added the iodide **16** (0.01 g, 0.03 mmol). The mixture was stirred for 1 h, poured into H_2O (10 mL), and extracted with ether (2 × 15 mL), and the extracts were washed with 10% aqueous HCl (5 mL) and H_2O (2 × 10 mL), dried ($MgSO_4$), and evaporated to yield a crude product **17b** heavily contaminated with PhSeSePh. Purification was not possible, and the crude product was used directly for the next reaction: ^1H NMR δ 7.50 (2 H, m, Ar H), 7.34 (3 H, m, Ar H), 7.1 (2 H, d, J = 8.35 Hz, Ar H), 6.85 (2 H, d, J = 8.38 Hz, Ar H), 5.83 (2 H, m, 2-H and 3-H), 3.80 (3 H, s, OMe), 3.55 (2 H, m, 1-H and 4-H), 2.30 (2 H, m, 5-H and 7-H), 1.95 (2 H, m, 6-H and 7-H), 1.65 (1 H, m, 6-H), 1.15 (3 H, d, J = 6.90 Hz, CH_3).

Conversion of Phenyl Selenide 17b to Alcohol 18. The crude product **17b** from above was stirred in THF (2 mL) while a large excess of 30% H_2O_2 (1 mL) was added. The reaction mixture was stirred for 1 h at 0 °C, and then a large excess of Et_3N was added. The mixture was allowed to reach room temperature over a period of 15 min and worked up as usual to afford the alcohol as an oil, which was purified by preparative TLC (silica gel/30% EtOAc in hexane) afforded pure alcohol **18** (0.04 g, 90%): IR ν_{max} ($CHCl_3$) 3600, 3520 cm^{-1} (OH); ^1H NMR δ 7.18 (2 H, d, J = 8.63 Hz, Ar H), 6.89 (2 H, d, J = 8.63 Hz, Ar H), 5.66 (2 H, m, vinyl), 4.49 (1 H, br d, J = 10.31 Hz, C*H*OH), 3.81 (3 H, s, OCH_3), 2.83 (1 H, td, J_t = 10.3 Hz, J_d = 4.2 Hz, benzylic CH), 2.49 (1 H, m, 4-H), 1.90 (2 H, m), 1.68 (2 H, m), 1.55 (1 H, s, OH), 1.07 (3 H, d, J = 7.22 Hz, CH_3); HRMS, M^+ calcd for $C_{15}H_{20}O_2$ M = 232.1467, found M = 232.1462.

Oxidation of Alcohol 18 to Enone 19 with Pyridinium Chlorochromate. To a stirred solution of the alcohol **18** (0.0052 g, 0.024 mmol) in CH_2Cl_2 (1 mL) was added PCC ($C_5H_5NHCrO_3Cl$) (0.0103 g, 0.048 mmol). The resultant mixture was stirred for 2 h in the dark at room temperature, then diluted with ether (10 mL), and filtered through Florisil. The filtrate was washed with H_2O (2 × 5 mL), dried ($MgSO_4$), and evaporated to afford enone **19** (0.005 g, 98%). The crude product was purified by preparative TLC (silica gel/30% EtOAc in hexane) to yield a pure solid enone **19** (0.004 g, 78.4%) when dried in high vacuum: mp 59–60 °C; IR ν_{max} 1685, 1610 cm^{-1}; ^1H NMR (C_6D_6) δ 7.13 (2 H, d, J = 8.76 Hz, Ar H), 6.84 (2 H, d, J = 8.76 Hz, Ar H), 6.02 (1 H, dd, J = 11.92, 2.71 Hz, 3-H), 5.81 (1 H, dd, J = 11.92, 3.12 Hz, 2-H), 3.64 (1 H, dd, J = 10.44, 5.88 Hz, 7-H), 3.34 (3 H, s, OMe), 2.07 (1 H, m, 4-H), 1.74 (2 H, m), 1.34 (2 H, m), 0.75 (3 H, d, J = 7.33 Hz, CH_3). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.26; H, 7.82. Found C, 78.34; H, 7.80.

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Structures and Energies of the Tricyclo[4.1.0.0^{1,3}]heptanes and the Tetracyclo[4.2.1.0^{2,9}0^{5,9}]nonanes. Extended Group Equivalents for Converting ab Initio Energies to Heats of Formation

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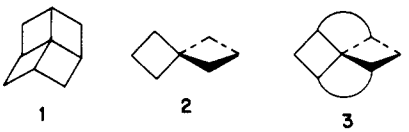
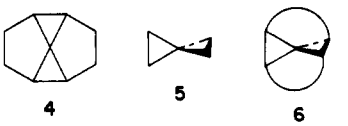
The structures of the two isomeric tricyclo[4.1.0.0^{1,3}]heptanes have been calculated by using the 3-21G basis set. The cis isomer was found to be 46 kcal/mol less stable than the known trans isomer. The calculated structures are compared with that obtained from an electron diffraction study. The modes of deformation of spiropentane were examined, and bending was found to be energetically more favorable than twisting. The structures and relative energies of three of the five isomeric tetracyclo[4.2.1.0.^{2,9}0.^{5,9}]nonanes also have been calculated. Group equivalents have been derived that permit the conversion of calculated total energies to heats of formation with reasonable accuracy, and the effect of basis set on both calculated energies and structures are examined. Equivalents for oxygen-containing groups also have been obtained.

