was determined by low-temperature X-ray crystallography. An ORTEP representation of the structure is presented in Figure 8 and the stereodiagram in Figure 11 of the supplementary material. Selected distances and angles are listed in Table VIII and distances from the best least-squares planes in Table IX. In this complex, the rhodium atom has four-coordinate geometry of ligating ligand atoms, which include the phosphorus atoms of the two triisopropyl phosphite groups, the terminal carbon atom of the butadienyl ligand, and the midpoint (C_2-m) of the terminal alkene carbon atoms in the butadienyl ligand. Structures such as this have been postulated,[28,29] and two have been crystallographically defined.[30,31] The structure of **4** and those of the two related palladium[30] and rhodium[31] heterocyclic structures are very similar even with respect to M–C and C–C distances in the ring portion of the molecules.

The butadienyl ligand is coordinated to the Rh atom through one alkene bond at one end with the phenyl substituents in a trans configuration and through a Rh–C σ bond on the other end with the phenyl substituents of the noncoordinated C=C bond in a cis configuration. The C–C bond distance of the coordinated C=C bond is 1.40 (1) Å, which is close to those of the palladium (1.408 (13) Å) and rhodium (1.428 (7) Å) analogues and which coincides exactly with the corresponding complexed alkene C–C bond distances of the vinyl ligands in the $(\mu\text{-H})[\mu\text{-}\eta^2\text{-RC}{=}\text{C}(\text{H})\text{R}]\text{Rh}_2\text{L}_4$ complexes discussed above. As expected, the uncomplexed alkene bond distance (1.357 (1) Å) of the butadiene ligand is normal and similar to those in the palladium (1.335 (13) Å) and rhodium (1.348 (7) Å) analogues.

Conclusions

These studies establish that a unique catalytic reaction can be effected in a polynuclear metal complex in which two (in this instance) or more metal atoms have reactive coordination sites. That the stereoselective catalytic alkyne hydrogenation cycle effected by $\{(\mu\text{-H})\text{Rh}[\text{P}(\text{O-}i\text{-C}_3\text{H}_7)_3]_2\}_2$ is destroyed in a competitive reaction whereby a monomeric complex is formed underscores an oft-described flaw in cluster catalysis, namely, generation of mononuclear metal species. Nevertheless, a principle has been established although utilization of such unique cluster-catalyzed reactions must await design of more robust, catalytically active coordinately unsaturated clusters.

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Registry No. 3a, 82135-60-2; **3b**, 82135-62-4; **3c**, 82135-63-5; **4**, 85354-14-9; $\{(\mu\text{-H})\text{Rh}[\text{P}(\text{O-}i\text{-C}_o\text{H}_7)_3]_2\}_2$, 70727-44-5; $\text{H}(\mu\text{-H})_3\text{Rh}_2[\text{P}(\text{O-}i\text{-C}_3\text{H}_7)_3]_4$, 70727-45-6.

Supplementary Material Available: Tables and figures pertaining to the X-ray crystallographic studies of **3b**, **3c**, and **4**, including thermal parameters (Tables X–XIII), calculated and observed structure factors (Tables XIV–XVI), and stereodiagrams (Figures 9–11) (84 pages). Ordering information is given on any current masthead page.

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Strain–Reactivity Relations as a Tool for the Localization of Transition States. Equilibria, Solvolysis, and Redox Reactions of Substituted Cycloalkanes[1]

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Abstract: MM2 force field calculations are used to obtain strain energy differences ΔSI between sp^2 and sp^3 hybridization states of substituted cycloalkanes with ring size $n = 4$–12. It is shown that arbitrarily chosen models with substituents such as X = H, OH, CH_3, Hal may lead to a description of steric hindrance around X, instead of $\Delta SI_{sp^2/sp^3}$. If cycloalkanes, which are found largely free from this ambiguity, are analyzed with a proper representation of the multiple reacting conformers, a wide range of reactions, for most of which experimental data are available in the literature, shows satisfactory correlations with sensitivities (slopes) $m = 0.1$–1.0. For equilibria of ketones (characterized by $\Delta G^\circ{}_{exp}$) one obtains: with HCN $m = 0.97$, with H_2SO_3 1.11, with ROH (Meerwein–Ponndorf–Verley isomerization) 0.74. Comparison with $\Delta G^*{}_{exptl}$ for solvolysis of tosylates leads to $m = 0.87$ in CF_3CH_2OH, to $m = 0.69$ in AcOH, to $m = 0.43$ in $EtOH/H_2O$, showing more scatter and less sp^2 character in the more nucleophilic solvents. The contribution to the strain differences ΔSI is ~60% Pitzer strain, ~25% bond angle strain, but only ~3% transannular strain, even for cyclodecanes. The rates of alcohol oxidation with $H_2Cr_2O_7$ ($m = 0.13$) indicate very early and those of $NaBH_4$ ketone reduction ($m = 1.00$) extremely late transition states. The results are compared to other mechanistic data, such as to reported stereoselectivities of reductions; they indicate any nonclassical participation in the tosylate solvolysis for cyclobutane to be small ($\Delta\Delta G^* \lesssim 2$ kcal/mol), and for medium rings to be unrecognizable ($\Delta\Delta G^* \lesssim 0.5$ kcal/mol). The correlation of enzymatic (HLADH) reduction rates of cycloalkanones shows considerable scatter, but indicates that the TS is more product- than reactant-like. A necessary revision of the OH orientation in the diamond lattice analysis of the active site is supported by MM2 calculations on axially disubstituted cyclohexanes, which suggest also that nonchair forms need to be considered.

A. Problems and Applications of Strain–Reactivity Calculations. Quantitative relations between steric effects and chemical reactivities hold much promise both for the study of reaction mechanism and for the rational planning, e.g., for stereoselective

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Table I. Strain Energies SI for Different Substituents in Different Environments[a]

compd	X pos	X = H (SI)	X = OH (ΔSI)	X = CH_3 (ΔSI)	X = =O (ΔSI)
cyclobutane	eq	26.59	0.05	−0.54	27.25
cyclohexane	eq	2.61	0.05	−0.06	3.50
cyclohexane	ax		0.61	1.68	
cyclooctane[b]	(weighted)	14.32	(Br 0.14)	0.50	11.80
cyclododecane		12.75		0.57	10.33
norbornane	7	18.45	1.24	2.00	22.10
norbornane	2-exo		0.31	0.71	18.79
norbornane	2-endo		0.84	1.33	
norbornane, 1,7,7-trimethyl	2-endo	24.03	1.23	2.49	22.00
(bornane)	2-exo		1.72	3.90	
norbornane, 1,3,3-trimethyl	2-endo	20.65	1.72	3.31	18.97
(fenchane)	2-exo		1.70	3.45	
norbornane, 3,3-dimethyl (camphenilol)	2-endo	21.41	1.02	2.35	21.21
3-*exo*-methylnorbornane	2-exo	19.16	1.04	2.11	19.56

