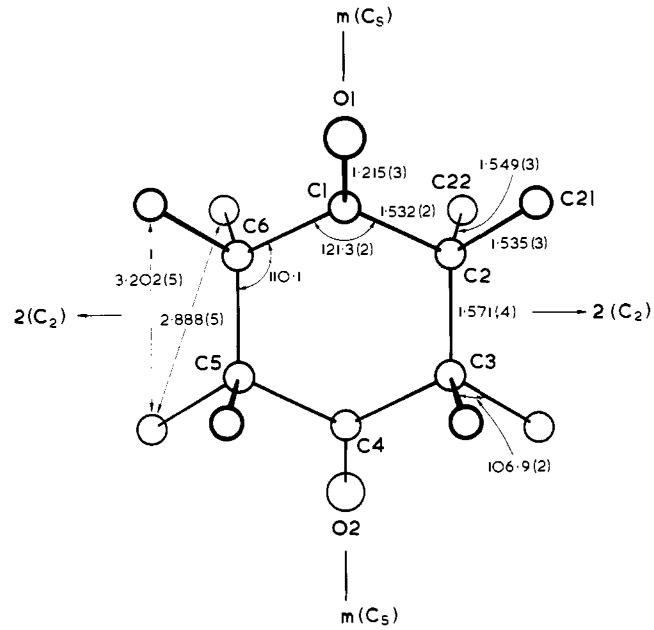

Figure 1. Structural data for octamethyl-1,4-cyclohexanedione. Note that atoms C1 and C4, O1 and O2, and C2, C3, C5, C6, and their substituents are crystallographically equivalent.

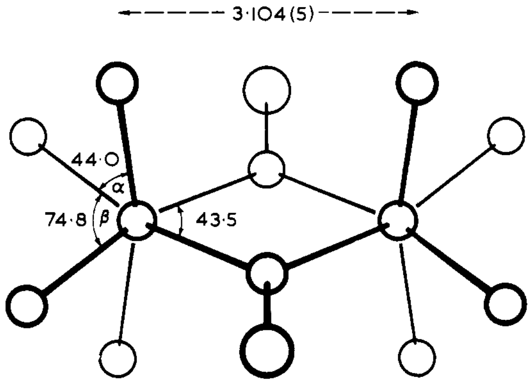

Figure 2. Newman projection of **1**.

in the parent **2**, as expected on general grounds and consistent with the relatively low IR$_{CO}$ frequency (1689 cm^{-1}) of **1**.[3] The presence of two internal carbonyl angles of 121.3° in **1** necessitates a marked flattening of the ring, as can be seen perhaps most clearly from the three consecutive torsion angles C1-C2-C3-C4 = 43.5°, C2-C3-C4-C5 = 49.2°, and C3-C4-C5-C6 = 43.5° and their sum of 136.2°. By comparison, the three torsion angles in cyclohexane, which is slightly flattened, sum to about 56 × 3 = 168°[6,7] compared with a value of 180° in "ideal" cyclohexane. The marked contraction of the axial-equatorial methyl-methyl torsion angle α by 16° from the ideal value of 60° and the corresponding expansion of the equatorial-equatorial angle β by 15° can be regarded as a further consequence of the adoption of a strongly flattened six-membered chair. Apart from generating unusual torsion angles the flattened chair conformation of **1** introduces an extremely short contact of 2.88 Å within each of the four equivalent pairs of vicinal axial-equatorial methyl groups. The resulting repulsion combined with the syndiaxial clash of 3.10 Å involving the two pairs of methyl groups may be a contributory cause of the compression of the four geminal dimethyl interbond angles to 106.9°.[8]

