9-Bromo-7,12-dimethylbenz[a]anthracene (26)*. Replacement of the amino group in **37** by bromine essentially as described for **24** gave only 85 mg of **26** (mp 173–175 °C) from 542 mg of **37**.

7-Bromo-1-bromomethylnaphthalene (38)*. Treatment of 11.05 g of 7-bromo-1-methylnaphthalene[20] with 10 g of NBS and 0.5 g of recrystallized benzoyl peroxide in 300 mL of CCl_4 at reflux for 6 h yielded 14.0 g (93%) of pure **38**, mp 108–109 °C (on recrystallization from benzene).

7-Bromo-1-naphthaldehyde (27)*. A suspension of 40 g of hexamethylenetetramine in 50 mL of alcohol and 25 mL of water and 6.0 g of **38** was held at reflux for 6 h. After the mixture cooled, 15 mL of concentrated HCl was added and refluxing continued for 1 h. After the usual workup there was obtained 4.0 g of pure **27**, mp 111–112 °C (on recrystallization from EtOH).

3-(7-Bromo-1-naphthyl)phthalide (28)*. To a stirred solution of 3.5 g of 4,4-dimethyl-2-phenyl-2-oxazoline[22] in 50 mL of dry THF at −20 °C was added 20 mL of *n*-butyllithium (1.2 M) during 15 min. After 0.5 h at −20 °C a solution of 4.7 g of **27** in 20 mL of THF was added in 15 min. After 1 h at −20 °C and 6 h at room temperature, the isolated reaction product was refluxed in 100 mL of EtOH and 5 mL of concentrated H_2SO_4 for 1 h to yield 5.2 g (77%) of **28** (mp 198–200 °C) pure enough for the next step. The analytical sample melted at 200–201 °C. Attempts to use the diethylamide[32] instead of **22** gave very poor results.

***o*-[(7-Bromo-1-napthyl)methyl]benzoic Acid (29)*.** A mixture of 1.5 g of **28**, 2 g of red phosphorus, 50 mL of acetic acid, and 3 mL of hydriodic acid[23] was refluxed for 4 h. The crude brown acid obtained yielded 1.25 g (83%) of colorless **29**, mp 206–707 °C (on crystallization from EtOH). Attempted reductions of **28** with zinc and formic acid or KOH removed bromine to a large degree.

***o*-[(7-Bromo-1-naphthyl)methyl]acetophenone (30)*.** Treatment of a solution of 1.7 g of **29** in ether–benzene with a small excess of 1.2 M CH_3Li at room temperature for 4 h and at reflux for 4 h yielded 1.6 g of crude product after the usual workup. Chromatography over silica gel and recrystallization from benzene–alcohol yielded 1.3 g (76%) of pure **30**, mp 133–134.5 °C.

2-Bromo-7-methylbenz[a]anthracene (31)*. Treatment of 680 mg of **30** with 20 mL of PPA at 110 °C for 2 h yielded crude product which was chromatographed over neutral alumina and recrystallized from benzene–alcohol to yield 480 mg (75%) of pure colorless **31**, mp 130–140 °C.

Registry No. **2**, 2422-79-9; **5**, 81830-40-2; **6**, 35670-68-9; **7**, 35670-69-0; **8**, 81830-41-3; **9**, 81830-42-4; **10**, 81830-43-5; **10** picrate, 81830-44-6; **12**, 69238-67-1; **13**, 81830-45-7; **13** acid chloride, 81830-46-8; **14**, 81830-47-9; **15**, 81830-48-0; **16**, 81830-49-1; **17**, 34698-71-0; **18**, 81830-50-4; **19**, 81830-51-5; **20**, 81830-52-6; **21**, 81830-53-7; **22**, 81830-54-8; **23**, 81830-55-9; **24**, 81830-56-0; **25**, 81830-57-1; **26**, 81830-58-2; **27**, 81830-59-3; **28**, 81830-60-6; **29**, 81846-82-4; **30**, 81830-61-7; **31**, 81830-62-8; **32**, 73453-83-5; **33**, 81830-63-9; **34**, 81830-64-0; **35**, 81830-65-1; **36**, 81830-66-2; **37**, 81830-67-3; **38**, 81830-68-4; 3-(1-naphthyl)phthalide, 81830-69-5; 4-bromo-7,12-benz[a]anthraquinone, 63715-52-6; 2-(2-lithio-4-methoxyphenyl)-4,4-dimethyl-2-oxazoline, 65335-64-0; 1-naphthaldehyde, 66-77-3; 4-methoxy-3-(1-naphthyl)phthalide, 81830-70-8; 9-hydroxy-7,12-dimethylbenz[a]anthracene, 66240-06-0; 7-bromo-1-methylnaphthalene, 33295-35-1; 4,4-dimethyl-2-phenyl-2-oxazoline, 19312-06-2.

(32) P. Beak and R. A. Brown, *J. Org. Chem.*, **44**, 4463 (1979).

Stereochemistry of 1,4-Addition of Nucleophiles to Ethyl Cyclohexylidenecyanoacetates[1]

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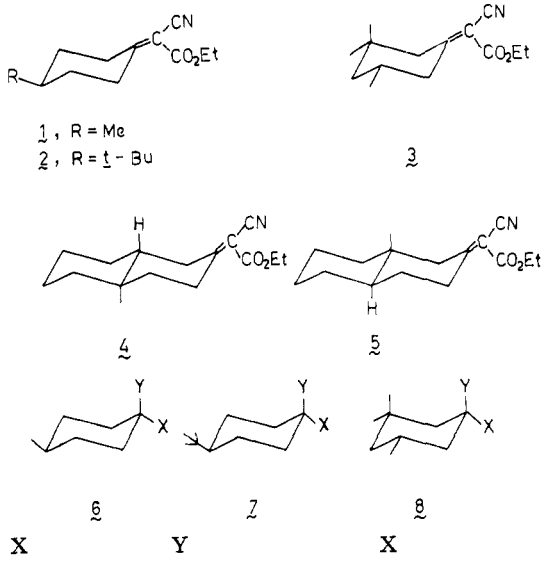
The stereochemistry of 1,4-addition of several nucleophiles such as cyanide, sodium borohydride, and methylmagnesium iodide to three substituted ethyl cyclohexylidenecyanoacetates (**1–3**) has been determined. A higher preference for equatorial attack is observed in these compounds than in related cyclohexanones, which is considerably diminished by the use of aprotic polar solvents. The results do not show any appreciable contribution of product stability control, recently shown to be important for hydride reduction of cyclohexanones, and have been rationalized on the basis of a six-center cyclic transition state in which steric factors play a dominant role. These compounds have also been reduced by catalytic hydrogenation (Pd/C), and, interestingly, with unhindered systems (**1**, **2**), hydrogenation takes place more from the axial side (40–60%) as compared to cyclohexanones.