[a] MM2 calculations; C–OH rotamers included as weighted averages; SI in kcal/mol; $\Delta SI = SI_X - SI_H$. [b] SI for cyclooctane was calculated as the weighted average for all e- and a-substituted BC and CC conformations, including X = F (0.13 kcal/mol).

syntheses. Classical linear free energy relations as pioneered for steric effects by Taft furnish substituent effects and reaction constants on the basis of empirical correlations between different reactions.[2] In contrast, the use of molecular mechanics force fields[3] (FF) for strain energy relations aims at the prediction of reactivities directly from the given molecular structures. The FF approach has been most widely applied to reactions which are characterized by interconversion between trigonal and tetrahedral carbon atoms.[4-14] The associated strain energy changes, $\Delta SI_{sp^2/sp^3}$, can be obtained from FF calculations for the corresponding sp^2 and sp^3 states, e.g., of ketones and alcohols, and compared to the observed reactivities.

If a reaction is essentially controlled by strain effects, a change in SI will produce numerically the same change in $\Delta H°$ in chemical *equilibria*, leading to sensitivities, or slopes of $m = 1$ in plots of $\Delta H°$ vs. ΔSI. The *kinetics* of a sterically controlled reaction again will show high sensitivities, or slopes close to 1, if the transition state is structurally far apart from the ground state, or late in terms of Hammonds postulate.[15] A slope close to zero is indicative of a very early transition state, which will of course be difficult to observe since in this case the rates will approach zero sensitivity toward the strain differences reflected in ΔSI.

Apart from the predictive use of FF calculated steric effects, the comparison of reactivity and strain energy changes could obviously be developed into a valuable tool for the localization of transition states in sterically controlled reactions. However, this aspect has been dealt with only occasionally so far, and indeed there are several prerequisites to be met before one can hope to arrive at a rigorous description of reactivity as a function of strain effects. One major problem, the FF description for the reacting substituent, will be the focus of section B, in which we also demonstrate that arbitrarely chosen models for substituents may possibly furnish values for steric hindrance around the reacting center, instead of the desired $\Delta SI_{sp^2/sp^3}$ differences. Another important problem arises with the occurrence of several conformers in a reaction and will be discussed in the context of chemical equilibria in section C. After resolving these problems it is possible to draw conclusions with respect to the structure of transition states for a wide range of cycloalkane and parent alkane reactions (sections D–G), including an enzyme-catalyzed redox reaction. Most of the necessary kinetic measurements are available from the literature (see Table III), with the exception of certain solvolysis data included in Tables III and S8, which were determined in the present work.

The cycloalkane derivatives investigated in the present study are known for a dramatic dependence of reactivity on ring size, which had been explained in Brown's "I-strain" rationalization on the basis of differences in torsional and nonbonded interactions in the sp^2 and sp^3 states of these molecules.[16-18] The force field

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Table II. Strain Energies of the Substituted Cycloalkanes[a]

	R = CH_3			R = =O		
n	conformations[b]	lowest	weighted	conformations[b]	lowest	weighted
4	eq, ax	26.05	26.21		27.25	(27.25)
5	E 1, 2*, 3*	7.84	8.10	E 2*, _3_*	7.68	7.30
	TC 1, 2*, _3_*			TC 1, 2*, 3*		
6	eq, ax	2.51[c]	2.59[c]		3.50	(3.50)
7	TC 2*, 3*, 4*, _5_*	10.10[d]	10.11[d]	TC 2*, _3_*, 4*, 5*	8.29	8.44
8	BC 1, _2_*, 3*, 4*, 5	14.59	14.82	BC 1‘ 2*, _3_*, 4	11.30	11.80
				TCC 3		
9	TBC _1_*, 2*					
	TCC 1*, 6*; TCB 1*, 2*	18.01	18.46	TBC _1_*	12.56	12.80
				TCC 1*, TCB 1*		
10	TCCC 1*, _3_*, 4*	18.47	18.69	TCCC 3*, 4*		
				BCB _1_*, 3*, 4*	13.70	13.82
11	TCCC[e] 2*, 3*, 4*, 5*, _6_*, 7*	18.38	18.58	TCCC 3*, _4_*, 5*, 6*, 7*	15.46	15.81
12	D_4 C, N	13.25	13.32	D_4 *N*	10.33	10.34

[a] From MM2 calculations in kcal/mol; for procedure, see text. Substituent position either (pseudo)equatorial, or isoclinal, if applicable. Conformers denoted by asterisks are multiple by symmetry, the one with the lowest strain is italicized. [b] Only conformers populated to >1% are noted, but others are also included in the calculation of weighted SI values. [c] For R = OH: 2.56 (L), 2.80 (W) (MM2). [d] For R = Br. [e] Ring geometry similar to the "335" conformation (Dale, J. *Top. Stereochem.* 1976, *9*, 199).

analysis provides not only a numerical basis for this explanation, but also information on the different strain energy contributions and on the geometry of the reacting species. In addition, the eventual deviation of a particular system from the $\Delta H^*/\Delta$SI regression line can be used as a test for nonclassical contributions, such as charge delocalization in solvolysis reactions of cyclobutane or transannular hydrogen participation in medium ring derivatives (see section D).

B. Force Field Description of Substituents. In the force field analysis of solvolysis reactions, hydrogen,[5] hydroxyl, or methyl[6,7a] groups have been used to mimic leaving groups such as, e.g., the tosyloxy substituent. The treatment of alcohol oxidations was based largely on the use of the methyl group for the hydroxy substituent.[12] However, the calculations were applied to skeletons which exhibit quite variable steric hindrance around the reacting centers. In consequence, the strain energy SI calculated for a selection of alicyclic frameworks (Table I) not only differs substantially for X = H, OH, Hal, or Me, but the difference itself is a function of the given ground-state geometry, increasing from $\Delta SI_{H,Me} = 0$ for unhindered positions to $\Delta SI_{H,Me} = 3.9$ kcal/mol for exo-substituted bornane structures (Table I). As a result the variation, or slope, obtained in such a strain–reactivity relation may be determined partially by the chosen calculational model. In consequence, if the influence of the substituent model is not clarified, one cannot be sure to which degree a successful correlation describes the change of internal strain during the reaction (which is the aim of the published correlations[4–13]), as distinct from steric hindrance around the substituent. The latter factor is expected to be relevant in the cases of a crowded environment around the functional site, of attack by bulky reagents,[16] or of severe front (F) strain release upon dissociation of the substituent.[19]

Use of hydrogen as a model instead of methyl will not solve the problem, since a part of the internal strain change will of course always be due to interactions with the substituent. A more realistic parameterization of the substituents would be advantageous but still open to ambiguity in view of the solvation of these groups or, e.g., the introduction of an ester group in chromic acid oxidations.