The question of how far carbon may be deformed toward planarity[1] has led to considerable interest in tetracyclo[5.1.1.0^{3,8}0.^{5,8}]nonane (**1**),[2-4] otherwise known as



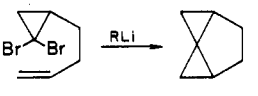
1 **2** **3**

"fenestrane"[2] or "windowpane".[3] One way in which to think about **1** is to consider it as formed from spiro[3.3]-heptane (**2**) by the introduction of rings **3** that will try to force the two four-membered rings into planarity. From this viewpoint, tetracyclo[4.2.1.0.^{2,9}0.^{5,9}]nonane (**4**) also is



4 **5** **6**

of interest. Again, starting with spiropentane (**5**), introduction of bridges **6** would tend to twist the two three-membered rings into planarity. A related compound, **7**,



7

has been prepared by Skattebøl[5] by a carbene ring closure:

(1) Cf.: Wiberg, K. B.; Ellison, G. B.; Wendoloski, J. J. *J. Am. Chem. Soc.* **1976**, *98*, 1212.
(2) Georgian, V.; Saltzman, M. *Tetrahedron Lett.* **1972**, 4315.
(3) Wiberg, K. B.; Hiatt, J. E.; Burgmaier, G. J. *Tetrahedron Lett.* **1968**, 5855. Wiberg, K. B.; Ellison, G. B.; *Tetrahedron* **1977**, *30*, 1573. Wiberg, K. B.; Olli, L. K.; Golembeski, N.; Adams, R. D. *J. Am Chem. Soc.* **1980**, *102*, 7467.
(4) Wolff, S.; Agosta, W. C. *J. Chem. Soc., Chem. Commun.* **1981**, 118; *J. Org. Chem.* **1981**, *46*, 4821. Rao, V. B.; Wolff, S.; Agosta, W. C. *Chem. Commun.* **1984**, 293.
(5) L. Skattebøl, *J. Org. Chem.* **1966**, *31*, 2789.

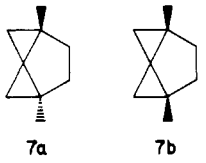
0022-3263/85/1950-5285$01.50/0

Table I. Calculated Energies

compd	energy,[a] hartree 3-21G/3-21G	ΔE^b	energy,[a] hartree 6-31G*/3-21G	ΔH_f^b	SE[b]
7a (trans)	−269.28287	0.0	−270.79885	59	80
7b (cis)	−269.20954	45.5		105	126
4a (tttt)	−345.66230	0.0		125	148
4c (tcct)	−345.64871	8.5		134	157
4c (cccc)	−345.65616	3.9		129	152

[a] 1 Hartree = 627.5 kcal/mol. [b] Units kcal/mol. The ΔH_f for **7a** is based on the 6-31G* energy, and that for **7b** is the sum of 59 and 46 kcal/mol. The 3-21G energies would lead to ΔH_f = 61 and 107 kcal/mol, respectively. The ΔH_f for **4a**, **4c**, and **4d** are based on the 3-21G energies.

It has, surprisingly, received very little attention. The cyclopentane ring may be fused onto the spiropentane unit either trans or cis (**7a** and **7b**, respectively). The geometry of **7** has been studied by electron diffraction,[6] but since C_{2v} symmetry was assumed (i.e., **7a**), it does not serve to



determine the structure. Models suggest that the trans isomer should be the more easily formed. An examination of the ^{13}C NMR spectrum of **7** showed only four different types of carbons, demonstrating that it was **7a**. The chemical shifts are δ 20.75, 25.48, 40.12, and 32.80 (quaternary).[7] They may be compared with the values for spiropentane: δ 6.11 and 8.53 (quaternary).

It was of interest to know the difference in energy between **7a** and **7b**. It is now well established that the structures and energies of compounds such as these may be satisfactorally estimated via ab initio molecular orbital calculations.[8] The structures and energies were calculated by using the 3-21G basis set.[9] The energies are summarized in Table I. It can be seen that **7b** is predicted to have an energy 46 kcal/mol greater than that of **7a**. In order to estimate the heat of formation of **7a**, the 6-31G* energy was calculated by using the 3-21G geometry (Table I). From the group equivalents given below, the ΔH_f was estimated to be 59 kcal/mol, which corresponds to a strain energy of 80 kcal/mol.[10] This may be compared with spiropentane, which has a strain energy of 63 kcal/mol.[11]

The calculated structures of **7a** and **7b** are shown in Figure 1. The structural parameters derived via electron diffraction[6] also are given for comparison, and the agreement is generally quite good. The reported uncertainties in the experimental data are ~0.02 Å for distances and ±2° for angles. One of the C–C–C angles in **7a** is remarkably large (158°) and probably is in considerable measure responsible for the increased strain over that in spiropentane. Here, the largest C–C–C angle is 137°.[6]