The stereochemical outcome of reactions of cyclic ketones with metal hydrides and metal alkyls has been intensively investigated and interpreted[2-4] during the last 25 years. A number of concepts[4] such as steric strain control (SSC), product stability control (PSC), torsional strain, and orbital interaction have been advanced to explain the results. Of these, SSC is universally accepted, PSC is severely criticized, and the rest are alternatives to PSC to explain the inherent preference for axial attack on unhindered cyclohexanones. The importance of PSC has, however, been recently revived. Wigfield[4] has rationalized $NaBH_4$ reduction of cyclohexanones by the "steric interactions involved in the product-like transition state" (a concept akin to PSC), and Rei[5] has claimed that the stereochemistry of $LiAlH_4$ reduction of cyclic ketones is "dictated simultaneously and linearly by both SSC and PSC". The C=C bond in ethyl cyclohexylidenecyanoacetates (such as **1**, Chart I) is similar in reactivity to C=O and undergoes comparable 1,4-additions with nucleophiles (including $NaBH_4$), giving products with a $CH(CN)CO_2Et$ side chain of high conformational free energy. If PSC plays a role in these reactions in the manner suggested for cy-

(1) Abstracted in part from the Ph.D. Thesis of A.S., Indian Institute of Technology, Kharagpur.
(2) Eliel, E. L.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411.
(3) (a) Ashby, E. C.; Boone, J. R. *J. Org. Chem.* **1976**, *41*, 2890. (b) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521.
(4) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449.
(5) Rei, M.-H. *J. Org. Chem.* **1979**, *44*, 2760.

0022-3263/82/1947-2840$01.25/0

Chart I



X	Y	X	Y
a, CN	$CH(CN)CO_2Et$	b, $CH(CN)CO_2Et$	CN
c, CO_2Me	CH_2CO_2Me	d, CH_2CO_2Me	CO_2Me
e, H	$CH(CN)CO_2Et$	f, $CH(CN)CO_2Et$	H
g, H	CH_2CO_2Me	h, CH_2CO_2Me	H
i, Me	$CH(CN)CO_2Et$	j, $CH(CN)CO_2Et$	Me
k, Me	CH_2CO_2Me	m, CH_2CO_2Me	Me

clohexanone reductions, a very high preference for axial attack on the unhindered cyclohexylidene derivatives 1 and 2 is anticipated. Marshall and Carroll[6] have reduced two decalylidenecyanoacetates (4, 5) with $NaBH_4$ and $LiAl(O\text{-}t\text{-}Bu)_3H$ and explained the results in terms of reactant-like transition states. We report here the additions of several nucleophiles such as NaCN, $NaBH_4$, and MeMgI to three typical cyclohexylidenecyanoacetates (1–3)[7] and also their catalytic hydrogenation. The results are discussed in the light of the existing concepts.

Results and Discussion

Ethyl cyclohexylidenecyanoacetates 1–3 were prepared essentially by the method of Cope et al.[8] by following an earlier procedure.[9] The 4-Me derivative 1 has been reported previously,[10] the 4-*t*-Bu one, 2, was a low-melting solid with its ^1H NMR spectrum showing two allylic equatorial H's as multiplets at δ 3.93 and 3.06 (J_{gem}, J_{ae}, and J_{ee} of 14, 6, and 3 Hz, respectively). The trimethyl derivative 3 was obtained as a mixture of diastereomers in a ratio of 45:55 (see the Experimental Section). The absence of any vinylic proton signal assured the completely exocyclic nature of the C=C bond.[11]

The addition of cyanide was effected by using sodium cyanide in two different solvents, ethanol and dimethylformamide (DMF), with or without NH_4Cl. The product in the presence of NH_4Cl afforded dicyano ester (**6a,b**) in yields of 88–92% but in its absence was extensively hydrolyzed and decarboxylated. The possibility of equilibration was effectively ruled out by the following observations: (i) the product at 0 °C, when resubmitted to the reaction conditions at 78 °C for 10 h, gave back the same epimeric mixture; (ii) the use of NH_4Cl, which neutralizes the liberated base[12] and thus prevents back-reaction, did not affect the stereochemistry; (iii) the addition of cyanide to 3 furnished predominantly (95%) the thermodynamically less stable epimer **8a**. The ratio of the stereoisomers at C-1 was determined by ^1H NMR of the initial adducts (**6a,b**, NH_4Cl method) and further corroborated by ^1H NMR and GLC of the corresponding hydrolysis–decarboxylation–esterification (CH_2N_2) products (**6c,d**).

Table I. Chemical Shifts[a] and Splitting Patterns of the Side Chain CH/CH_2 of Cyclohexyl Derivatives

compd	shift, δ	multiplicity (J, Hz)
6a	3.65	s
6b	3.40	s
7a	3.70	s
7b	3.50	s
8a	3.90, 3.94	ss
8b	3.57, 3.63	ss
6c	2.77	s
6d	2.51	s
7c	2.73	s
7d	2.48	s
8c	2.70	s
8d	2.50	s
6e	3.47	d (7.2)
6f	3.37	d (5.6)
7e	3.60	d (11.0)[b]
7f	3.38	d (5.0)[b]
8e	3.50, 3.45	dd (7.8, 7.2)
8f	3.10, 3.00	dd (5.0, 4.5)
6g	2.24	d (9.0)
6h	2.10	d (7.0)
7g	2.35[b]	s
7h	2.17[b]	d (5.0)
8g	2.30	d (0.6)
8h	2.20	d (1.0)
6i	3.80	s
6j	3.23	s
7i	3.83	s
7j	3.20	s
8i	4.00[c]	s
6k	2.28	s
6m	2.19	s
7k	2.30	s
7m	2.17	s

[a] Spectra were taken on a Varian EM390 90-MHz spectrometer in $CDCl_3$ with Me_4Si as an internal standard. [b] Very similar results are reported[6] for system 4. [c] Only one isomer was available.

