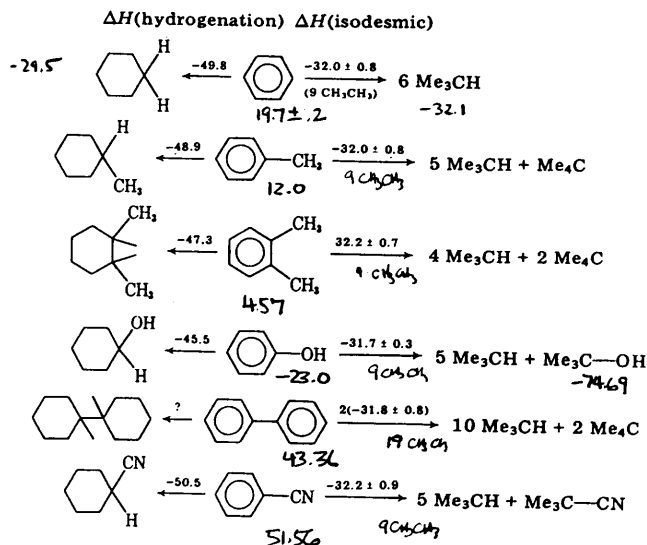
ethane	-20.0
propane	-25.0
butane	-30.2
2-methylpropane	-32.1
pentane	-35.0
2-methylbutane	36.8
2,2-dimethylpropane	-40.0
ethylene	12.55 ± 1
propene	4.78 ± 2
cis-butene	-1.7
trans butene	-2.7
2-methyl-2-butene	-10.0
2,3-dimethyl-2-butene	-16.3
cyclohexene	-1.2
cyclohexane	-29.5

There have been many years of discussion of how the methyl group of propylene stabilizes that compound by 2.7 kcal/mole relative to ethylene. Similarly, additional methyl groups attached to the ethylenic carbons lead to additional stabilization, although *cis* methyls also contribute some steric destabilization. The most stable alkenes are those with the least exothermic heats of hydrogenation.

To gain insight into the problem, let us consider  $\Delta H_f(g)$  for alkanes: propane ( $-25.0$  kcal/mole), butane ( $-30.2$ ), 2-methylpropane ( $-32.1$ ), pentane ( $-35.0$ ), 2-methylbutane ( $-36.8$ ), and 2,2-dimethylpropane ( $-40.0$ ). If we insert a methylene group into a *primary* C—H bond of propane or butane,  $\Delta H_f(g)$  of the resulting products (butane and pentane) are 5 kcal/mole more exothermic. In the insertion of  $\text{CH}_2$  into the *secondary* C—H bond of propane,  $\Delta H_f(g)$  of the product 2-methylpropane is 7.1 kcal/mole more exothermic.  $\text{CH}_2$  insertion into the *tertiary* C—H bond of 2-methylpropane produces 2,2-dimethylpropane, and  $\Delta H_f(g)$  becomes 7.9 kcal/mole more exothermic. This is equivalent to saying that branched alkanes have more highly exothermic values of  $\Delta H_f(g)$  than do the normal isomers, possibly because the former have a larger number of strong primary C—H bonds.

With alkenes each  $\text{CH}_2$  insertion into the primary (methyl) C—H bonds in the series propene  $\rightarrow$  1-butene  $\rightarrow$  1-pentene changes  $\Delta H_f(g)$  by the usual  $-5$  kcal/mole. But the change from ethylene to propylene is  $-7.7$  kcal/mole. This, however, involves  $\text{CH}_2$  insertion into a *secondary* C—H bond (each

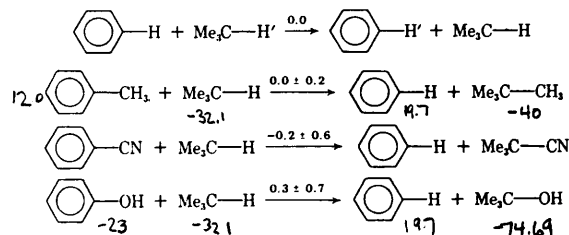
radical intermediates than for the ground states of neutral molecules. However, the heats of hydrogenation of benzene derivatives (to the cyclohexanes) vary with the substituent. This has been taken as evidence of conjugation, although the effect of methyl substitution is somewhat less than in alkenes. The cyano group appears to have a destabilizing effect.



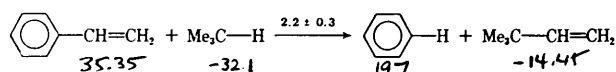
However, enthalpies of the isodesmic reactions are essentially identical, demonstrating that neither methyl, hydroxyl, phenyl, nor cyano substituents promotes significant net stabilization, although cancelling stabilizing and destabilizing effects may be occurring.