Are there systems which are largely free from the arbitrariness of the substituent model selection? We believe that monocyclic alkanes provide such a series, which at the same time show large reactivity differences, traditionally ascribed to conformational effects as proposed in Brown's I strain explanation.[16,17a,18] Here the choice of the substituent model does not significantly influence the calculated strain energy, as illustrated by cyclooctanes showing $\Delta SI \leq 0.5$ kcal/mol for X = H, F, Br, Me (Table I). The reason for this insensitivity is of course the small steric interaction of X with neighbor atoms in less hindered equatorial or pseudo equatorial positions, which dominate also in the medium rings. Thus, other than in axially substituted cyclohexanes or in most bicyclic compounds, the strain energy changes in reactions of monocycloalkanes of different ring size occur largely in the residual molecular parts and not to a different degree in the surroundings of the substituent; such cases may therefore be described as internal strain controlled systems.

C. Equilibria and Reactions between Multiple Conformers. The occurence of flexible conformers of comparable energy is typical not only for medium rings, but for many other aliphatic compounds. A force field description of the ground state in such cases must start from the weighted average SI given by

$$SI = aSI_a + bSI_b \ldots + iSI_i$$

with the population $a \ldots i$ and the strain $SI_{a \ldots i}$ for a given conformer. For the comparison of equilibrium constants *K* and strain energy differences ΔSI, one has to use the weighted SI values for both sides of the reaction. Table II contains weighted SI for both sp^3 and sp^2 ground states for cycloalkanes, based on calculations with Allinger's MM2 field[3] for methyl compounds as sp^3 models, and cycloalkanones representing rings containing one sp^2 center. The use of the MM1 field led generally to somewhat less satisfactory correlations and to sensitivities, *m*, lower by 5–10%, which is to be expected from the slightly exaggerated hydrogen nonbonded interactions in this parameterization. Experimental data for cycloalkane $sp^3 \rightleftharpoons sp^2$ equilibria are available for the cyanohydrin[20] and the bisulfite addition[21] (reactions 1 and 2 in Table III); comparison of the experimental $\Delta G°$ values ($\Delta H°$ not being available) with the calculated $\Delta SI_{sp^2,sp^3}$ (weighted) shows satisfactory[22] linear relations and slopes close to $m = 1$ (Figure 1A,B) indicating that the equilibrium is indeed dictated by the strain energy differences between the sp^2 and sp^3 states. The recently investigated Meerwein-Ponndorf-Verley (MPV) equilibria between oxo- and hydroxycycloalkanes[12d] correlate only with a sensitivity of $m = 0.74$ (Figure 1C); it should be noted, however, that the experimental data here refer to less well-defined species,

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Table III. Strain–Reactivity Correlations for Alicyclic Compounds[a]

no.	reaction	ref	n	ΔG (H)$_{exp}$	m	$\pm\Delta m$	r	ψ	s
1	$C_nH_{2n-2}O + HCN$	20	5-12, A	G°4.50	0.97	0.09	0.971	28	0.36
2	$C_nH_{2n-2}O + H_2SO_3$	21	5-7, A	G°3.30	1.11	0.09	0.991	19	0.20
3	$C_nH_{2n-2}O$ + ROH(MPV)	12d	4-12	G°3.84	0.74	0.08	0.954	34	0.40
4	$C_nH_{2n-1}OTS + CF_3CH_2OH$[b]	*c*	4-12, A	G*4.75	0.87	0.09	0.966	30	0.43
5	$C_nH_{2n-1}OTS + H_2O/EtOH$[b]	*c*	4-12, A	G*3.04	0.43	0.12	0.826	67	0.69
6a	$C_nH_{2n-1}OTS + CH_3COOH$[b]	18b	5-12	G*4.04	0.69	0.16	0.853	60	0.78
6b	$C_nH_{2n-1}OTS + CH_3COOH$[b]	18d	5-12	G*4.05	0.70	0.05	0.986	21	0.25
7	$C_nH_{2n-2}O + NH_2OH$	44	4-9	G*3.54	0.52	0.17	0.803	73	0.74
8a	$C_nH_{2n-2}O + NaBH_4$	35	4-12, A	G*5.27	1.00	0.09	0.967	28	0.49
8b	$C_nH_{2n-2}O + NaBH_4$	35	4-12, A	H*7.50	0.99	0.17	0.887	51	0.99
9	$C_nH_{2n-1}OH + H_2Cr_2O_7$	43	4-12	G*0.93	0.13	0.025	0.857	60	0.17
10	$C_nH_{2n-1}OTs + KI$[d]	46	5-12, A	E_A5.11	(0.39	0.30	0.381	99	1.73)[d]
11	$C_nH_{2n-1}OH + V_2O_5$[d]	47	5-8	G*0.8	(0.13	0.05	0.777	89	0.20)[d]
12	"B" values	45	4-7	"B"(1.3)	0.45	0.13	0.890	63	0.29

[a] Alicyclic compounds with ring size n; Acyclic: A; ΔG (H)$_{exptl}$ in kcal/mol, variation from experimental K or k. m: slope (or sensitivity) from plots of ΔG (ΔH)$_{exp}$ vs. SI (SI from MM2 calculations, Table I). r, ψ (%): ref 22, s, standard deviation in ΔG (ΔH) (kcal/mol). [b] Regression analysis without compounds $n = 12$ and $n = 4$, if applicable (see text). Values m (r) *with* these derivatives: *nr.* 4: 0.63 (0.797); *nr.* 5: 0.41 (0.688); *nr.* 6: 0.68 (0.848). [c] This work, see also ref 7a. Kinetic data measured in 97% TFE and 80% EtOH (see supplementary material). [d] No correlation to be expected.