In assigning the configuration, we mainly relied on the position of the side-chain methine and methylene protons, axial protons having more downfield signals than equatorial ones (method used by Marshall and Carroll[6]). The chemical shifts of these protons along with the J values are summarized in Table I for ready reference. The configurations of the two diastereomeric 1-(carbomethoxy)-4-methylcyclohexane-1-acetates **6c,d** had previously been confirmed in our laboratory[9] by ^{13}C NMR, the axial side-chain CH_2 having the more upfield carbon (δ 37.63) relative to the equatorial one (δ 46.15).[13] The 4-*t*-Bu analogues **7c,d** were also separated (via the corresponding acids) and their configurations determined by ^1H and ^{13}C NMR. In the ^1H NMR, the isomers **6d** and **7d** with axial CO_2Me had the 3,5-diaxial protons appreciably downfield (δ 2.20), a fact which may be useful for configurational assignment

(6) Marshall, J. A.; Carroll, R. D. *J. Org. Chem.* **1965**, *30*, 2748.
(7) System 1 should exist very largely with 4-Me in the equatorial position, and its behavior generally resembles that of the completely anancomeric system 2.
(8) Cope, A. C.; Hofmann, C. M.; Wykoff, C.; Hardenbergh, E. *J. Am. Chem. Soc.* **1941**, *63*, 3452.
(9) Nasipuri, D.; Konar, S. K.; Natschke, S. M.; Eliel, E. L. *Indian J. Chem., Sect. B* **1979**, *17B*, 127.
(10) Bajaj, H. S.; Desai, R. D.; Sagar, J. M.; Saharia, G. S. *J. Indian Chem. Soc.* **1974**, *51*, 624.
(11) Lehnert, W. *Tetrahedron* **1973**, *29*, 635.
(12) The failure to equilibrate the addition product with the liberated base in the absence of NH_4Cl is conceivably due to its rapid destruction through ester hydrolysis.
(13) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, **1972**; p 116.

Table II. Results of 1,4-Additions to Ethyl Cyclohexylidenecyanoacetates 1-5

		% [a] of equatorial attack in reaction with						
		NaCN in		$NaBH_4$ in				
entry	compd	EtOH	DMF	EtOH	DME	THF	Pd-C/H_2	MeMgI
1	1	37	10	60 (25)[b]	41	40	58	70
2	2	35 (10)[c]	10	65 (15)[d]	45	45	42 (80)	72 (53)[e]
3	3	95 (91)[f]	85	98 (64)[g]	93	94	100	100 (100)[f]
4	4			50 (15)	30 (15)	27	59	
5	5			100 (60)	100 (60)			

[a] Results from this work are the averages of at least two reactions and are within ±2%; values in parentheses refer to data for related ketones. [b] Dauben, G.; Fonken, G. J.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579. [c] Reference 17. [d] Reference 2. [e] Reference 3b. [f] Landor, S. R.; O'Connor, P. W.; Tatchell, A. R.; Blair, I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 473. [g] Reference 16.

of a carboxy function in a rigid cyclohexane ring. The esters **8c,d** were available only as a mixture, and the configurational assignment was based on ^1H NMR. As expected, H-5 in **8d** appeared at comparatively low field (δ 2.31) as a fractional proton (multiplet) in the spectrum, its integration corresponding approximately to the percentage of **8d** in the mixture (15% in the case of hydrocyanation of **3** in DMF).

Sodium borohydride reduction of **1–3** was carried out in ethanol, dimethoxyethane (DME), and tetrahydrofuran (THF) and catalytic hydrogenation with 10% Pd/C in both neutral and acidic media. The products were analyzed by GLC and ^1H NMR spectroscopy of the cyano esters (**6e,f**) as well as of the derived methyl cyclohexylacetates (**6g,h**). A special feature of the ^1H NMR of the 3,3,5-trimethylcyclohexane derivatives (**8e,f**) was that each epimer at C-1, consisting of two diastereomers at the side chain, gave two doublets for the methine proton (Table I). Nevertheless, the two cis diastereomers were well separated in their H-α-signals from the two trans isomers, and there was no problem in determining the cis–trans ratio from area measurements of the two (narrowly spaced) pairs of proton signals. The coupling constants for H-1 and H-α in the reduced cyano esters varied from 11 to 5 Hz (Table I) and might be used for additional information regarding the configurational and conformational aspects of the molecules (see also ref 6, footnote 10). The highest J value (11 Hz) in **7e** is consistent with the axial disposition of $CH(CN)CO_2Et$ frozen in a conformation with the two carbon substituents pointing outside the ring so that the two protons are antiperiplanar. The moderate J values (7–8 Hz) in **6e** and **8e** indicate that these two compounds are conformationally heterogeneous, which is expected. The low J values (5 Hz) in **6f–8f** fit nicely for an equatorially disposed $CH(CN)CO_2Et$ in an averaged conformation. The close similarity of the J values for the two pairs of compounds **6e**, **8e** and **6f**, **8f** suggests similarity in the ring conformation of the two systems **6** and **8** and speaks against a twist conformation for the latter. Conformational nonhomogeneity is again expected for compounds **6g** and **8g** and is to some extent reflected in the converging trend in chemical shifts of the methylene side-chain protons in the two diastereomeric pairs **6g,h** and **8g,h**. The low values of J (H-1/CH_2) in system **8** and the absence of such coupling in **7g** (Table I) are unusual but in conformity with those for system **4**.[6]