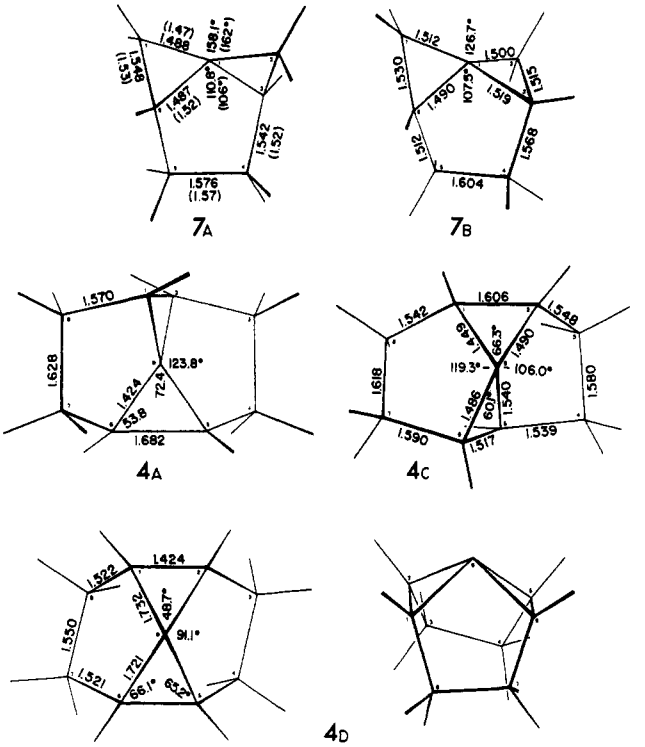


Figure 1. Calculated structures for tricycloheptanes and tetracyclononanes. In the case of **7a**, the experimental structural parameters are given in parentheses. The unmarked angles are as follows: **7a**, 123 = 58.6°, 213 = 62.7°, 134 = 105.3°, 234 = 120.4°, 345 = 103.0°, 216 = 132.4°; **7b**, 123 = 60.5°, 213 = 60.2°, 132 = 59.3°, 134 = 103.1°, 234 = 107.4°, 345 = 106.7°, 456 = 97.8°, 567 = 143.9°, 165 = 105.4°, 612 = 122.1°, 317 = 168.6°, 176 = 58.6°, 617 = 61.3°, 167 = 60.1°; **4a**, 195 = 138.2°, 123 = 123.2°, 234 = 102.9°, 923 = 98.2°; **4c**, 912 = 58.1°, 921 = 55.7°, 195 = 116.8°, 296 = 166.1°, 123 = 123.9°, 234 = 101.1°, 345 = 96.1°, 459 = 98.8°, 456 = 134.9°, 567 = 102.6°, 569 = 61.7°, 967 = 98.1°, 659 = 58.2°, 678 = 107.6°, 187 = 101.2°, 812 = 138.0°, 195 = 116.8°, 296 = 166.1°, 918 = 102.2°. **4d**, 923 = 116.2°, 123 = 122.2°, 234 = 107.1°, 345 = 106.1°, 459 = 116.3°, 456 = 123.1°, 195 = 106.0°.

Two types of distortion were found to result from the introduction of the two-carbon bridge. First, one ring may be bent away from the bisector of the other ring:

Second, one ring may be twisted with respect to the other:

We were interested in separating the energy changes due to twisting and bending of the spiropentane system, and therefore a series of calculations for distorted spiropentanes were carried out. The optimized geometries were obtained by using the 3-21G basis set for structures that were twisted by 0, 10, 25, 45, and 90° (planar) and those that were bent in the same fashion. The energies are summarized in Table II. In other work, we found that polarization functions (d orbitals) were frequently needed at carbon in order to correctly account for energy differences among highly strained compounds.[12] Therefore, the geometries were reoptimized using this more flexible basis set. It can be seen (Table II) that in this case there was no significant change on going from the 3-21G basis to 6-31G*. The energy required to twist the rings into pla-

(6) Smith, Z.; Andersen, B.; Bunce, S. *Acta Chem. Scand.* **1977**, *31A*, 557. Frey, H. M.; Hopkins, R. G.; Skattebøl, L. *J. Chem. Soc. B* **1971**, 539.
(7) I thank John McClusky for providing this information.
(8) Pople, J. A. *Mod. Theor. Chem.* **1977**, *4*, 1.
(9) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939. Hariharan, P. C.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *16*, 217.
(10) The strain energies were calculated by using Franklin's group equivalents to define unstrained models: Franklin, J. L. *Ind. Eng. Chem.* **1949**, *41*, 1070; *J. Chem. Phys.* **1953**, *21*, 2029.
(11) Cox, J. D.; Pilcher, G. "Thermochemistry of Organic and Organometallic Compounds"; Academic Press: London, 1970.
(12) Wiberg, K. B. *J. Am. Chem. Soc.* **1983**, *105*, 1227.

Table II. Energies of Deformed Spiropentanes[a]

angle, deg	3-21G/3-21G	ΔE	6-31G*/6-31G*	ΔE
		(a) Twist		
0	-192.82114	0.0	-193.91752	0.0
10	-192.81750	2.3	-193.91414	2.1
25	-192.79900	13.9	-193.89529	13.9
45	-192.75355	42.4	-193.85065	42.0
90	-192.62552	122.8	-193.72472	121.0
		(b) Bend		
0	-192.82114	0.0	-193.91752	0.0
10	-192.81895	1.4	-193.91518	1.5
25	-192.80695	8.9	-193.90244	9.5
45	-192.77261	30.5	-193.86873	30.6

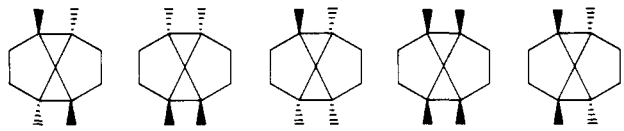
[a] The total energies are given in hartree units, and the energy changes are given in kcal/mol.

narity is significantly less than that required to twist methane into planarity (160 kcal/mol[1]). However, the initial strain energy is considerably higher for spiropentane, and so the total strain energy of its planar form is higher than that for planar methane.

Bending was found to be energetically more favorable than twisting. This is in accord with the calculated structures of **7a** and **7b**. Bending may conveniently be defined by taking the angle between the midpoint of the back C–C bond of one ring, the central carbon, and the midpoint in the other ring. Zero bending would correspond to 180°. Twisting may be defined by obtaining the torsional angle formed by the back bonds of the two rings. Zero twist corresponds to a 90° torsional angle:

The optimized geometry for the cis isomer has 35.7° bend and 37.5° twist, whereas for the trans isomer the angles are 25.6° bend and 5.1° twist. The latter are in agreement with bending being more facile than twisting. The large values for both angles for the former leads to its greatly increased energy. We have found that **7a** has considerably increased reactivity as compared to spiropentane,[13] and it will be interesting to study the reactivity of **7b**. We are examining the synthesis of this isomer.