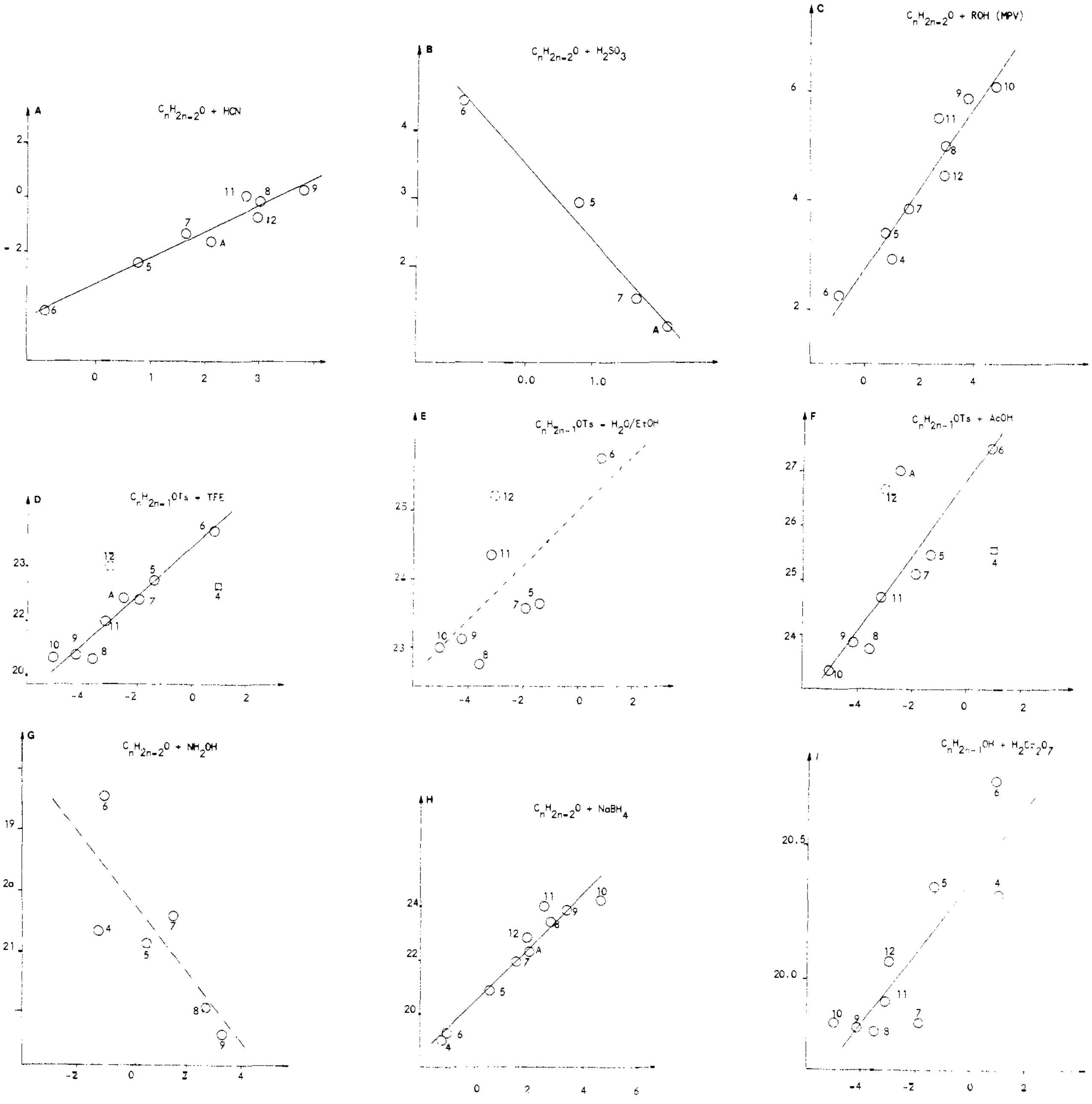

Figure 1. Plots of ΔG (ΔH)$_{exp}$ vs. ΔSI for the reactions listed in Table III. The numbers refer to rings size n; acyclic compounds = A. Ordinates and abscissas are given in kcal/mol.

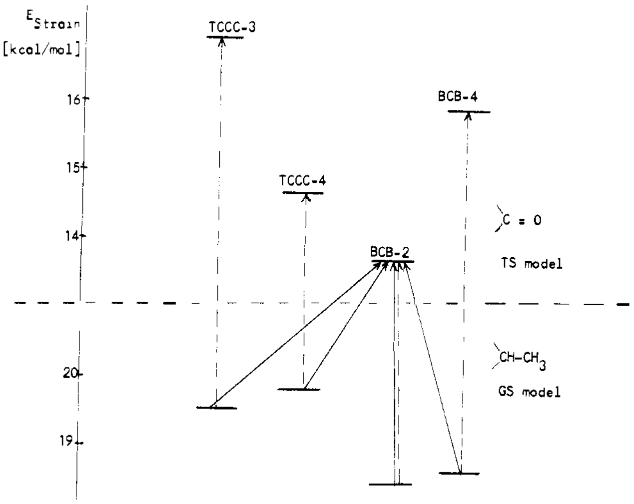

Figure 2. Reactions with multiple conformers, illustrated with cyclodecane BCB and TCCC forms. Solid lines correspond to reaction pathways via the most stable TS (following the Curtin–Hammett principle), dashed lines to a separate TS for each conformer.

since the alcohols are partially present as aluminum alkoxides, and particularly as dimers or polymers. The association by hydrogen bonds is known to lead to concentration-dependent conformational free energy values for cyclohexanol ($\Delta G°$ 0.6–1.1 kcal/mol)[23] which are not reflected in the force field description of the monomers ($\Delta G° = 0.55$ kcal/mol for the e-OH/a-OH difference; see Table I). Due to these complications the MPV equilibration values[12d] are less suited for the evaluation of ΔSI in cycloalkane reactions.

Whereas the calculation of internal strain controlled equilibrium constants on the basis of weighted strain energies is straightforward, the force field application to chemical rates involves an interesting complication which is illustrated by a cyclodecane reaction (Figure 2). If we extend the Curtin–Hammett principle[15b,17b] here to intermediates and transition states, only the one transition state of the lowest energy (SI_{min}) will be passed through, starting from the different ground-state populations represented by $SI_{weighted}$. This model will apply as long as conformational interconversion at points close to the transition state is fast compared to the rate-determining step; consequently, the experimental values of ΔG^* (if available with acceptable accuracy, ΔH^*) are correlated to $\Delta SI = SI_{min} - SI_{weighted}$ (Figure 1D–I). As pointed out earlier,[7a] the assumption of faster conformational equilibration breaks down eventually with cyclododecane which is known to be the only relevant ring where conformational exchange is rather slow.[24] If weighted SI are used for both ground- and transition-state models in the case of cyclododecyl tosylate solvolysis, the calculated ΔSI value comes indeed closer to experimental ΔG^*.[7a] An additional reason for the deviation of cyclododecane from the regression lines can be seen in a larger influence of the chosen substituent model for this particular ring system (see Table I), which is due to partially pseudoaxial substituents. In most systems the difference between ΔSI based on weighted or minimum SI (Curtin–Hammett) values are small compared to $\Delta\Delta G^*_{exp}$ (Table II).