Finally, MeMgI was allowed to react with **1–3** in ethereal solution and the initial products **6i,j** as well as the derived dimethyl esters **6k,m** were analyzed by GLC in combination with ^1H NMR. In a few cases, the products from reduction and Grignard addition were studied by ^{13}C NMR for further confirmation of the configurations. Thus a cis–trans mixture (65:35) of **7g,h** obtained from $NaBH_4$ reduction of **2** followed by hydrolysis–decarboxylation–esterification was examined by ^{13}C NMR, and pairs of analogous carbons in the two isomers showed intensity ratios in good agreement with GLC and ^1H NMR analysis.[14] The assignment of the peaks is given in the Experimental Section and is unequivocal, C-1, C-2,6, C-3,5, and α-CH_2 being upfield in the cis isomer **7g** from the corresponding carbon signals in *trans*-**7h**. The analogous 3,3,5-trimethyl derivative, obtained virtually as a single isomer, **8g**, from the reduction of **3** was also studied by ^{13}C NMR. Because of its conformational nonhomogeneity and uncertain compression shifts resulting from syn-axial C–C interactions, we were unable to make an unequivocal assignment of the peaks. The chemical shifts, however, appeared to conform more to those calculated[15] for the trans isomer **8g** rather than to those for *cis*-**8h**. There were, however, large deviations particularly for the methyl signals, and the assignment (see the Experimental Section) should be regarded as tentative. The ^{13}C NMR spectrum of a cis–trans mixture (70:30) of **7k,m** derived from the addition of MeMgI to **2** was taken, and the side chain CH_2 could be recognized at δ 40.20 (t) and 49.49 (t) for **7k** and **7m**, respectively, with an intensity ratio of 70:30. It is thus noted that (i) consistent stereochemical assignments were obtained from ^1H NMR spectra of the initial products of nucleophilic additions and of the corresponding hydrolysis–decarboxylation–esterification products and that (ii) where comparison was made between proton and carbon shifts, a good agreement of configurational assignments resulted.

The stereochemical results of the addition reactions along with those for reduction of two decalylidene derivatives (**4**, **5**)[6] are summarized in Table II. A few available data for similar reactions with related cyclohexanones are also included (in parentheses) for the sake of comparison. The following observations can be made on the basis of examination of Table II.

(1) Reduction of the cyclohexylidene derivatives with $NaBH_4$ in ethanol (and also reaction with MeMgI in ether) proceeds with high preference for equatorial attack, 50–100% vs. 15–64% for reduction of cyclohexanones of comparable geometry. The values diminish considerably for unhindered substrates (entries 1, 2, and 4) in polar aprotic solvents, though such solvents do not change the product ratio for the decalones (entries 4 and 5 values in parentheses; see, however, Haubenstock and Eliel[16]).

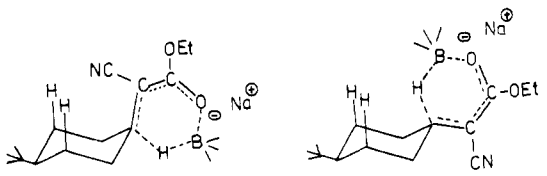
(2) Addition of CN^- in ethanol follows the opposite stereochemistry, the unhindered cyclohexylidene compounds undergoing predominant axial attack (65%) which

(14) Evidently, the relaxation times and NOE of pairs of analogous carbons in the two diastereomers are nearly equal.

(15) The chemical shifts for different carbons were calculated from the data available for 1,1,3-trimethylcyclohexane (ref 13, p 64) taking into account α, β, and γ shifts.

(16) Haubenstock, H.; Eliel, E. L. *J. Am. Chem. Soc.* **1962**, *84*, 2368.

Chart II



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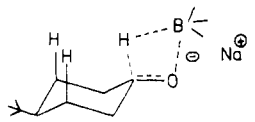
10



11

increases further to 90% in DMF, resembling, in effect, the stereochemistry of $LiAlH_4$ reduction and hydrocyanation[17] of 4-*tert*-butylcyclohexanone (under comparable conditions, however, equatorial attack is still more pronounced than for related cyclohexanones). Evidently, steric strain has much less control over this reaction than over $NaBH_4$ reduction or Grignard addition. For hindered substrates, both $NaBH_4$ reduction and cyanide addition proceed with high equatorial attack (>90%), and the solvent effect levels off.

(3) In contrast, hydrogenation over Pd/C of the unhindered cyclohexylidene derivatives takes place significantly more from the axial side as compared to that for cyclohexanones of similar geometry, which undergo nearly 80% equatorial attack.[18] The isomer ratio is independent of reaction time and reaction medium (acidic or neutral), which shows that the hydrogenation is kinetically controlled.

On the assumption that there is no serious conformational distortion in cyclohexylidene systems 1–3 compared to cyclohexanones, the stereochemistry of the addition reactions may be interpreted in terms of the concepts previously discussed. The predominant equatorial attack clearly militates against any appreciable effect of PSC in these reactions.[19] Equatorial attack, it may be noted, not only leads to products of high conformational energy but also suffers from a "compression factor", similar to that proposed by Ashby,[20] arising out of the eclipsing of $CH(CN)CO_2Et$ with the two adjacent equatorial H's on the way to the transition state. In contrast, axial attack has the advantage of a favorable PSC, does not suffer from the compression effect, and helps to relieve the $A^{1,3}$ strain[21] present in the original molecule. The results unmistakably point to predominance of a steric factor which is not so obvious in a reactant-like transition state.[6] For the 1,4-additions of nucleophiles to the system (i.e., 2), the transition state may conceivably be represented by six-center cyclic structures (Chart II), shown for $NaBH_4$ reduction as **9** and **10** for equatorial and axial attack, respectively. The extent of bond formation and ion-pair association will depend on the attacking nucleophile and on solvent polarity. The involvement of the enolic form (also proposed by Marshall and Carroll[6] from experimental results) automatically rules out the compression factor or $A^{1,3}$ strain which owes its existence to the exocyclic C=C bond.