Turning to **4**, it must be recognized that there are five structures represented by the given connectivity. Each cyclopropane ring may have the bridges attached either cis or trans. In addition, in each of the five-membered rings, the 1,3-substituents may be either cis or trans leading to trans,trans,trans,trans (**4a**), cis,trans,cis,trans (**4b**), trans,cis,cis,trans (**4c**), cis,cis,cis,cis (**4d**), and trans,cis,-trans,cis (**4e**) isomers:



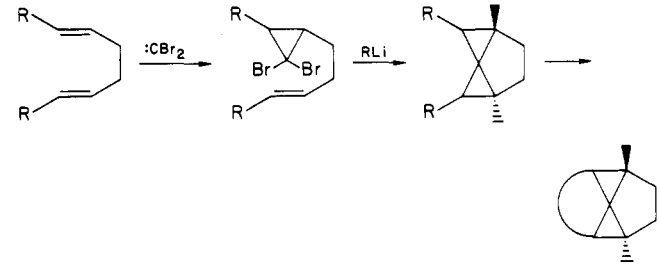
Starting with a model of the trans isomer **7a**, it appeared relatively easy to introduce a second two-carbon bridge if the hydrogens on the cyclopropane rings were trans, leading to **4a**. Geometry optimization was carried out by using the 3-21G basis set, assuming D_2 symmetry, and gave the energy shown in Table I and the geometry shown in Figure 1. The structure has 0° bend (required by the symmetry constraint) and 15.5° twist and is subject to large bond length distortion in the three-membered rings. It is possible that there may be a lower energy structure with reduced symmetry.

When the hydrogens on the cyclopropane rings were cis, as required to form **4b**, the new carbons that were attached pointed in opposite directions and ring closure could be affected only by greatly distorting the rest of the molecule. It has not as yet been possible to find a structure for **4b** that would not be subject to bond cleavage during geometry optimization. The formation of **4c** was possible with considerably less distortion than required for **4b**. Geometry optimization assuming no symmetry gave the energy shown in Table I and the structure shown in Figure 1. Here, the twist and bend angles are 36.6 and 41.1°, respectively. The calculated energy is only 8.5 kcal/mol higher than that for **4a** despite the considerable distortion at the central carbon.

Starting with a model of the cis isomer **7b**, it was difficult to attach a second two-carbon bridge without forcing the central carbon into a pyramidal geometry. A rather distorted nonpyramidal geometry for **4d**, with C_2 symmetry was used as the starting point, and geometry optimization led to a pyramidal structure (Table I; Figure 1). It was difficult to construct a trial structure for **4e**, and attempted geometry optimization using MM2[14] led to inversion at one center giving **4c**. It is difficult to know whether or not some other starting structure might lead to a stable geometry for **4b** or **4e**, but the results do suggest that they may not be reasonable synthetic targets.

The heats of formation and strain energies of **4a**, **4c**, and **4d** were estimated by the procedure described below. Since the energy of spiropentane was well reproduced by the 3-21G basis set, and since the calculated ΔH_f for **7b** was essentially the same from either the 3-21G or 6-31G* basis sets, the energies obtained using the former should be adequate. The energies are given in Table I. It can be seen that the strain energies are quite large, but still somewhat smaller than that for windowpane (**1**) ($\Delta H_f \sim 148$ kcal/mol, SE $\sim$ 171 kcal/mol).[15] Surprisingly, the estimated energies of **4a** and **4d** differed only by 3 kcal/mol despite the unusual geometry of **4d**.

Models suggest that rings larger than **2** could be fused onto **7a** without significant further distortion to form homologues of **4a** and **4c**. Thus, they should present no unusual difficulties with regard to preparation. It appears possible to adapt the method of Skattebol to the preparation of these compounds:



It is known that alkyl substitution facilitates the initial ring closure,[5] and with suitable substituents, it should be possible to close the fourth ring. The implementation of this scheme will be described at a later time.

If the homologues can be prepared, ring contraction sequences may lead to the desired compounds. The final ring contraction step would result in a 50–60 kcal/mol

(13) Wiberg, K. B.; McClusky, J., unpublished results.

(14) Burkert, U.; Allinger, N. L. *ACS Monograph* **1980**, No. 177.

(15) A total energy of -347.56427 was found by using the 6-31G* basis set: Wiberg, K. B.; Wendoloski, J. J. *J. Am. Chem. Soc.* **1982** *104*, 5679. This was converted to ΔH_f by using the group equivalents given herein.

Table III. Effect of Basis Set on Correlation between Calculated and Observed Energies[a]