D. Solvolysis Reactions. The force field analyses of nucleophilic substitutions at bridgehead derivatives, introduced by Schleyer et al., belong to the most successful strain–reactivity applications.[5] They are likely to be less obscured by differential steric hindrance of solvation, or front strain effects, since the internal strain built up during the reaction is probably larger by orders of magnitude. Therefore, the choice of the leaving group model here will have little influence on SI, as has already been found by Smith and Harris[6] for severely strained polycyclic secondary esters. The bridgehead derivatives are also essentially free from a participation of nucleophilic solvent attack (k_s).[25] The opposite holds for solvolysis reactions of secondary cycloalkyl sulfonates, as evident from the large improvement in the correlation if the weakly nucleophilic trifluoroethanol (TFE) is used instead of an aqueous solvent (see Figure 1D,E and Table III). In acetic acid, which is of intermediate nucleophilicity, one obtains a poorer correlation and smaller slope (Figure 1F), indicating a stronger solvent-assisted pathway k_s as compared to TFE. It appears, that solvolytic data for many secondary sulfonates in conventional solvents are too divergent in mechanism to be useful in strain–reactivity studies.

In addition to the correlations obtained earlier on the basis of MM1 calculations,[7a] our analysis, now based on MM2 generated SI values, includes 3-pentyl tosylate as a model for an acyclic compound (A), which fits well into the correlations, as well as cyclobutyl tosylate. Solvolysis reactions with the four-membered ring have frequently been associated with the formation of a nonclassical ion,[26] mainly on the basis of the reactivity which seems very high in view of the necessary bond angle widening occuring in the $sp^3 \rightarrow sp^2$ interconversion. Our analysis (Figure 1D) shows that the activation energy for cyclobutyl tosylate is smaller than expected for an entirely classical mechanism, but only by 2 kcal/mol at most. This difference would become larger if a correction were made for the inductive effect of the longer carbon chain in the other cycloalkanes. In view of the present uncertainty of polar alkyl effects[27] and their dependence on orientation and hybridization of the participating bonds, such a correction was not attempted.

The deduction of neighbor group assisted pathways (k_Δ)[25] from the deviation of observed rates from force field calculated unassisted mechanisms (k_c)[25] was carefully investigated recently by Smith and Harris,[6] and earlier by Foote and Schleyer on the basis of their known correlations.[28] Even though we were able to remove largely the ambiguities of the leaving group model and the solvent-assisted pathway (k_s) in this study, the scatter of the correlation (Figure 1D) only allows assignment of significant participation (k_Δ) to compounds which deviate by >0.5 kcal/mol from the regression line. With respect to the solvolysis mechanisms of medium rings, our analysis provides no evidence for nonclassical participation but shows steric effects to be responsible for the high rates of these reactions. Thus, the fast solvolysis of cyclooctane derivatives, which are partially ascribed to transannular hydrogen bridging,[29,30] is predicted to within ±0.5 kcal/mol by steric effects alone, which is in accord with recent interpretations of corresponding solvolysis products.[31] Force field calculations of the different strain energy contributions also give insight into the detailed origin of the total strain change in going from the sp^3 to the sp^2 state.[7a] If torsional strain (E_T) and 1.4 repulsions (E_{V_1}) are taken together (since both describe torsional interactions), the data (see supplementary material, also ref 7a) indicate that they account for 55–65% of the strain relief in the reactions of the medium ring compounds, whereas bond angle energies (E_B) change by 20–30% between sp^3 and sp^2. Transannular strain, represented by the E_{V_2} term, which in absolute numbers is smaller than anticipated earlier,[32] contributes not more than 3%, the bond length

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(28) (a) Foote, C. S. *J. Am. Chem. Soc.* **1964**, *86*, 1853. (b) Schleyer, P. v. R. *Ibid.* **1964**, *86*, 1854.

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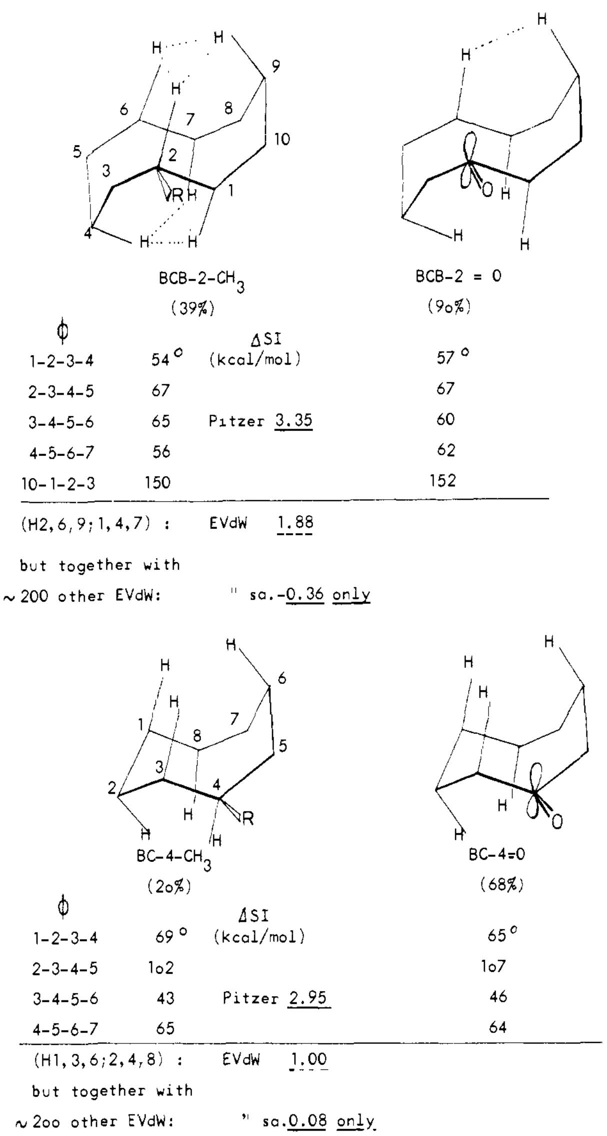
(32) See: (a) Prelog, V.; Traynham, J. G. In "Molecular Rearrangements"; de Mayo, P., Ed.; Interscience: New York, 1963; Part I, p 593 ff. (b) Dunitz, J. D.; Prelog, V. *Angew. Chem.* **1960**, *72*, 896.