Supplementary Material Available: Atomic coordinates and temperature factor parameters for octamethyl-1,4-cyclohexanedione (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) X-ray analysis: (a) P. Groth and O. Hassel, *Proc. Chem. Soc., London,* 218 (1963); *Acta Chem. Scand.,* **18,** 923 (1964); (b) A. Mossel and C. Romers, *Acta Crystallogr.,* **17,** 1217 (1964); (c) A. Mossel, C. Romers, and E. Havinga, *Tetrahedron Lett.,* 1247 (1963); there has been disagreement with the statement of these authors that the IR spectra of 1,4-cyclohexanedione in the solid state and in solution are similar; see J. Dale, *J. Chem. Soc.,* 1028 (1965), Figure 2; T. Alvik, G. Borgen, and J. Dale, *Acta Chem. Scand.,* **26,** 1805 (1972), Figure 10. Vibrational spectra and dipole moments: (d) N. L. Allinger, H. M. Blatter, L. A. Freiberg, and F. M. Karkowski, *J. Am. Chem. Soc.,* **88,** 2999 (1966); (e) A. Aihara and C. Kitazawa, *Bull. Chem. Soc. Jpn.,* **44,** 99 (1971); (f) D. S. Bailey and J. B. Lambert, *J. Org. Chem.,* **38,** 134 (1973). Electron-diffraction and molecular-beam scattering: (g) D. J. Gregory-Allen and K. Hedberg, personal communication to O. Bastiansen, H. M. Seip, and J. E. Boggs, cited in "Perspectives in Structural Chemistry", Vol. IV, Wiley, New York, N.Y., 1971, p 137; (h) see, however, P. Dowd, T. Dyke, and W. Klemperer, *J. Am. Chem. Soc.,* **92,** 6327 (1970) for further discussion of earlier false trails and for the proposal that 1,4-cyclohexanedione is nonpolar in the gas phase, suggestive of a chair or fully extended twist-boat. Two recent reviews discuss and argue that 1,4-cyclohexanedione exists as a twist conformer in the gas phase: G. M. Kellie and F. G. Riddell, *Top. Stereochem.,* **8,** 226 (1974); N. L. Allinger and D. H. Wertz, *Rev. Latinoam. Quim.,* **4,** 127 (1973) [*Chem. Abstr.,* **81,** 151 117s (1974)]; the statement on p 128, lines 4–5, that ". . .there were found no bands in the infrared spectrum of the liquid which were not present in the solid [1,4-cyclohexanedione]" is debatable; see footnote 1c, above, for published spectra.

(2) (a) R. D. Stolow and M. M. Bonaventura, *Tetrahedron Lett.,* 95 (1964); (b) R. D. Stolow and C. B. Boyce, *J. Am. Chem. Soc.,* **83,** 3722 (1961).

(3) B. K. Carpenter, D. I. Rawson, and H. M. R. Hoffmann, *Chem. Ind.,* 886 (1975).

(4) The possibility that 1 adopts a C_{2h} conformation was suggested by the Raman spectrum of the powdered solid, which shows a single, very sharp carbonyl absorption at 1693 cm^{-1} (B. K. Carpenter, Ph.D. Thesis, University of London, 1973). Since **1** shows a 24 H proton singlet in the NMR spectrum in two solvents down to −140 °C[3] one must conclude that *either* 1 suffers rapid degenerate chair–chair interconversion on the NMR time scale in solution or the conformation in solution is different from that in the solid; the possibility that the two methyl signals expected for a chair converting slowly on the NMR time scale coincide accidentally in both solvents is considered less likely.

(5) Written by Dr. G. M. Sheldrick, University of Cambridge, England.

(6) H. R. Buys and H. J. Geise, *Tetrahedron Lett.,* 2991 (1970).

(7) R. Bucourt, *Top. Stereochem.,* **8,** 159 (1974).

(8) Work at University College supported by the Science Research Council and the Petroleum Research Fund, administered by the American Chemical Society, and at Queen Mary College by the Science Research Council.

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Asymmetric Syntheses Using *tert*-Leucine. 1. An Asymmetric Synthesis of β-Substituted Aldehydes via 1,4-Addition of Grignard Reagents to Chiral α,β-Unsaturated Aldimines

Sir:

The exciting development of a variety of methods for asymmetric induction continues to present a major challenge to the syntheses of optically active natural products, pharmaceuticals, etc.[1,2]