compd	3-21G energy	3-21G ΔH_f(obsd)	3-21G ΔH_f(calcd)	3-21G diff	4-31G energy	4-31G ΔH_f (calcd)	4-31G diff	6-31G energy	6-31G ΔH_f (calcd)	6-31G diff
ethane	−78.79395	−20.04	−18.32	−1.72	−79.11593	−19.32	−0.72	−79.22876	−20.10	0.06
propane	−117.61330	−25.02	−23.85	−1.17	−118.09381	−24.69	−0.33	−118.26365	−25.29	0.27
butane	−156.43246	−30.03	−29.26	−0.77	−157.07159	−30.01	−0.02	−157.29840	−30.39	0.36
isobutane	−156.43446	−32.07	−29.17	−2.90	−157.07259	−31.12	−0.95	−157.29897	−31.61	−0.46
pentane	−195.25146	−35.08	−34.58	−0.50	−196.04922	−35.22	0.14	−196.33302	−35.41	0.33
neopentane	−195.25671	−40.14	−44.48	4.34	−196.05135	−39.96	−0.18	−196.33383	−38.55	−1.59
cyclopropane	−116.40121	12.73	19.08	−6.35	−116.88386	15.11	−2.38	−117.05887	13.17	−0.44
cyclobutane	−155.23132	6.78	6.80	−0.02	−155.86681	6.56	0.22	−156.09703	5.94	0.84
cyclopentane	−194.08847	−18.44	−22.44	4.00	−194.87399	−17.20	−1.24	−195.16124[c]	−17.65	−0.79
cyclohexane	−232.91673	−29.50	−33.57	4.07	−233.86681	−31.95	2.45	−234.20800	−30.26	0.76
bicyclo[1.1.0]butane	−153.98663	51.90	72.90	−21.00	−154.62473	65.53	−13.63	−154.87177	55.53	−3.63
bicyclo[2.1.0]pentane	−192.83981	37.70	46.15	−8.45	−193.63249	41.40	−3.70	−193.92697	37.58	0.12
bicyclo[2.2.0]hexane	−231.67450	29.90	30.99	−1.09	−232.62021	29.85	0.05	−232.96519[c]	30.30	−0.40
bicyclo[2.2.1]heptane	−270.56650	−12.40	−20.11	7.71	−271.66467	−17.29	4.89	−272.06116	−13.19	0.79
bicyclo[2.2.2]octane	−309.39252	−24.30	−29.84	5.54	−310.64923	−26.87	2.57	−311.10358	−23.12	−1.18
spiropentane	−192.82104	44.25	48.60	−4.35	−193.62440	44.08	0.17	−193.91753	42.62	1.58
cubane	−305.69568	148.70	145.14	3.56	−306.92889	146.36	2.34	−307.39362	147.07	1.63
ethylene	−77.60099	12.50	12.96	−0.46	−77.92216	13.35	−0.85	−78.03172	12.71	−0.21
propene	−116.42401	4.88	4.78	0.10	−116.90509	4.23	0.65	−117.07147	3.92	0.96
1-butene	−155.24315	−0.20	−0.61	0.41	−155.88150	−0.22	0.02	−156.10487	−0.33	0.13
cis-2-butene	−155.24387	−1.86	−1.41	−0.45	−155.88472	−2.82	0.96	−156.10773	−2.69	0.83
trans-2-butene	−155.24637	−2.99	−2.98	−0.01	−155.88724	−4.41	1.42	−156.11041	−4.36	1.37
isobutene	−155.24715	−4.26	−5.00	0.74	−155.88753	−5.14	0.88	−156.11058	−5.49	1.23
2,3-dimethyl-2-butene	−232.88229	−16.42	−16.05	−0.37	−233.84071	−15.98	−0.44	−234.17690	−15.80	−0.62
cyclopropene	−115.16201	66.20	78.69	−12.49	−115.64259	76.43	−10.23	−115.82305	69.21	−3.01
cyclobutene	−154.03072	37.45	42.18	−4.73	−154.66792	41.28	−3.83	−154.89961	37.87	−0.42
cyclopentene	−192.90180	8.23	4.19	4.04	−193.69559	4.66	3.57	−193.97719	5.89	2.34
1,3-butadiene	−154.05946	26.11	24.50	1.61	−154.69997	24.19	1.92	−154.91965	24.50	1.61
1.4-pentadiene	−192.86588	25.30	27.09	−1.79	−193.66460	27.13	−1.83	−193.94093	27.86	−2.56
cyclopentadiene	−191.71708	31.94	29.61	2.33	−192.51317	29.06	2.88	−192.79172	30.34	1.60
norbornadiene	−268.16171	57.40	52.91	4.49	−269.26010	56.42	0.98	−269.65244	59.37	−1.97
acetylene	−76.39596	54.34	54.62	−0.28	−76.71141	54.56	−0.22	−76.81783	54.56	−0.22
propyne	−115.22539	44.39	44.44	−0.05	−115.70131	44.32	0.07	−115.86432	44.25	0.14
1-butyne	−154.04482	39.49	38.88	0.61	−154.67892	39.12	0.37	−154.89903	39.18	0.31
2-butyne	−154.05365	34.71	35.00	−0.29	−154.68987	34.93	−0.22	−154.90926	34.93	−0.22
methanol	−114.39802	−48.07	−47.65	−0.42	−114.87152	−47.51	−0.56	−115.03542	−47.86	−0.21
ethanol	−153.22292	−56.24	−56.66	0.42	−153.85564	−56.80	0.56	−154.07574	−56.45	0.21
acetaldehyde	−152.05525	−39.73	−38.88	−0.85	−152.68653	−39.45	−0.28	−152.91596	−39.85	0.12
propanal	−190.87776	−45.54	−46.39	0.85	−191.66599	−45.72	0.28	−191.95223	−45.32	−0.12
acetone	−190.88722	−51.90	−50.84	−1.06	−191.67771	−51.40	−0.50	−191.96225	−51.60	−0.30
2-butanone	−229.70930	−57.02	−58.08	1.06	−230.65675	−57.51	0.49	−230.99800	−57.32	0.30
dimethyl ether	−153.21321	−43.99	−43.99	0.00	−153.83834	−43.99	0.00	−154.06474	−43.99	0.00
rms error				4.87 (2.57)[b]			3.14 (1.62)[b]			1.23 (1.00)[b]

[a] The total energies are given in hartree units (1 Hartree = 627.5 kcal/mol). The ΔH_f are given in kcal/mol. [b] The rms errors in parentheses were calculated leaaving out the compounds containing cyclopropane rings. [c] In this case, the 4-31G optimized geometry was used.

Table IV. Group Equivalents[a]

group	basis set 3-21G	4-31G	6-31G*
saturated			
CH_3	-39.38237	-39.54257	-39.59836
CH_2	-38.81054	-38.96931	-39.02662
CH	-38.24087	-38.39527	-38.45350
C	-37.65633	-37.81738	-37.87895
olefinic			
CH_2	-38.81082	-38.97172	-39.02599
CH_2	-38.23843	-38.39754	-38.45336
C	-37.66361	-37.82248	-37.87913
acetylinic			
CH	-38.24151	-38.39918	-38.45239
C	-37.67233	-37.83019	-37.88410
other			
OH	-74.93971	-75.25324	-75.36079
-O-	-74.37837	-74.68310	-74.79792
CHO	-112.61093	-113.08110	-113.25449
C=O	-112.04146	-112.51065	-112.68329

[a] Units Hartree. The values for -OH and -O- were derived for groups attached to primary centers. It remains to be seen whether or not they also are applicable to groups attached to secondary or tertiary centers.

increase in strain, which may prove difficult. The problem is rather similar to that of forming 1 via a ring contraction where the estimated increase in strain is ~70 kcal/mol. Even if this step proves impractical, the structures of the homologues and their reactions should prove interesting.