ϕ	BCB-2-CH$_3$ (39%)	ΔSI (kcal/mol)	BCB-2 = O (9o%)
1-2-3-4	54°		57°
2-3-4-5	67		67
3-4-5-6	65	Pitzer 3.35	60
4-5-6-7	56		62
10-1-2-3	150		152

(H2,6,9;1,4,7) : EVdW 1.88

but together with

~200 other EVdW: " sa.-0.36 only

ϕ	BC-4-CH$_3$ (2o%)	ΔSI (kcal/mol)	BC-4=O (68%)
1-2-3-4	69°		65°
2-3-4-5	1o2		1o7
3-4-5-6	43	Pitzer 2.95	46
4-5-6-7	65		64

(H1,3,6;2,4,8) : EVdW 1.00

but together with

~2oo other EVdW: " sa.0.08 only

Figure 3. Selected cyclooctane and cyclodecane conformations with typical torsional angle and Pitzer energy changes, and transannular interaction differences between the sp^3 and sp^2 state.

differences (E_C) up to 9%. (The sum of the steric energy E here is given by $E = E_C + E_B + E_{V_1} + E_T + E_{V_2}$.[3]) This dissection of the strain energy applies, of course, also to other reactions of cycloalkanes which fit into the strain-reactivity correlation.

Whereas the unusual reactivity of medium ring compounds has been largely ascribed to Pitzer strain changes, which is supported by the present analysis, the high solvolysis rate of cyclodecane derivatives was believed to originate mainly in the relief of transannular repulsion between pseudoaxial hydrogens[32b] (Figure 3). This assumption was based largely on earlier X-ray analyses suggesting the absence of severe torsional angle ϕ distortions in the sp^3 state of ten-membered rings. Force field calculations, generally in accord with some more recent structural measurements (see supplementary material), show that there are ϕ deviations from 60° or 180° by up to 10°, which appear to be smaller in cyclodecanone ($\Delta\phi$ av ±3°). This leads to a dominating Pitzer strain relief in the case of cyclodecanes also. The transannular repulsions between e.g. the axial hydrogens at C(2), C(6), and C(9), and at C(1), C(4), and C(7) (Figure 3) decrease, according to MM2 calculations, from the sp^3 to the sp^2 state by 1.9 kcal/mol, but a simultaneous strain enhancement for other interactions reduces the total gain due to these nonbonded interactions to 0.36 kcal, or ~3% of the total $\Delta SI_{sp^2/sp^3}$. Similar observations apply to other cyclodecane conformations as well as to other rings, such as cyclooctanes (see Figure 3). The energy minimized structures show the strain to reside largely in torsional distortions, which certainly are the consequence of severe transannular repulsions in the nonrelaxed conformations.[34]

E. Redox Reactions and Ketones and Alcohols. The strong dependence of the reaction rates of cycloalkanones with sodium borohydride on ring size is one of the cornerstones of Brown's I-strain hypothesis.[16-19,35] In this case we can use not only ΔG^*, but also the ΔH^* values measured by the earlier workers[35] for the comparison with ΔSI and obtain fairly linear correlations even with the necessarily less accurate activation enthalpies (Figure 1H, Table III).

The observed slope of $m = 1.0$ indicates a very late transition state in this addition reaction of rather small nucleophiles to relatively unhindered ketones.[36] One of the practically important implications from this is that one expects little stereoselectivity in the $NaBH_4$ reduction of substituted cycloalkanones (as long as the substituent does not come close to the carbonyl group). In view of the small scatter of ΔG^* in the correlation, steric hindrance to nucleophilic approach, which is of course taken as zero in our model, should contribute <0.5 kcal/mol. The small stereoselectivities observed so far for cycloalkanones of different ring sizes accord indeed with this prediction ($n = 5$,[37a-c] $n = 6$,[36,37a] $n = 8$[31]), as does the predominance of the more stable epimer in the $NaBH_4$ reductions.

There have been several attempts in the literature aiming at a quantitative description of nucleophilic additions to aliphatic ketones,[37a,b,38] the more recent ones by Müller and Perlberger also based on molecular mechanics calculations.[12b,c] These correlations also comprise hindered ketones, for which the assumption of similar transition states as for the unhindered substrates becomes mechanistically less valid. The correlations obtained are less satisfactory ($r = 0.85$), and the rates are predicted with an average error of a factor of 10.[12b] The problem is also evident in some deviations between observed and calculated stereoselectivities of reduction.[12b] That the transition state for norbornanones, e.g., is largely characterized by steric hindrance to nucleophilic approach, in sharp contrast to, e.g., cyclohexanone, is already evident from the contrasting stereoselectivities, which with $NaBH_4$ change from 90:10 (favoring approach from the less hindered side) in the former to 20:80 in the latter.[39,40] Consequently, our correlation with SI, which is based on a homogeneous transition-state model for unhindered nucleophilic approach, is less satisfactory if applied to reduction rates[40] of hindered ketones with $NaBH_4$.[41]

Oxidation mechanisms of aliphatic alcohols have mostly been studied with chromic acid; they were thoroughly reviewed recently by Müller[42a,b] and will not be discussed in detail here. It has been recognized that the rates are sensitive toward strain differences between sp^3 and sp^2 states of the compounds; this is also visible in Sicher's[42c] relation of oxidation rates to the stability differences in epimeric alcohols. There is, however, a major unresolved controversy as to whether the transition states are more product- or reactant-like.[42a,b] Similar reasons as put forward for the ketone reduction would lead to the conclusion that for hindered alcohols

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[33] For selected numerical data and references on cyclohexane, -octane, and -decane conformations, see the supplementary material.

[34] We thank a referee for pertinent comments.

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[41] Schneider, H.-J.; Schmidt, G., unpublished results.

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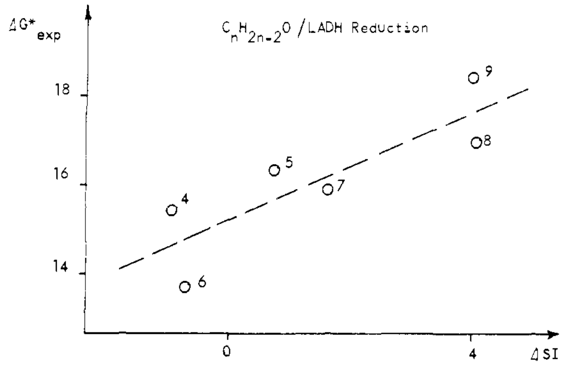

Figure 4. Plot of ΔG^* of the HLADH-catalyzed reduction[49b] of cycloalkanones vs. SI.

on should expect early transition states; this is in fact supported by a corresponding variation in isotope effects.[42a]

Nevertheless, Müller and Perlberger have applied molecular mechanics for a strain-reactivity correlation containing both unhindered and hindered alcohols, for which the difficulty involved with the choice of the substituent model was also clearly recognized.[12b] If we compare the chromic acid oxidation rates for unhindered cycloalkanols, which have been carefully measured by Richer et al.,[43] with our SI values, again assuming passage only through the sp^3-like transition state of lowest energy (applying the Curtin–Hammett principle), we obtain a correlation of gratifying linearity in view of the very small differences in the experimental activation free energies (Figure 1I, Table III). The slope $m = 0.13$ is complementary to the late transition states found for the $NaBH_4$ reduction ($m = 1.0$). The transition state in both reactions resembles more the alcohol (sp^3) than the ketone (sp^2) moiety.