### Metathetical Isodesmic Reactions

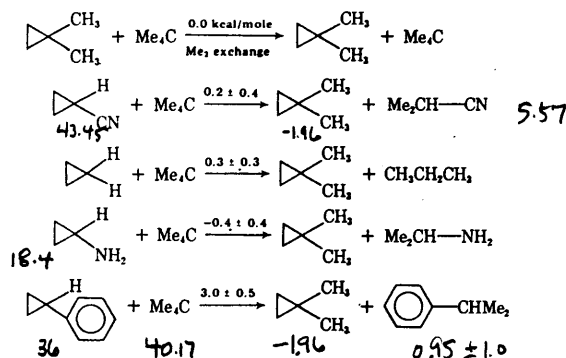
An alternative, and somewhat more accurate treatment of aromatic reactions involves a metathetical relationship (11). Since only two reacting molecules and two product molecules are involved, the uncertainties in  $\Delta H(\text{reaction})$  are relatively small compared to group separation reactions involving many molecules.



A compound which does show stabilization is



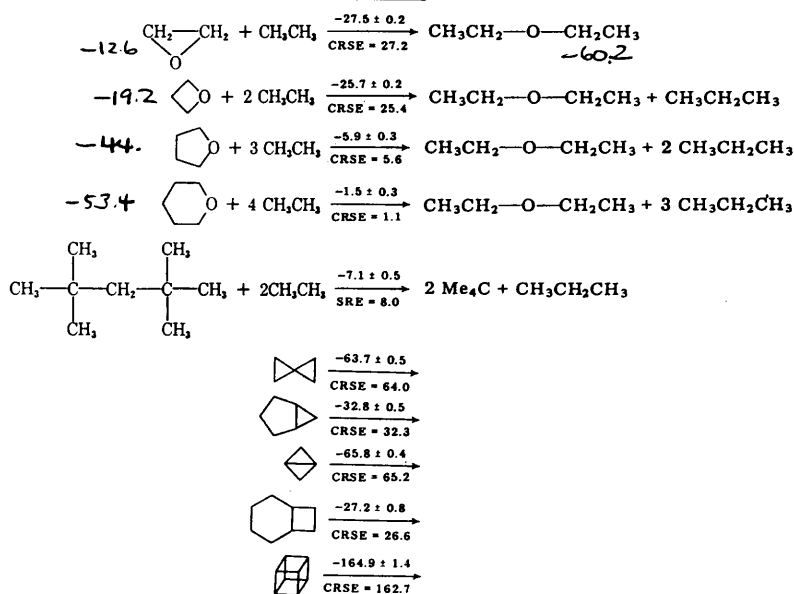
The reaction is unfavorable (endothermic) primarily because of the stabilization of styrene.



The data demonstrate that *no* net stabilization occurs in cyclopropyl cyanide, 1,1-dimethylcyclopropane, or cyclopropylamine. Only in cyclopropylbenzene is there a substantial (3.0 kcal/mole) stabilizing effect.

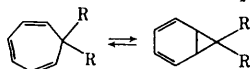
### Other Compounds

Isodesmic reactions are not a substitute for various semi-empirical or *ab initio* methods of calculating molecular energies but may be used in conjunction with these methods (4, 6). Isodesmic reactions can, simply and conveniently, permit the estimation of strain and conjugation energies based on experimental (or calculated) heats of formation. The versatility can be further illustrated with examples of cyclic ethers, a highly branched hydrocarbon, bicyclic hydrocarbons, and acetylenes, and is limited only by the availability of thermochemical data for the compound of interest and appropriate reference compounds.



### Conjugation in Cyclopropane Derivatives

The cycloheptatriene-norcaradiene equilibrium



favors the norcaradiene only when the groups R are  $\pi$  electron acceptor groups such as  $-\text{CN}$  or phenyl. In a 1970 article (12), Hoffmann noted the ability of cyclopropane to enter into  $\pi$ -type conjugation with neighboring  $\pi$  electron systems such as cyano, and this is believed to be involved in the stabilization of cyano-substituted norcaradienes. Others have supported the concept of cyclopropane conjugation. Dill, Greenberg, and Liebman (6) calculated (at the STO-3G level) the following stabilizations of cyclopropanes by substituents:  $\text{CH}_3$ , 2.4 kcal/mole;  $\text{CN}$ , 5.8; and  $\text{NH}_2$ , 2.9. With the help of some new thermochemical data we recently measured (13), we may examine isodesmic reaction enthalpies for some cyclopropane derivatives:

Conventional ring strain energies (CRSE) of the cyclic ethers (2) and the steric repulsion energy (SRE) of 2,2,4,4-tetramethylpentane (2) are very well reproduced by  $-\Delta H$  values of the isodesmic reactions, as are the CRSE values of spiropentane, bicyclo[3.1.0]hexane, bicyclo[1.1.0]butane, bicyclo[4.2.0]octane, and cubane. Acetylenes are stabilized by 2 kcal/mole per alkyl group, a value much larger than that for alkenes, but much less than that implied by heats of hydrogenation.

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