Six-center transition states have previously been proposed in organometallic alkylation reactions and appeared to produce substantially different stereochemical results than the four-center ones,[22,23] depending on the nature of reagents and the reaction mechanism. We now suggest that such transition states under comparable conditions face more steric interference in the axial approach (**10**), the nucleophile being positioned at a greater distance from C-1 and interacting more severely with the 3,5-diaxial H's in the Marshall–Carroll model,[6] than the corresponding four-center one (**11**) in which the "pinching" of the cyclic activated complex minimizes axial interaction (see also Jones et al.[24] for similar arguments) by bringing the nucleophile closer to the electrophilic center and away from the 3,5-diaxial H's. There is no such adverse effect in either equatorial attack, except for PSC, which is less favorable for the six-center transition state, and torsional strain,[22a] which operates more effectively in the four-center one. The anticipated large effect of PSC favoring axial attack is considerably diminished because the cyanoacetate side chain in **9** (equatorial attack) is in a vertical plane with the linear CN conveniently placed between the 3,5-syn–axial H's. The dominating factor in the six-center transition state in these reactions is thus steric interaction affecting the incoming nucleophile in axial attack. As a result, the nucleophiles react more from the equatorial side in the cyclohexylidene derivatives (1–3) than in related cyclohexanones which presumably pass through a "tighter" four-center transition state.[25] This explains the reactions of $NaBH_4$ and MeMgI.

In the case of CN^- addition, the ion pair (O···B···H is now replaced by O···Na···CN in **9** and **10**) undergoes extensive dissociation, the six-center transition state no longer operates effectively, and the linear CN^- faces little steric interference from the axial side, which explains a higher percentage of axial attack on unhindered cyclohexylidene compounds compared to that for borohydride reduction. Use of polar aprotic solvents further promotes dissociation of the ion pair without solvating the nucleophiles and favors the axial attack (comparatively) both in the $NaBH_4$ and CN^- reactions.

An alternative explanation may be offered if one assumes that replacement of carbonyl oxygen in cyclohexanones by bulkier $C(CN)CO_2Et$ introduces an enhanced steric demand for the encounter of a nucleophile with the electrophilic center in compounds 1–3. The transition states under such circumstances will have the nucleophile at a longer distance from C-1 for a given reagent and set of conditions. The rest of the arguments will be same as above. In the absence of any proof, this is, however, a purely speculative hypothesis. On the other hand, the

(17) Richer, J.-C. *J. Org. Chem.* **1965**, *30*, 324.
(18) Peppiat, E. G.; Wicker, R. J. *J. Chem. Soc.* **1955**, 3122. Wicker, R. J. *Ibid* **1956**, 2165. Eliel, E. L.; Ro, R. S. *J. Am. Chem. Soc.* **1957**, *79*, 5992.
(19) The lack of evidence for PSC in these reactions does not necessarily invalidate the proposition that PSC plays a major role in hydride reduction of cyclohexanones, which goes through a different mechanism, but certainly weakens it.
(20) Laemmle, J. T.; Ashby, E. C.; Roling, P. V. *J. Org. Chem.* **1973**, *38*, 2526.
(21) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. Johnson, F.; Malhotra, S. K. *J. Am. Chem. Soc.* **1965**, *87*, 5492.
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(23) Jones, P. R.; Kauffman, W. J.; Goller, E. J. *J. Org. Chem.* **1971**, *36*, 186.
(24) Jones, P. R.; Goller, E. J.; Kauffman, W. J. *J. Org. Chem.* **1969**, *34*, 3566.
(25) The four-center transition state for hydride reductions of cyclohexanones is consistent with the inverse isotope effect observed in borodeuteride reduction[26] and also with the I-strain concept.[27] Wigfield[4], however, prefers an acyclic mechanism for $NaBH_4$ reduction. Nevertheless, as long as the hydride approaches the carbonyl carbon from a short distance in the transition state, the above arguments stand.
(26) Geneste, P.; Lamaty, G. *Bull. Soc. Chim. Fr.* **1968**, 669; *Tetrahedron Lett.* **1965**, 4633.
(27) Brown, H. C.; Ichikawa, K. *Tetrahedron* **1957**, *1*, 221.

participation of enolate forms of the cyclohexylidenecyanoacetates in the reactions is an established fact[6] and is in consonance with the proposed six-center transition state.

The mechanism of calatylic hydrogenation is in no way related to that of nucleophilic additions and should be viewed in an altogether different perspective. The high percentage of axial attack in catalytic hydrogenation of unhindered cyclohexylidene compounds 1 and 2 relative to cyclohexanones may be ascribed to a "compression factor" which comes into play when the catalyst surface approaching the equatorial side pushes the $CH(CN)CO_2Et$ chain up into the plane of the 2,6-diequatorial H's. Axial approach, on the other hand, relieves the $A^{1,3}$ strain in the original molecule. However, because of the complex character of catalytic hydrogenation, the suggestion is at best tentative.

Experimental Section

General Procedures. Melting points are uncorrected. GLC analyses were performed on 6 ft × 0.25 in. columns packed with 10% DEGS and 10% EGSS-X on GasChrom Z (60–80 mesh) on a Hewlett-Packard 5730A or on a Pye Unicam GCD equipped with a flame-ionization detector using N_2 as the carrier gas and working at 150–170 °C. IR spectra of $CHCl_3$ solutions were recorded on a Perkin-Elmer 237B spectrophotometer. ^1H NMR spectra were recorded with a Varian EM390 90-MHz spectrometer and ^{13}C NMR spectra with a Varian CFT-20 spectrometer in $CDCl_3$ with Me_4Si as an internal standard; the multiplicity in ^{13}C NMR was determined by off-resonance proton decoupling. Petroleum ether refers to the fraction with a boiling point of 40–60 °C. Organic solutions were dried over anhydrous Na_2SO_4. 4-*tert*-Butylcyclohexanone was supplied by Aldrich Chemical Co.