F. Other Reactions. Any cycloalkane reaction in which the TS hybridization differs from that in the reactant ground state, and in which other, e.g., polar effects, differ less than ΔSI, are amenable to a strain–reactivity analysis. Geneste et al.[44] have found that the oximation rates for cycloalkanones show a similar dependence on ring size as, e.g., the borohydride reduction. The correlation with SI (Figure 1G), although of lower quality than the others (Table III), indeed suggests the transition state for hydroxylamine addition lies about halfway between sp^2 and sp^3.

Geneste et al. have also demonstrated that one variable, "*B*"[45]—presumably related to sp^2 – sp^3 strain energy differences—can give apparent linear correlations with log *k* for reactions with either reactant- *or* product-like TS, if compounds with a very large range of velocities are considered. As expected, these *B* values correlate less satisfactorily with the strain energy differences calculated for the cycloalkanes (see Table III). Strain–reactivity correlations can also be used as a test for the *absence* of rate-determining strain effects. Examples are the hydrolysis of cycloalkyltosylates (Figure 1E), as well as their bimolecular substitution,[46] or the cycloalkanol oxidation with vanadium pentoxide[47] (see Table III).

Application to a Bioorganic Mechanism: ADH Reactions

Horse liver alcohol dehydrogenase (HLADH) accepts an unusual wide range of substrates, which has stimulated theoretical and practical investigations with many aliphatic compounds.[48] For the reaction of cycloalkanones with HLADH, Lemière, Alderweireldt, et al.[49a] have reported a dependence on ring size similar to that found in the $NaBH_4$ reduction. Comparison of the enzymatic reduction rates[49b] with our MM2-calculated sp^2 – sp^3 strain energy differences ΔSI (Figure 4) shows considerable scatter of the points ($r = 0.838$, $\psi = 67\%$, $m = 0.54$). This is not unexpected in view of the recently reported[49b] strong and differential entropy contributions in the enzymatic catalysis for several cycloalkanone reductions. The ΔG^* dependence of ΔSI (Figure 4) suggests that a major contribution to the reactivity differences of these ketones in the active site of the protein stems from internal strain variations in the substrate and that the transition state is closer to sp^3 hybridization, although not as extreme as in the $NaBH_4$ reduction ($m = 1.0$).

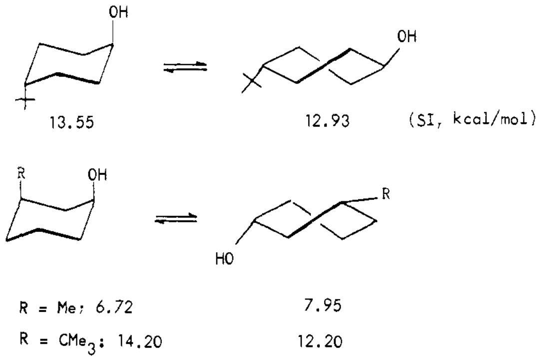

Figure 5. Diaxially substituted cyclohexane chair forms and alternative twist boat conformations; SI values from MM2 calculations.

In the often used fitting procedures of the substrate to the active site of ADH,[48,50] it is invariably assumed that the hydride will approach the carbonyl group from the less hindered side, yielding an axial OH group orientation in cyclohexanes. This stereochemistry would require very early and ketone-like transition states, with little dependence of the rates on internal strain changes of the substrate ($m \sim 0$), and no resemblance to $NaBH_4$ reductions, in contradiction to the findings with the cycloalkanones. That *unhindered* ketones indeed react similarly with ADH as with $NaBH_4$ is indicated also by the comparable ratios of epimers formed in both reactions with most 4-alkylcyclohexanones.[49c] Even the 4-*tert*-butyl- and the 3-alkylcyclohexanones undergo nucleophilic attack from the axial side at the expense of not more than 1.9–2.5 kcal/mol over equatorial approach.[49c] The corresponding cyclohexane chair forms bearing axial hydroxyl and alkyl substituents would require considerable strain energy, as calculated with MM2, e.g., for trans-4-*tert*-butylcyclohexanol (see Figure 5 and supplementary material). Although a compensation of this strain energy could always be ascribed to favorable substrate–protein interactions in the active site,[50a] it should be taken into consideration that these epimers could be formed with less internal strain from twist boat forms (Figure 5).

Recent investigations by Lemière et al.[49b,c] indicate not only significant activation entropy differences as a function of the alkyl substituent, but also the occurrence of nonchair cyclohexane forms in the rate and product-determining step of the enzymatic redox reaction.[51]

Experimental and Computational Details

Cycloalkyl tosylates were prepared as described in the literature.[18b,d]

Solvolysis rates were measured by recording automatically the conductivity change of 10^{-3} M tosylate solutions in a thermostated (±0.05°) cell with platinized platinum electrodes (cell constant 0.24 cm^{-1}). Within the concentration range used, the conductivity (~1 m S) was found to be a linear function of the *p*-toluenesulfonic acid (TsOH) concentration.

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(43) (a) Richer, J.-C.; Hoa, T. T. N. *Can. J. Chem.* **1969**, *47*, 2479. For reactions with cyclobutanol, see: (b) Rocek, J.; Radkowsky, A. E. *J. Am. Chem. Soc.* **1973**, *95*, 7123. For reactions with cyclopentanoles, see: (c) Wechsler, P. S.; Fuchs, B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 943.

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(50) For recent references, see: (a) Dutler, H.; Bränden, C.-I. *Bioorg. Chem.* **1981**, *10*, 1. (b) Jones, J. B.; Jakovac, I. J. *Can. J. Chem.* **1982**, *60*, 19.

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J. Am. Chem. Soc. **1983**, *105*, 3563-3567

The reactions were usually followed for 5 half-life times; the end point obtained after increasing the temperature for some time was 95–100% in most cases, if compared to the calculated end point on the basis of curves calibrated with TsOH. The recorded data were analyzed with suitable computer programs, indicating no deviation from fist-order kineics (see supplementary material). The alcohols used as solvents contained <0.2% water (Karl-Fischer titration) and were brought to the composition as given in the tables by adding distilled water.

Force field calculations were carried out with Allinger's MM2 program[3a] on the Siemens 7.760 of the Rechenzentrum der Universität des Saarlandes. The starting geometries for the conformers were generated by attaching substituents at the different carbon atoms, methyl usually only in (pseudo)equatorial or isoclinal positions. In a few cases the strain energies of (pseudo)axial methylcycloalkanes were also tested and found to be >2 kcal/mol less stable (e.g., with cyclooctanes, see supplementary material).