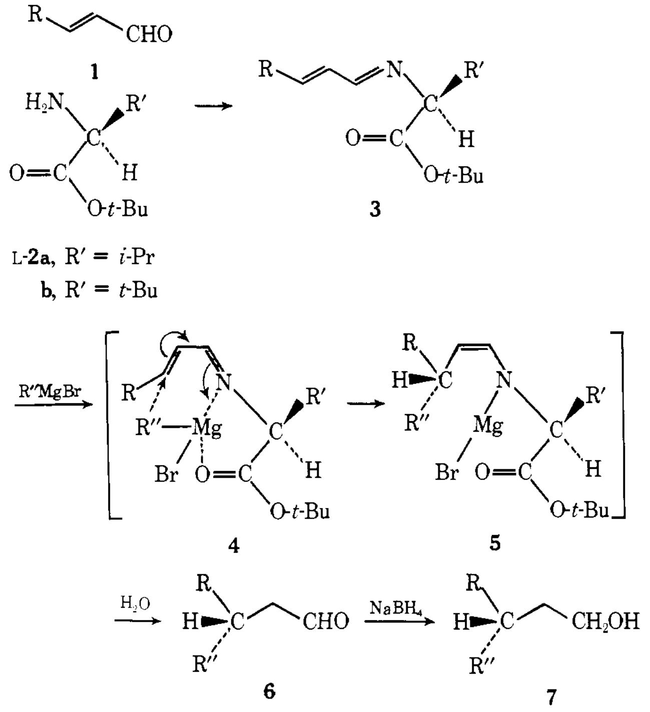
Meyers and Whitten have recently reported an asymmetric 1,4-addition of organolithium reagents to chiral oxazoline derivatives giving, after hydrolysis, β-substituted carboxylic acids in high enantiomeric purity.[3] We now wish to report that the 1,4-addition of Grignard reagents to the chiral α,β-unsaturated aldimines **3**, prepared from α,β-unsaturated aldehydes **1** and optically active α-amino acid *tert*-butyl esters **2**, gave, after hydrolysis, optically active β-substituted aldehydes **6**, which are useful intermediates for the synthesis of various optically active compounds.

Table I. Asymmetric 1,4-Addition of Grignard Reagents to α,β-Unsaturated Aldimines **3**

					Alcohols **7**^{d}			
Run	R	R′	R″	Synthetic yield, %	Optical rotation^{e} Obsd (calcd)^{f}	Lit.	Optical yield, %^{l}	Confign
1	Me	*i*-Pr^{a}	Ph	41	$\alpha^{25}{}_{D}$ − 24.5°	−39.0°^{g}	63	*R*
2	Me	*t*-Bu^{b}	Ph	52	$\alpha^{25}{}_{D}$ −32.8° (−35.6°)	−39.0°^{g}	91	*R*
3	Me	*t*-Bu^{b}	c-C_6H_{11}	53	$[\alpha]^{20}{}_{D}$ +10.7° (+11.6°)	+12.1°^{h}	96	*R*
4	Me	*t*-Bu^{b}	*n*-Bu	40	$[\alpha]^{25}{}_{D}$ −2.76° (−2.99°)	−3.07°^{i}	98	*S*
5	Me	*t*-Bu^{c}	$(CH_3)_2C{=}CHCH_2CH_2$	48	$[\alpha]^{25}{}_{D}$ +5.22° (+5.59°)	+5.51°^{j}	98^{m}	*R*
6	Ph	*t*-Bu^{b}	Et	56	$[\alpha]^{25}{}_{D}$ +14.2° (+15.4°)	−15.1°^{k}	95^{n}	*S*

[a] Optically pure L-**2a** was used. [b] L-**2b** of 92.2% optical purity was used. [c] D-**2b** of 93.4% optical purity was used. [d] All alcohols were purified by column chromatography on silica gel and subsequent vacuum distillation. [e] All optical rotations were taken neat. [f] Values in parentheses were obtained after correction for the optical purity of **2b** used. [g] D. J. Cram, *J. Am. Chem. Soc.*, **74,** 2137 (1952). [h] This value was obtained by correlation with (*R*)-(−)-3-phenylbutanol of known optical purity. [i] P. A. Levene and A. Rothen, *J. Org. Chem.*, **1,** 76 (1936). [j] C. G. Overberger and H. Kaye, *J. Am. Chem. Soc.*, **89,** 5640 (1967). [k] P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **100,** 685 (1933). [l] Corrected for the optical purity of **2b** used. [m] Calculated from the specific rotation of optically pure (*R*)-(+)-citronellol, $[\alpha]^{25}{}_{D}$ +5.68° (neat), obtained by correlation with (*R*)-(+)-citronellic acid; D. Valentine, Jr., K. K. Chan, C. G. Scott, K. K. Johnson, K. Toth, and G. Saucy, *J. Org. Chem.*, **41,** 62 (1976). [n] After permanganate oxidation, the optical yield was calculated from the specific rotation of optically pure (*R*)-(−)-3-phenylpentanoic acid, $[\alpha]^{25}{}_{D}$ −47.3° (neat), reported by P. A. Levene ard R. E. Marker, *J. Biol. Chem.*, **100,** 685 (1933).