As in the above case, it is often found that ab initio molecular orbital calculations provide valuable insights into the structure, energy, and possible reactivity of strained compounds prior to their preparation. One of the main problems has been that of converting the calculated energies to heats of formation. This is commonly done by using homoisodesmic[16] reactions, followed by correction for zero-point energies and the conversion from 0 to 298 K.[17] We have pointed out that the use of homoisodesmic reactions may be considered as a group equivalent scheme and that the zero-point energies[18] as well as the change in energy on going to 298 K may both reasonably be approximated using group equivalents.[19] This was found to be successful and, using 6-31G* energies, was able to reproduce the heats of formation of a variety of compounds with an average error on the order of 1 kcal/mol:

$$\Delta H_f = 627.5(E_T - n_{CH_3}E_{CH_3} - n_{CH_2}E_{CH_2} - ...)$$

Here, the constant is the conversion factor between atomic units and kcal/mol, E_T is the calculated total energy, n_{CH_3} is the number of methyl groups, and E_{CH_3} is the group equivalent for a methyl group. The group equivalents may be considered to be the values corresponding to hypothetical compounds with $\Delta H_f = 0.0$. A similar scheme was subsequently reported by Schleyer et al.[20] and applied to a larger group of compounds.

It is sometimes not practical to obtain 6-31G* energies for larger molecules with low symmetry, and therefore we wished to see how well other basis sets such as 3-21G and 4-31G would reproduce experimental data. We have obtained the energies of a variety of types of hydrocarbons with each of the basis sets and have chosen the compounds to contain at least two examples of each of the groups used and to include monocyclic, bicyclic, and tricyclic hydrocarbons. Some oxygen-containing compounds also were included. The data are shown in Table III. A regression analysis was carried out in each case on the groups shown in Table IV. The results of the analysis is included in Table III, and the values of the group equivalents are given in Table IV.

Table V. Execution Times for Energy Gradients (s)

compd	3-21G	4-31G	6-31G*
2-butyne	624	889	8130
1-butyne	2126	3011	25034
cyclobutane	769	1077	11124
neopentane	953	1270	8750
spiropentane	2384	2999	25594
norborane	10104	13350	103674
bicyclo[2.2.2]octane	5960	7866	62157
propanal	2118	2928	26348

Table VI. Change in Energy on Reoptimizing with New Basis Set (kcal/mol)

compd	opt basis[a]	change on reopt[b]
ethane	4-31G	0.01
cyclopropane	3-21G	0.27
	4-31G	0.07
cyclobutane	4-31G	0.11
bicyclo[1.1.0]butane	4-31G	0.50
bicyclo[2.2.1]heptane	4-31G	0.09
bicyclo[2.2.2]octane	4-31G	0.03
1-butene	3-21G	0.10
	4-31G	0.02
cyclopropene	4-31G	0.32
cyclopentene	3-21G	0.36
	4-31G	0.01
cyclopentadiene	4-31G	0.05
bicyclo[2.2.0]hex-1(4)-ene	4-31G	0.34
propanal	3-21G	0.62
	4-31G	0.57

[a] Basis set for original geometry optimization. [b] Change in energy for 6-31G* calculation at the smaller basis set geometry vs. at the 6-31G* geometry.

The estimates of the enthalpies of formation using the 6-31G* basis set are uniformly quite good, with an average error of only 1.2 kcal/mol. Smaller basis sets give correspondingly larger errors; with 4-31G it is 3.1 kcal/mol, and with 3.21G it is 4.9 kcal/mol. However, in the latter cases, most of the error results from compounds with three-membered rings. If they are eliminated, the error drops to 1.0 kcal/mol for 6-31G* (a relatively small change), 1.6 kcal/mol for 4-31G, and 2.6 kcal/mol for 3-21G. It is clear that the flexibility afforded by including polarization functions into the basis set are essential for the proper description of cyclopropane derivatives. Equivalents for some oxygen-containing groups also are given but must be considered as tentative because they were not derived from a large set of compounds. For example, it will be important to determine whether or not the hydroxy group equivalent is the same for primary, secondary, and tertiary alcohols. This question will receive further study.

It is interesting to note that the CH_2, CH, and C group equivalents for saturated and olefinic groups are remarkably close with the 6-31G* basis set and that the deviation between the values appears to increase as the flexibility of the basis set decreases. This suggests that the values for a given type of group may converge with a sufficiently flexible basis set.