Ethyl Cyclohexylidenecyanoacetates 1–3 were prepared from the respective cyclohexanones by condensation with ethyl cyanoacetate in yields of 70–75% by the method previously described for 1.[9] Cyanoacetate **2** [bp 177–180 °C (2 mm)] was a low-melting solid: IR 2225 (CN), 1720 (CO_2Et), 1600 cm^{-1} (C=C). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.3; H, 9.2. Found: C, 72.4; H, 9.5.

Cyanoacetate **3**, obtained from dihydroisophorone as a liquid, had the following: bp 137–140 °C (2 mm); IR 2230, 1720, 1600 cm^{-1}; ^1H NMR δ 4.22 (q, 2, J = 7 Hz, OCH_2), 4.00–3.62 (m, 1, 2-H_e cis to CN), 3.10–2.60 (m, 1, 6-H_e cis to CO_2Et), 2.00 (d, 1, J_{gem} = 12 Hz, 2-H_a), 1.90–1.20 (m, 4, ring H's), 1.33 (t, 3, J =7 Hz, H_3CCH_2O) 1.08 (d, 6, 3-CH_3), 0.85 (d, 3, J = 7 Hz, 5-CH_3). The triplet and quartets of H_3CCH_2O were split further ($\Delta\nu$ = 1 Hz), showing the presence of two geometrical isomers in an approximate ratio of 45:55, as determined by the relative heights of the individual peaks in the triplets and quartets. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.5; H, 8.9. Found: C, 71.3; H, 9.1.

Hydrocyanation of Ethyl Cyclohexylidenecyanoacetates (1–3). (a) Sodium Cyanide in Ethanol. In a typical experiment, NaCN (0.72 g, 14.7 mmol) in water (1 mL) was added to a solution of **2** (1.85 g, 7.4 mmol) in ethanol (8 mL), and the mixture was left at ambient temperature for 24 h. Ethanol was removed in vacuo, and the residue (1.88 g) was hydrolyzed with a refluxing mixture of concentrated HCl (15 mL) and glacial AcOH (2.5 mL) for 50 h. The mixture of dicarboxylic acids (1.37 g, mp 145–158 °C) thus obtained was esterified with CH_2N_2 to the dimethyl esters **7c,d**: 1.39 g (70%); bp 120–125 °C (0.8 mm). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.7; H, 9.6. Found: C, 66.5; H, 9.5.

The ^1H NMR spectra of the mixed esters **7c,d** showed the methylene protons peaks at δ 2.73 and 2.48 with relative areas of 35:65; the same ratio was obtained by GLC. The two 3,5-diaxial H's in the trans isomer **7d** appeared at δ 2.20, integrating for 1.3 H. The ratio remained practically unaltered when the reaction was carried out at 78 °C (boiling ethanol) or when the previous reaction product was heated at 100 °C for 10 h with a small amount of KOH. In one experiment, the crude acid (mp 145–158 °C) was fractionally crystallized from benzene–petroleum ether into two pure isomers (mp 192 and 162 °C) in an approximate ratio of 30:70. The derived methyl esters **7c** and **7d** showed the side-chain methylene carbon and hydrogens at δ 37.47, 2.73 (for cis) and δ 46.96, 2.48 (for trans) in ^{13}C and ^1H NMR. The trans isomer **7d** showed a two-proton mulitplet at δ 2.20.

The 3,3,5-trimethyl derivative **3** on similar addition of NaCN and subsequent hydrolysis afforded the corresponding dicarboxylic acids, mp 154–156 °C. The dimethyl esters **8c,d** (80%) had the following: bp 125–130 °C (1.5 mm); IR 1735 cm^{-1}. This was analyzed by ^1H NMR and GLC and showed a trans–cis ratio of 95:5. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.6; H, 9.4. Found: C, 65.3; H, 9.8.

Crystallization of the above crude acid from benzene–petroleum ether furnished *trans*-1-carboxy-3,3,5-trimethylcyclohexane-1-acetic acid: mp 158 °C; ^1H NMR δ 2.72 (s, 2, axial CH_2C=O). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.1; H, 8.8. Found: C, 63.4; H, 8.4.

(b) Sodium Cyanide in Ethanol with NH_4Cl. The addition of NaCN in the presence of NH_4Cl (2 mol) was carried out under identical conditions. Ethyl (1-cyano-4-methyl-cyclohex-1-yl)-cyanoacetate [92%; bp 130–135 °C (1 mm)], ethyl (1-cyano-4-*tert*-butylcyclohex-1-yl)cyanoacetate [90%; bp 152–156 °C (1 mm)], and ethyl (1-cyano-3,3,5-trimethylcyclohex-1-yl)cyanoacetate [88%, bp 110 °C (1 mm)] were all obtained as diastereometric mixtures **6–8a,b**: IR 2250 (CN), 1745 cm^{-1} (CO_2Et). The diastereomeric pairs were not separated by GLC, and the product ratios were determined from ^1H NMR from the intensity ratio of the side-chain methine proton signals (Table I). The dicyano esters were hydrolyzed, the acidic mixtures esterified (CH_2N_2), and the methyl esters analyzed again both by GLC and ^1H NMR spectroscopy. The three sets of analytical results corresponded closely; those reported in Table II are averages of the three. Acceptable elemental analyses (C and H within ±0.4% of the theory) were obtained for pairs **6–8a,b** and **6–8c,d**.

(c) Sodium Cyanide in DMF with NH_4Cl. In a typical experiment, NaCN (0.72 g, 14.7 mmol) in H_2O (1 mL) was added to a solution of **2** (1.85 g, 7.4 mmol) in DMF (55 mL) in the presence of NH_4Cl (0.583 g, 11 mmol), and the mixture was left at ambient temperature for 24 h. DMF was removed in vacuo, and the product was worked up and analyzed as before.

Reduction of Ethyl Cyclohexylidenecyanoacetates 1–3. (a) With $NaBH_4$. To 1.49 g (5.9 mmol) of **2** in ethanol (2 mL) cooled to 0 °C was added (0.072 g, 1.8 mmol) of $NaBH_4$ in ethanol (2 mL) dropwise with stirring over 25 min. After 1 h at 0 °C, the mixture was decomposed with saturated brine and the product worked up in the usual way.[6] The cyanoacetates **7e,f** [bp 170–175 °C (2 mm)] were obtained as oil. Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.7; H, 10.0. Found: C, 71.5; H, 10.2.