Scheme I



An ether-THF (5:1) solution of **3** was added dropwise to the Grignard reagent (2.0 equv, 1.0-1.2 M in ether-THF (5:1)) at −55 °C under nitrogen. After 1.5 h of stirring, the resulting orange-red mixture was poured into 2 N aqueous hydrochloric acid at 0 °C with vigorous stirring. A usual workup gave crude aldehyde **6,** which was reduced to alcohol **7** with sodium borohydride in order to calculate the chemical (overall from **3**) and the optical yields (Table I). From the acidic aqueous phase, amino acid ester **2** was recovered in good yield.

Besides 1,4-addition, several competitive reactions seem to be possible under the present reaction condition, i.e., abstraction of a proton from the asymmetric carbon and from the carbon adjacent to the olefinic double bond by the Grignard reagent as a base, as well as addition to the ester carbonyl and 1,2-addition by the same reagent as a nucleophile. It was found that these competitive reactions are highly dependent on the bulkiness of the R′ group attached to the asymmetric carbon. Thus, in cases where *tert*-leucine *tert*-butyl ester, **2b,** was used, 1,4-adducts **6** were obtained as the only isolable compounds. The amino ester **2b** was recovered without any racemization, and the optical yields of the products were found to be remarkably high.

The absolute configuration of the aldehydes **6** obtained in the present method using L-**2b**[4] as a chiral reagent was as shown in Scheme I, while that of the aldehyde **6** was reversed by using D-**2b**[4] (run 5). It is now possible to prepare, in a predictable manner, either *R* or *S* aldehydes **6** by choosing either enantiomer of the amino ester **2b.** Furthermore, the results from runs 2 and 6 show that either enantiomer of the aldehydes **6** can also be prepared by simply exchanging the R group in **1** for the R″ group in the Grignard reagent using a common chiral reagent.

The following mechanism may be set forth based on the above results (Scheme I). The initial attack of the Grignard reagent to the α,β-unsaturated aldimine **3** prepared from **1** and L-**2** is expected to form the cyclic complex **4** by virtue of the chelation[5] of the Grignard magnesium with the unshared electron pairs on the nitrogen and oxygen atoms suitably disposed. Subsequent attack of the R″ group to the β-carbon atom from the less hindered side in *S*-cis conformation[6] would lead to **5,** which provides, upon acidic cleavage, the β-substituted aldehydes **6** with the configuration shown.[7]

The present method has advantages in giving aldehydes **6** in high enantiomeric purity, allowing easy preparation of aldimines **3** as well as easy recovery of the chiral reagent **2b** without any racemization for reuse, and exhibiting general utility. We are currently investigating various modifications and applications of the present synthetic method.