It should be noted that the group equilvalents given in Table IV are not applicable to delocalized π-electron systems such as benzene.[19] The correlation energy would be expected to be significantly different for these compounds than for simple alkenes or polyenes for which two

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Table VII

compd	r_{CC} 3-21G	4-31G	6-31G	obsd
(a) Effect of Basis Set on Calculated C–C Bond Lengths[a,b]				
ethane	1.543	1.529	1.527	1.531
propane	1.541	1.531	1.528	1.532
butane (1,2)	1.541	1.531	1.528	1.533
(2,3)	1.541	1.532	1.530	1.533
isobutane	1.540	1.533	1.530	1.535
pentane (1,2)	1.535	1.529	1.527	1.531
(2,3)	1.536	1.530	1.528	1.531
neopentane	1.539	1.535	1.533	1.540
cyclopropane	1.513	1.503	1.497	1.514
cyclobutane	1.570	1.555	1.548	1.555
cyclohexane	1.538	1.534	1.533	1.536
bicyclo[1.1.0]butane (1,3)	1.483	1.478	1.467	1.497
(2,3)	1.513	1.502	1.489	1.498
bicyclo[2.1.0]pentane (1,2)	1.546	1.535	1.528	1.528
(1,4)	1.540	1.527	1.513	1.536
(1,5)	1.513	1.503	1.494	1.507
(2,3)	1.583	1.569	1.558	1.565
bicyclo[2.2.1]heptane (1,2)	1.550	1.546	1.543	1.539
(2,3)	1.572	1.560	1.558	1.557
(1,7)	1.549	1.544	1.539	1.560
bicyclo[2.2.2]octane (1,2)	1.538	1.536	1.535	1.538
(2,3)	1.558	1.551	1.551	1.552
spiropentane (1,2)	1.482	1.481	1.479	1.469
(2,3)	1.529	1.517	1.513	1.519
cubane	1.577	1.574	1.563	1.551
ethylene	1.315	1.316	1.316	1.335
propene (1,2)	1.316	1.318	1.317	1.336
(2,3)	1.510	1.500	1.511	1.501
1-butene (1,2)	1.316	1.318	1.318	1.336
(2,3)	1.514	1.507	1.507	1.507
(3,4)	1.538	1.527	1.524	1.536
cis-2-butene (1,2)	1.524	1.501	1.504	1.506
(2,3)	1.312	1.322	1.322	1.346
trans-2-butene (1,2)	1.510	1.502	1.502	1.508
(2,3)	1.317	1.319	1.318	1.347
2,3-dimethyl-2-butene (1,2)	1.326	1.331	1.331	1.335
(2,3)	1.526	1.515	1.515	1.511
cyclopropene (1,2)	1.282	1.282	1.276	1.296
(2,3)	1.523	1.512	1.495	1.509
cyclobutene (1,2)	1.326	1.326	1.322	1.342
(2,3)	1.534	1.525	1.515	1.517
(3,4)	1.593	1.576	1.562	1.566
cyclopentene (1,2)	1.318	1.319	1.319	1.35
(2,3)	1.524	1.512	1.511	1.518
(3,4)	1.559	1.549	1.543	1.54
1,3-butadiene (1,2)	1.320	1.322	1.323	1.345
(2,3)	1.467	1.462	1.469	1.465
1,4-pentadiene (1,2)	1.316	1.317	1.318	
(2,3)	1.521	1.512	1.516	
cyclopentadiene (1,2)	1.329	1.330	1.329	1.342
(2,3)	1.485	1.474	1.476	1.469
(4,5)	1.519	1.509	1.507	1.509
norbornadiene (1,2)	1.548	1.543	1.539	1.535
(2,3)	1.319	1.321	1.318	1.343
(1,7)	1.565	1.562	1.554	1.573
acetylene	1.188	1.190	1.186	1.207
propyne (1,2)	1.189	1.191	1.187	1.206
(2,3)	1.466	1.460	1.468	1.459
1-butyne (1,2)	1.189	1.191	1.187	
(2,3)	1.466	1.460	1.468	
(3,4)	1.547	1.534	1.530	
2-butyne (1,2)	1.467	1.460	1.468	1.468
(2,3)	1.189	1.191	1.187	1.214
ethanol	1.531	1.520	1.516	1.512
acetaldehyde	1.507	1.494	1.505	1.515
propanal (1,2)	1.507	1.498	1.508	
(2,3)	1.534	1.524	1.522	
acetone	1.515	1.503	1.513	1.520
(b) Effect of Basis Set on Calculated C–O Bond Length				
methanol	1.440	1.430	1.400	1.427
ethanol	1.444	1.434	1.405	1.431
acetaldehyde	1.209	1.209	1.188	1.210
propanal	1.209	1.209	1.188	
acetone	1.211	1.214	1.192	1.214
dimethyl ether	1.433	1.423	1.391	1.410

[a] The structural data were taken from: Harmony, M. D.; Laurie, V. W.; Kuczkowski, R. L.; Schwendeman, R. H.; Ramsay, D. A.; Lovas, F. J.; Lafferty, W. J.; Maki, A. G. *J. Phys. Chem. Ref. Data* **1979**, *8*, 619. Callomon, J. H.; Kirota, E.; Kuchitsu, K.; Lafferty, W. J.; Maki, A. G.; Pote, C. S. "Lanoldt-Bornstein", New Series, Group II; Springer-Verlag: Heidelberg, 1976; Vol. 7. [b] Many of the 3-21G structures and some of the 6-31G* structures were taken from: Whiteside, R. A.; Frisch, M. J.; Pople, J. A. "The Carnegie-Mellon Quantum Chemistry Archive", 3rd ed.; Carnegie-Mellon University, 1983. The remaining 3-21G structures, all of the 4-31G structures and most of the 6-31G* structures were obtained at Yale: Wiberg, K. B.; Wendoloski, J. J. *J. Am. Chem. Soc.* **1982**, *104*, 5679. Wiberg, K. B. *Ibid.* **1983**, *105*, 1227. Unpublished results.

equivalent resonance structures cannot be written. As a result, the correction for the correlation energy will be different.

With some larger molecules, it is not practical to carry out a geometry optimization with the 6-31G* basis set, but it can be done by using one of the smaller basis sets (the times for the computation of the energy gradient for some compounds are shown in Table V). How much error will be introduced by doing a single-point 6-31G* calculation at the optimized geometry obtained using a smaller basis set? Some data are given in Table VI. It can be seen that the 4-31G geometries can generally be used with a 6-31G* calculation without introducing significant error. Somewhat larger changes in energy are found when the 3-21G geometries are used, but even here the error is generally not large.