The 4-methyl derivatives **6e,f** had a boiling point of 140–145 °C (2 mm). Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.9; H, 9.1. Found: C, 68.9; H, 9.5.

The 3,3,5-trimethyl derivatives **8e,f** had a boiling point of 110–115 °C (2 mm). Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.9; H, 9.7. Found: C, 70.6; H, 9.6.

The products were characterized by ^1H NMR and IR, the integration of the side chain methine protons (Table I) giving the ratio of the two diastereomers in each case. The reduction products of **2** and **3** were also analyzed by GLC, but that of **1** did not separate on any column. Its ^1H NMR spectrum in $CDCl_3$ did not give enough resolution of the two diastereomeric methine protons for accurate determination of the ratio, but that in C_6D_6 showed the two quite distinct signals: δ (C_6D_6) 3.90 (q, 2, J = 7 Hz, CH_2O), 3.07 (d, 0.58, J = 7.2 Hz, axial α-CH), 2.95 (d, 0.42, J = 5.6 Hz, equatorial α-CH), 1.90–1.00 (m, 10, ring H's), 0.94 (t, 3, J = 7 Hz, H_3CCH_2O), 0.80 (d, 3, J = 7 Hz, 4-CH_3); IR 2250 (CN), 1750 cm^{-1} (CO_2Et).

The reductions of the three compounds were likewise carried out with $NaBH_4$ in dimethoxyethane (DME) and THF and the products analyzed in the same way.

(b) With Hydrogen over Pd/C. Hydrogenation of 1–3 was carried out in presence of Pd/C (10%) both in ethanol and in acetic acid containing 1 drop of HCl at room temperature and under atmospheric pressure. The uptake of the theoretical amount of H_2 was complete within 1–2 h; use of a longer period did not change the compositions of the diastereomeric mixtures. The reduced products **6–8e,f** were all analyzed by ^1H NMR and GLC (Table II).

Methyl Cyclohexane-1-acetates (6–8g,h). The foregoing ethyl cyclohexane-1-cyanoacetates from $NaBH_4$ or catalytic re-

duction were hydrolyzed with KOH in ethylene glycol[6] and the resultant cyclohexane-1-acetic acids esterified with CH_2N_2 to **6–8g,h**, IR 1740 cm^{-1} (CO_2Me). The 4-methyl derivatives **6g,h** had the following: bp 100 °C (1 mm); yield 93%. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.6; H, 10.6. Found: C, 70.2; H, 10.4.

The 4-*tert*-butyl derivatives **7g,h** had the following: bp 115 °C (1 mm); yield 94%. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.6; H, 11.3. Found: C, 73.3; H, 11.5.

The 3,3,5-trimethyl derivatives **8g,h** had the following: bp 90 °C (1 mm); yield 88%. Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.7; H, 11.1. Found: C, 72.3; H, 11.0.

They were analyzed by the intensity ratio of the side-chain CH_2 doublets (Table I), and the results corresponded closely to those of the initial reduction products **6–8e,f**.

The ester obtained from $NaBH_4$ reduction of **2** was a cis–trans mixture of **7g,h** in the ratio of 65:35 (determined by GLC and corroborated by ^1H NMR): ^{13}C NMR δ 171.53, 173.04 (s, C=O), 50.94 (q, OCH_3), 48.14, 47.62 (d, C-4), 36.03, 41.59 (t, CH_2C=O), 32.27, 32.12 (s, CMe_3), 30.36, 33.27 (t, C-2,6), 29.50, 34.81 (d, C-1), 27.24 (q, CMe_3) 21.44, 26.85 (t, C-3,5). The first value of the pair refers to the cis isomer **7g** and the second to *trans*-**7h**. The methoxy and the three β-methyls predictably have identical chemical shifts in the two isomers. The intensity ratios of the analogous carbon pairs were between 60:40 and 64:36. The esters **7g,h** on saponification afforded a mixture of acids which on fractional crystallization (benzene–petroleum ether) furnished *cis*-4-*tert*-butylcyclohexane-1-acetic acid: mp 99 °C; ^1H NMR δ 10.80 (s, 1, CO_2H), 2.30 (br s, 2, CH_2CO), 1.63–1.00 (m, 10, ring H's), 0.85 (s, 9, $3CH_3$). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.7; H, 11.1. Found: C, 72.5; H, 11.2.

The almost pure *trans*-3,3,5-trimethylcyclohexane-1-acetic acid (both from $NaBH_4$ reduction and catalytic hydrogenation of **3**) could not be obtained in crystalline form. The methyl ester **8g** had the following: ^{13}C NMR δ 173.62 (s, C=O), 51.14 (q, OCH_3), 46.49 (49.06)[28] (t, C-4), 44.03 (44.46) (t, C-2), 40.62 (39.06) (t, C-6), 38.32 (36.3) (t, CH_2C=O), 31.64 (34.30) (q, equatorial-3-Me), 30.90 (25.00) (q + s, axial 3-Me, C-3), 28.56 (23.70) (q, 5-Me), 25.34 (24.00) (d, C-1), 22.01 (22.00) (d, C-5). As already stated, some of the assignments are uncertain.

Reaction of MeMgI with 1–3. In a typical experiment, MeMgI prepared from Mg (0.548 g, 0.0238 mol) and MeI (1.8 mL, 0.025 mol) in ether (25 mL) was added to **2** (4.8 g, 0.0192 mol) in ether (25 mL) at 0 °C. The solution was refluxed for 2 h and then decomposed with cold dilute HCl. The products upon the usual workup and distillation afforded **7i,j**: 4.1 g (80%); bp 140–143 °C (0.1 mm); IR 2250, 1750 cm^{-1}; ^1H NMR δ 4.26 (q, 2, CH_2O), 3.83 (s, 0.70, axial α-CH), 3.20 (s, 0.30 equatorial α-CH), 2.10–1.10 (m, 9, ring H's), 1.30 (t, 3, H_3CCH_2O), 1.23, 1.13, (2 s, 3, 1-CH_3), 0.88 (s, 9, $3CH_3$). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.4; H, 10.2. Found: C, 72.2; H, 10.0.