References and Notes

(1) For reviews, see J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971; J. W. Scott and D. Valentine, Jr., *Science*, **184**, 943 (1974).
(2) For some interesting examples, see E. J. Corey ard H. E. Ensley, *J. Am. Chem. Soc.*, **97**, 6908 (1975); A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *ibid.*, **98**, 567 (1976).
(3) A. I. Meyers and C. E. Whitten, *J. Am. Chem. Soc.*, **97**, 6266 (1975).
(4) DL-*tert*-Leucine was prepared and resolved in quantities essentially by the method of E. Abderhalden, W. Faust, and E. Haase, *Hoppe-Seyler's Z. Physiol. Chem.*, **228**, 187 (1934). The reported value, $[\alpha]_D$ −10.15° (H_2O), for optically pure L-*tert*-leucine was used for the calculation of optical purities. The reliability of these optical purities was confirmed by NMR spectra of *tert*-butyl esters (92.2% optically pure L-**2b** of $[\alpha]^{20}{}_{D}$ +54.6° (c 2.61, benzene) and 93.4% optically pure D-**2b** of $[\alpha]^{20}{}_{D}$ −55.2° (c 2.52, benzene)) in the presence of tris(3-trifluoroacetyl-*d*-camphorato)europium(III).
(5) We have found previously that an asymmetric hydrocyanation of the chiral Schiff bases prepared from benzaldehyde and L-α-amino acid *tert*-butyl esters proceeded highly efficiently due to the rigid cyclic intermediates formed by intramolecular hydrogen bonding: S. Yamada and S. Hashimoto, *Chem. Lett.*, 921 (1976).
(6) It has been reported that the 1,4-addition of Grignard reagent to an α,β-unsaturated ester may proceed through a cyclic intermediate. See S. Jacobsen, A. Jart, T. Kindt-Larsen, I. G. K. Andersen, and J. Munch-Petersen,

Acta Chem. Scand., 17, 2423 (1963); J. Munch-Petersen, Bull. Soc. Chim. Fr., 33, 471 (1966).
(7) The reaction of diethyl malonate with **3b** using KO-*t*-Bu as a base afforded the corresponding 1,4-adduct in an optical yield of 86%, but its absolute configuration was found to be contrary to that predicted by Scheme I. Details will be published in due course.

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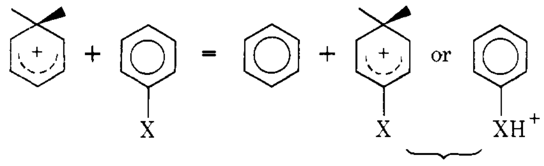
Substituent Effects on the Intrinsic Basicity of Benzene: Proton Affinities of Substituted Benzenes

Sir:

Recently there has been considerable interest in examining the intrinsic substituent effects on the basicity of benzene. The interest is justified by the fact that the protonation of benzene represents a prototype of electrophilic attack on the benzene ring and is therefore closely connected with the Hammett type linear free relationships and σ values for substituents. The intrinsic or "dilute gas phase" basicities are independent of solvent and therefore indispensible in separating true electronic effects from solvent effects of substituents.

Theoretical calculations for the energy change in the isodesmic[1] proton transfer (1) and experimental measurements by ICR of the equilibrium (1) where X = alkyl were reported recently by Hehre et al.[2] More extensive calculations including heterosubstituents were also reported later.[3] A brief discussion of the halo-substituent effects was published recently from our laboratory in connection with a general survey of compounds having proton affinities between those of water and ammonia.[4]


(1)

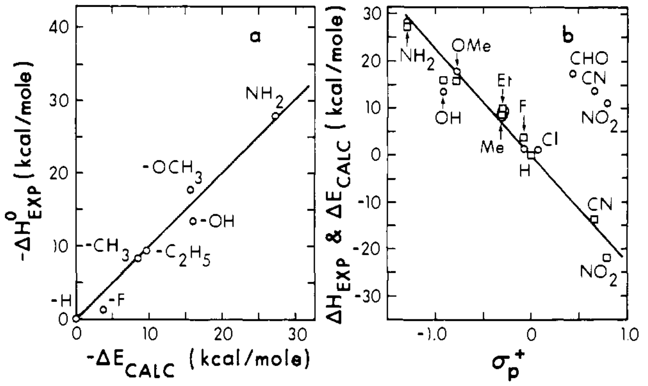


Figure 1. (a) Comparison between experimental ΔH_1 values and STO-3G calculated values for reaction 1: $C_6H_7^+ + XC_6H_5 = C_6H_6 + XC_6H_5H^+$. Straight line corresponds to 45° angle or perfect agreement. (b) Comparison between ΔH_1 ○ and ΔE_1 □ in a σ_p^+ plot of substituent constants. Deviations of ΔH_1 values for X = CHO, CN, NO$_2$ due to substituent protonation for these compounds.