All ring systems retained their basic conformation during the energy minimization, with the exception of cyclopentanes, which therefore had to be analyzed by inspection of the full pseudorotational circle.[52]

Other calculations, such as of weighted strain energies and populations of conformers, or linear regression analyses were performed with Fortran and BASIC programs on the Siemens 7.760 or an Apple II+ computer.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support and two referees for helpful suggestions.

Registry No. Cyclobutane, 287-23-0; cyclohexane, 110-82-7; cyclooctane, 292-64-8; cyclododecane, 294-62-2; norborane, 279-23-2; 1,7,7-trimethylnorborane, 464-15-3; 1,3,3-trimethylnorborane, 6248-88-0; 2,2-dimethylbicyclo[2.2.1]heptane, 6248-85-7; 2-*exo*-methylnorbornane, 872-78-6; hydroxycyclobutane, 2919-23-5; hydroxycyclohexane, 108-93-0; hydroxycyclooctane, 696-71-9; 7-hydroxybicyclo[2.2.1]heptane, 2566-48-5; 2-*exo*-hydroxybicyclo[2.2.1]heptane, 497-37-0; 2-*endo*-hydroxybicyclo[2.2.1]heptane, 497-36-9; 2-*endo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane, 507-70-0; 2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane, 124-76-5; 2-*endo*-hydroxy-1,3,3-trimethylbicyclo[2.2.1]heptane, 14575-74-7; 2-*exo*-hydroxy-1,3,3-trimethylbicyclo[2.2.1]heptane, 22627-95-8; 3,3-dimethylbicyclo[2.2.1]heptan-2-*endo*-ol, 640-54-0; 2-*exo*-hydroxy-3-*exo*-methylbicyclo[2.2.1]heptane, 16745-65-6; methylcyclobutane, 598-61-8; methylcyclohexane, 108-87-2; methylcyclooctane, 1502-38-1; methylcyclododecane, 1731-43-7; 7-methylbicyclo[2.2.1]heptane, 1679-14-7; 2-*exo*-methylbicyclo[2.2.1]heptane, 872-78-6; 2-*endo*-methylbicyclo[2.2.1]heptane, 765-90-2; 2-*endo*-methyl-1,7,7-trimethyltricyclo[2.2.1]heptane, 57905-88-1; 2-*exo*-methyl-1,7,7-trimethylbicyclo[2.2.1]heptane, 57905-87-0; 2-*endo*-methyl-1,3,3-trimethylbicyclo[2.2.1]heptane, 85283-01-8; 2-exo-methyl-1,3,3-trimethylbicyclo[2.2.1]heptane, 85283-02-9; 2-*endo*-methyl-3,3-dimethylbicyclo[2.2.1]heptane, 20536-40-7; 2-*exo*-methyl-3-*exo*-methylbicyclo[2.2.1]heptane, 20536-41-8; cyclobutanone, 1191-95-3; cyclohexanone, 108-94-1; cyclooctanone, 502-49-8; cyclododecanone, 830-13-7; bicyclo[2.2.1]heptan-7-one, 10218-02-7; bicyclo[2.2.1]heptan-2-one, 497-38-1; 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, 76-22-2; 1,3,3-trimethylbicyclo[2.2.1]heptan-2-one, 1195-79-5; 3,3-dimethylbicyclo[2.2.1]heptan-2-one, 13211-15-9; 3-*exo*-methylbicyclo[2.2.1]heptan-2-one, 3915-75-1; methylcyclopentane, 96-37-7; bromocycloheptane, 2404-35-5; methylcyclononane, 874-99-7; methylcyclodecane, 13151-43-4; methylcycloundecane, 13151-44-5; cyclopentanone, 120-92-3; cycloheptanone, 502-42-1; cyclononanone, 3350-30-9; cyclodecanone, 1502-06-3; cycloundecanone, 878-13-7; 3-pentyl tosylate, 950-25-4; cyclobutyl tosylate, 10437-85-1.

Supplementary Material Available: Strain energies of cycloalkanone and methylcycloalkane conformations, selected data on cyclohexane, cyclodecane, and cyclooctane conformations (torsional angles, strain energy distributions and populations, from MM2 calculations); kinetic data on solvolysis of cycloalkyl tosylates in ethanol/water (1:1) and trifluoroethanol (10 pages). Ordering information is given on any current masthead page.

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Diazotetrakis(trifluoromethyl)cyclopentadiene and Ylides of Electronegative Elements

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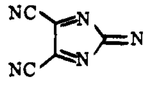
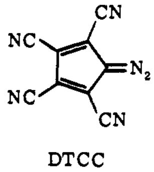
Abstract: The synthesis of diazotetrakis(trifluoromethyl)cyclopentadiene (**1**) is described. This stable perfluorinated diazo compound undergoes a photochemical loss of nitrogen to yield a reactive intermediate which reacts with a variety of elements bearing lone pairs to give tetrakis(trifluoromethyl)cyclopentadiene ylides. The synthesis of carbonyl, thiocarbonyl, and halonium ylides is described as well as evidence for oxonium and nitrilium ylides.

Introduction

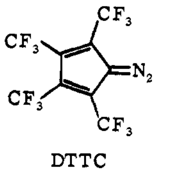
Our interest in diazocyclopentadienes bearing strong electron-attracting substituents as sources of extremely electrophilic carbenes led us to synthesize diazotetrakis(trifluoromethyl)cyclopentadiene (**1**). Attempts to use the tetrakis(trifluoromethyl)cyclopentadienone[1] as a precursor were unsuccessful owing to the severe umpolung displayed by this molecule.[2] The recent synthesis of 5*H*-perfluoropentamethylcyclopentadiene[3] led us to attempt the synthesis of the tetrakis(trifluoromethyl)cyclopentadienide anion by a similar route. We hoped that the diazo compound **1** could be derived from this anion by one of the established techniques for such conversions. The electrophilic nature of the carbene derived from **1** should make it a good candidate for the formation of ylides with electronegative elements (e.g., the halogens or chalogens). Similar diazo compounds, for example, diazodicyanoimidazole (DDI)[4] and diazotetracyanocyclo-



DDI



DTCC



DTTC

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(1) We are grateful to D. M. Lemal for providing the details of his synthesis of this ketone.

(2) (a) J. L. Boston, W. A. Sharp, and G. Wilkinson, *J. Chem. Soc.*, 3488 (1962); (b) R. S. Dickson and G. Wilkinson, *ibid.*, 2699 (1964); (c) D. M. Roundhill and G. Wilkinson, *J. Org. Chem.*, **35**, 3561 (1970).

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