The product was analyzed by GLC, and the result corresponded to that of ^1H NMR spectroscopy. The cyano ester (2.5 g) was hydrolyzed first by being refluxed with a mixture of HCl (42 mL) and acetic acid (10 mL) for 60 h and then with aqueous 20% KOH for 24 h. The crude acid (1.9 g, 89%) was directly esterified with CH_2N_2 to **7k,m**: yield 95%; bp 120 °C (1 mm).

An analysis based on ^1H NMR and GLC showed it to be a cis–trans mixture in a 70:30 ratio in agreement with the original product (see above): ^{13}C NMR δ 168.648 168.25 (s, C=O), 52.88 (q, CH_3O), 40.20, 49.49 (t, CH_2C=O), 47.57, 47.71 (d, C-4), 38.27, 37.56 (t, C-2,6), 35.78, 35.71 (s, C-1), 32.09, 32.18 (s, CMe_3), 31.08, 25.44 (q, 1-CH_3), 27.28 (q, CMe_3), 22.15, 22.50 (t, C-3,5). Some of the assignments are tentative. The ratios of the intensities of the analogous carbons are roughly 70:30. Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.3; H, 11.5. Found: C, 74.5; H, 11.7.

The ester on hydrolysis afforded a mixture of acids which on fractional crystallization gave *cis*-4-*tert*-butyl-1-methylcyclohexane-1-acetic acid: mp 72 °C; IR 1710 cm^{-1}; ^1H NMR δ 9.40 (s, 1, CO_2H), 2.34 (s, 2, axial CH_2C=O), 1.80–1.00 (m, 9, ring H's), 1.05 (d, 3, 1-CH_3), 0.90 (s, 9, $3CH_3$). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.6; H, 11.3. Found: C, 73.3; H, 11.4.

The reaction of MeMgI with **1** afforded **6i,j**: 82%; bp 120–122 °C (2 mm); ^1H NMR δ 4.20 (q, 2, CH_2O), 3.80 (s, 0.70, axial α-CH), 3.22 (s, 0.30, equatorial α-CH), 1.90–1.30 (m, 9, ring H's), 1.30 (t, 3, H_3CCH_2O), 1.10 (d, 3, 1-CH_3), 0.90 (d, 3, J = 7 Hz, 4-CH_3). Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.9; H, 9.4. Found: C, 69.5; H, 10.0.

The mixture did not separate well by GLC, and the analysis was based on the ratio of the 3.80- and 3.22-ppm proton signals. On hydrolysis–decarboxylation–esterification, it afforded **6k,m**: 80%; bp 115 °C (1 mm); IR 1740 cm^{-1}; ^1H NMR showed the side-chain CH_2 signals at δ 2.28 and 2.19 in an approximate ratio of 70:30, consistent with the original product. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.7; H, 10.9. Found: C, 71.3; H, 11.2.

Addition of MeMgI to **3** under the same conditions afforded only a single isomer, **8i**: bp 125–130 °C (1.5 mm); 90%; IR 2250, 1740 cm^{-1}; ^1H NMR δ 4.30 (q, 2, CH_2O), 4.00 (s, 1, axial α-CH), 1.90–1.30 (m, 7, ring H's), 1.33 (t, 3, H_3CCH_2O), 1.10 (s, 6, $2CH_3$), 0.92 (d, 6, $2CH_3$). Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.7; H, 10.0. Found: C, 71.5; H, 10.3.

Since it was found to be 100% pure both by GLC and ^1H NMR, no further conversion into the corresponding methyl ester by hydrolysis–decarboxylation–esterification (which proved very difficult in this case) was undertaken. Although no proof is given for the configuration of this product, the stereochemical course assumed (100% equatorial attack) is clearly anticipated from the previous two analogies.

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Registry No. **1**, 57093-77-3; **2**, 22700-58-9; *cis*-**3**, 81831-39-2; *trans*-**3**, 81831-40-5; **4**, 81873-42-9; **5**, 81873-43-0; **6a**, 81831-41-6; **6b**, 81831-42-7; **6c**, 81831-43-8; **6d**, 81831-44-9; **6e**, 57093-63-7; **6f**, 57093-62-6; **6g**, 57093-76-2; **6h**, 57093-75-1; **6i**, 81831-45-0; **6j**, 81831-46-1; **6k**, 54277-36-0; **6m**, 54277-37-1; **7a**, 81831-47-2; **7b**, 81831-48-3; **7c**, 81831-49-4; **7d**, 81831-50-7; **7e**, 22803-98-1; **7f**, 22803-97-0; **7g**, 28125-15-7; **7h**, 28125-17-9; **7i**, 53618-45-4; **7j**, 53618-44-3; **7k**, 57093-73-9; **7m**, 57093-74-0; **8a** (isomer 1), 81831-51-8; **8a** (isomer 2), 81873-87-2; **8b** (isomer 1), 81873-44-1; **8b** (isomer 2), 81873-45-2; **8c**, 81831-52-9; **8d**, 81831-53-0; **8e** (isomer 1), 81831-54-1; **8e** (isomer 2), 81873-46-3; **8f** (isomer 1), 81873-47-4; **8f** (isomer 2), 81873-48-5; **8g**, 81831-55-2; **8h**, 81831-56-3; **8i**, 81831-57-4; dihydroisophorone, 873-94-9; *cis*-3,3,5-trimethylcyclohexylidenecyanoacetic acid, 81831-58-5; *trans*-3,3,5-trimethylcyclohexylidenecyanoacetic acid, 81831-59-6; *cis*-4-*tert*-butylcyclohexane-1-acetic acid, 28125-16-8; *trans*-3,3,5-trimethylcyclohexane-1-acetic acid, 56933-46-1.

(28) The values in parentheses are calculated (see footnote 15).