These results suggest that the 4-31G structures are close to those obtained with the 6-31G* basis set but that the 3-21G structures are slightly different. This is examined in Table VII, which gives the C–C bond lengths for the compounds in Table III. The calculated bond angles differ only slightly between basis sets and generally are in very good agreement with the observed angles.[21] The C–H bond lengths are not given because they are frequently subject to relatively large anharmonicity corrections, do not determine the basic structure of a molecule, and have experimental variations that result from the different ways in which averaging is done over the anharmonic vibration. The 4-31G C–C bond lengths are very close to those obtained with the 6-31G* basis set, but the 3-21G values are somewhat different, especially for C–C single bonds. This may be expressed in more quantitative fashion by the following relationships:

$$r_{CC}(\text{3-21G}) = 1.120 r_{CC}(\text{obsd}) - 0.176$$
$$\text{std dev} = 0.013 \qquad R = 0.996$$
$$r_{CC}(\text{4-31G}) = 1.073 r_{CC}(\text{obsd}) - 0.113$$
$$\text{std dev} = 0.011 \qquad R = 0.997$$
$$r_{CC}(\text{6-31G*}) = 1.064 r_{CC}(\text{obsd}) - 0.102$$
$$\text{std dev} = 0.012 \qquad R = 0.996$$
$$r_{CC}(\text{3-21G}) = 0.9477 r_{CC}(\text{6-31G*}) + 0.068$$
$$\text{std dev} = 0.008 \qquad R = 0.998$$
$$r_{CC}(\text{4-31G}) = 0.9906 r_{CC}(\text{6-31G*}) + 0.011$$
$$\text{std dev} = 0.007 \qquad R = 0.999$$

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From these relationships, the standard deviation in the calculated C–C bond lengths is reduced to only ~0.01 Å, which is comparable to the accuracy of the measurements. The 4-31G geometries are closely related to the 6-31G* structures (slope 0.99), but the 3-21G geometries are slightly different (slope 0.95).

Calculations. The calculations were carried out by the program GAMESS.[22] Except for the two cases noted in the table, all energies in Table III correspond to structures that have been optimized with the same basis set. The times required for the computation of the gradient of the energy with respect to the coordinates, which is the most time-consuming part of the calculations, are given in Table V for a VAX-11/750 with a floating point accelerator. The differences in times for compounds with the same number of atoms results from the differences in symmetry.

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A Gradative Deprotection Strategy for the Solid-Phase Synthesis of Peptide Amides Using *p*-(Acyloxy)benzhydrylamine Resin and the S_N2 Deprotection Method

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An efficient deprotection strategy for the preparation of peptide amides by solid-phase peptide synthesis is described. The new method, gradative deprotection approach, utilized a multidetachable benzhydrylamine resin, *p*-(acyloxy)benzhydrylamine resin, and a mild S_N2 deprotection method for the removal of benzyl protecting groups. The multidetachable resin was designed to contain dual properties. The weakly electron-withdrawing *p*-acyloxy substituent on the benzhydrylamine linkage to the resin provided the required acid stability for the repetitive CF_3CO_2H treatments during synthesis and the S_N2 deprotection of all benzyl protecting groups after the completion of the synthesis. Under such a treatment, the crude and deprotected peptide remained attached on the resin support. Liberation of the peptide from the resin support by a nucleophile also concomitantly converted the *p*-acyloxy moiety to a strongly electron-donating *p*-hydroxy substituent on the benzhydrylamine, which would be smoothly removed by a mild acidic solvolytic treatment to give the peptide amide. Thus, the gradative deprotection approach consisted of multisteps and deprotected peptides from the resin support in discrete and controlled conditions to minimize strong-acid-catalyzed side reactions. Pentagastrin, H-Gly-Trp-Met-Asp-Phe-NH_2, was obtained in 90% overall yield and greater than 98% purity when deprotected by this new approach.

The conventional strategy in the chemical synthesis of peptides[1] by the solid-phase method[2] usually adopts a final, one-step, S_N1 cleavage process to remove protecting groups and the resin support by a very strong acid. It is now known that many protecting groups and side chain functionalities of the peptide product would best be removed under a milder condition to avoid the consequence of generating several serious side reactions.[3] A practical approach to this problem is to adopt a gradative process of deprotection that is discretely gradual and controlled.[4,5] Such an approach will deprotect the synthetic peptide after the completion of the synthesis in a stepwise fashion with the minimal required strength of acidity at each step and, thus, will likely avoid many of the known side reactions catalyzed by strong acids.

In essence, the gradative deprotection method is a multistep deprotection process after the completion of the peptide synthesis to produce peptide amides[6-10] using the conventional combination of N^{α}-(*tert*-butyloxy)carbonyl and benzyl side chain protection groups on a modified benzhydrylamine support, *p*-(acyloxy)benzhydrylamine[5] (Figure 1). The deprotection is carried out in four steps: First, the N^{α}-(*tert*-butyloxy)carbonyl group is removed by trifluoroacetic acid to eliminate the *tert*-butyl cationic source, which may lead to alkylation side reactions.[11] Second, the benzyl protecting groups are removed by a mild S_N2 deprotection method[5] with the crude and free peptide still attached to the resin after this treatment.

(1) Abbreviations follow the tentative rules of the IUPAC–IUB commission on Biochemical Nomenclature, published in: *J. Biol. Chem.* **1972**, *247*, 979–982. Others: ABA, *p*-(acyloxy)benzhydrylamine; Boc, (*tert*-butyloxy)carbonyl; DCC, dicyclohexylcarbodiimide; DIEA, diisopropylethylamine; DMAP, (*N,N*-dimethylamino)pyridine; HOBt, 1-hydroxybenzotriazole; TEA, triethylamine; TFA, trifluoroacetic acid; TFMSA, trifluoromethanesulfonic acid.

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