The present experimental results are summarized in Table I. The data are based on proton transfer equilibria measurements at 600 K, involving also a number of other bases like dimethyl ether, acetone, ethyl formate, isobutene etc., such that a complete ladder of equilibria[4] was obtained between the compounds with lowest and highest basicity. An average of three thermodynamic cycles connected each compound to the ladder. The proton affinity of aniline was obtained on basis of PA(NH_3) = 202 kcal/mol[4,5] and earlier work.[6] The present results, where overlapping with our earlier measurements,[4] were in agreement within ~0.3 kcal/mol. However, the PA values quoted in the present work are higher by ~1 kcal/mol because here we have used the new $\Delta H_f(H^+)$ = 367 kcal/mol.[7]

The measurements were done at 600 K in order to avoid interference from the dimers B_2H^+. These dimers can become the major ions at lower temperatures if the charge in BH^+ is concentrated on a few hydrogens as is the cases NH_4+ or H_3O^+. The tendency to form dimers for ring protonated BH^+ is very much lower. This allowed us to examine the temperature dependence of K_1 for the two reactions where X = F and Cl, over a wide temperature range (25-360 °C). The linear van't Hoff plots gave in both cases $\Delta S°_1 = -3.5 \pm 0.1$ eu. The entropy change expected, because of changes of rotational symmetry numbers in these two reactions, is $\Delta S_{\text{rot.s.}} = (R \ln 1)/6 = -3.56$ eu. The closeness of the experimental entropy

Table I. Proton Affinities of Substituted Benzenes and Energy Differences for Reaction 1[a]

Substituent X	PA,[b] kcal/mol	$-\Delta G°_1(600)$[c]	σ_B/σ_{BH^+}[d]	$-T\Delta S_{\text{rot.s.}}$	$-\Delta H°$[f]	$-\Delta E$[g]	σ_p·[h]
NH_2	209.3[i]	25.6[i]	1	2.1	27.7	27.2	−1.3
OMe	199.4	15.7	1	2.1	17.8	15.7	−0.778
CHO	199.1	15.4	1	2.1	17.5		0.44
CN	195.1	11.4	1	2.1	13.5	−13.8	0.66
OH	195.0	11.3	1	2.1	13.4	16.0	−0.92
NO_2	192.6	8.9	1	2.1	11.0	−22.1	0.79
Et	191.0	7.3	1	2.1	9.4	9.7	−0.295
Me	190.0	6.3	1	2.1	8.4	8.5	−0.311
H	183.7	0	6	0	0	0	0
F	182.9	−0.8	1	2.1	1.3	3.7	−0.073
Cl	182.7	−1.0	1	2.1	1.1		0.114

[a] All energy values in kcal/mol. [b] Based on $\Delta H_f(t\text{-}C_4H_9^+)$ = 169 kcal/mol (ref 5), which with new $\Delta H_f(H^+)$ = 367 kcal/mol[7] leads to PA(isobutene) = 194.2 kcal/mol, and experimental $\Delta G°(600)$ for proton transfer reactions. [c] Free energy change at 600 K for reaction 1. [d] Ratio of rotational symmetry numbers. [e] $\Delta S_{\text{rot.s.}}$ represents entropy change for reaction 1 due to changes of the rotational symmetry σ numbers. This is believed to be the major contribution to the total entropy change of reaction 1. [f] Experimental enthalpy change for reaction 1 calculated from: $\Delta G°_1(600) = \Delta H - T\Delta S_{\text{rot.s.}}$. [g] Theoretical results LCAO-MO, STO-3G obtained by Hehre[2] for reaction 1. [h] σ constants for para substituents from ref 8. $\sigma_p^+(NH_2) = -1.3$ from J. E. Leffler and E. Grunwald, "Rates and Equilibria in Organic Chemistry", Wiley, New York, N.Y., 1963, p 204. $\sigma_p(CHO) = 0.44$ from J. Hine, "Structural Effects on Equilibria in Organic Chemistry", Wiley, New York, N.Y., 1975, p 66. [i] From previous measurement in ref 6 and PA(NH_3) = 202 kcal/mol[4] based on $\Delta H_f(H^+)$ = 367 kcal/mol.[7]