Photolysis of 1,8-NMN and 1,1-Diphenylethylene in Methanol. A nitrogen-purged solution of 200 mg (0.95 mmol) of 1,8-NMN, 2.5 mL (14 mmol) of 1,1-diphenylethylene, 20 mL of methanol, and 15 mL of acetonitrile was irradiated in a Pyrex tube for 24 h. Solvents were removed in vacuo, and the crude reaction mixture was separated via flash column chromatography (20% ether; 80% Skelly F), affording 49 mg (12%) of **19**, which was recrystallized from ether. Pure product **19**: mp 202.5–204 °C; IR (CCl_4) 1710, 1775 cm^{-1}; ^1H NMR ($CDCl_3$) 8.12 (dd, 1 H, J = 7.9, 1.2 Hz), 7.67–7.28 (m, 7 H), 7.00–6.95 (m, 3 H), 6.77–6.69 (m, 2 H), 5.17 (s, 1 H), 3.93 (t, 1 H, 2.6 Hz), 3.44 (s, 3 H), 2.96 (s, 3 H), 2.29–2.14 (m, 1 H), 1.82–1.68 (m, 1 H), 1.50–1.30 (m, 1 H), 1.21–1.03 ppm (m, 1 H). Anal. Calcd for $C_{28}H_{25}NO_3$: C, 79.41; H, 5.95; N, 3.31. Found: C, 79.18; H, 5.86; N, 3.10.

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Supplementary Material Available: ^1H NMR spectra of **10** and **17** and 2-D Cosy ^1H NMR spectrum, positional parameters, and anisotropic thermal parameters for **10** (4 pages); tables of observed and calculated structure factors (12 pages). Ordering information is given on any current masthead page.

Studies on the Stereoselectivity of Hydride Reductions on 2-(Methylthio)- and 2-(Methylsulfonyl)cyclohexanones

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The results obtained in the reductions of 2-X-cyclohexanones and *cis*- and *trans*-4-*tert*-butyl-2-X-cyclohexanones (X = SMe, SO_2Me) with different hydrides are reported. When the sulfur functions adopt the axial disposition, the cyclohexanol resulting from the axial approach of the hydride is the only one obtained, even when bulky hydrides are used. This suggests that the unshared electron pairs on sulfenylic sulfur and the sulfonylic oxygen exert a stereoelectronic repulsive effect on the hydride approach that reinforces the tendency derived from their steric hindrance. When the sulfur functions adopt the equatorial disposition, mixtures of diastereoisomers were obtained. The mentioned stereoelectronic effect must be considered, in addition to the steric effect, to explain the observed diastereoisomer ratios.

The mechanism and stereochemistry of alkyl-substituted cyclic ketones reductions with hydrides have been extensively studied.[1] The main conclusions inferred from these studies indicate that the preferred direction of hydride attack (axial or equatorial) are related to both the bulkiness of the reagents and the steric environment surrounding the carbonyl group. Preferential axial attack of small hydrides ($NaBH_4$ and $LiAlH_4$) on unhindered cyclohexanones is well established, but the reason for such discrimination is not clear, with the torsional strain experienced by the approaching hydride being the assumption that has received the widest acceptance. Other electronic factors have also been invoked to explain these results.[1] Increase of the steric congestion around the carbonyl group lowers, often drastically, the favored axial attack for the small hydrides.[1] The bulkiest reagents[1e] (tri-*sec*-butylborohydride, trisiamylborohydride, dimesitylborohydride, and triisopropoxyborohydride) show the almost exclusive equatorial attack for all cyclohexanones and yield nearly isomerically pure axial alcohols.

The influence of polar substituents on the stereoselectivity of cyclohexanone reductions had not been well studied yet. Several isolated results have been published concerning halo-, acetoxy-, and (dimethylamino)cyclohexanones.[2] Recently, some studies concerning reduction of acyclic 2-alkylthio and 2-alkylsulfinyl ketones,[3] very important in the asymmetric synthesis of chiral alcohols, have appeared. Nevertheless, the reduction of cyclo-

Scheme I

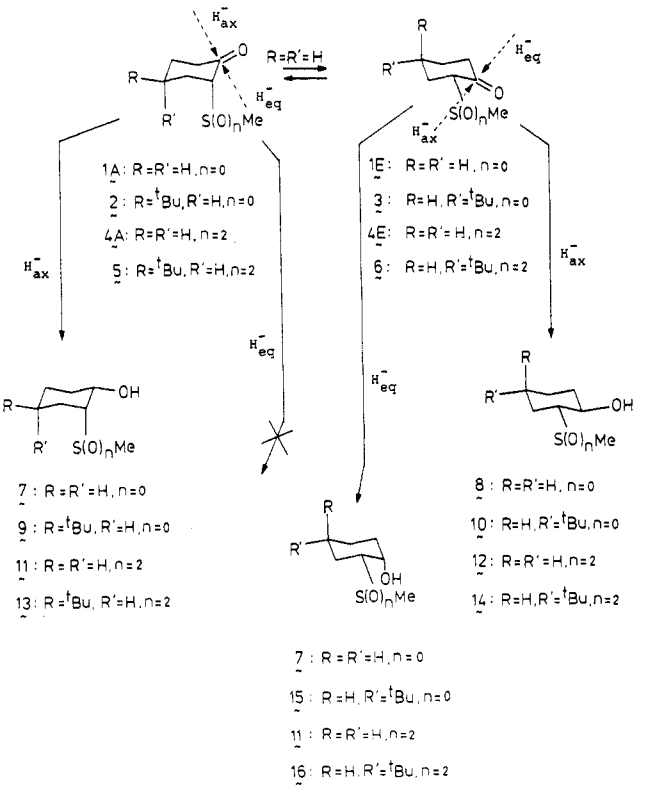

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Table I. Reductions of 2-(Methylthio)cyclohexanone (1) and *trans*- and *cis*-4-*tert*-Butyl-2-(methylthio)cyclohexanone (2 and 3)

entry	start materl	hydride[a]	T, °C	diastereoisomers ratio[b]	reacn time, h	yield, %[c]
				7/8		
1	1	A	25	83/17	0.5	98
2	1	A	−15	90/10	3	99
3	1	A	−78	97/3	6	99
4	1	B	25	40/60	0.5	98
5	1	C	25	89/11	0.5	81
6	1	C	−15	95/5	4	98
7	1	C	−78	96/4	8	91
8	1	D	−78	90/10	3	85
9	1	E	−78	92/8	1	88
10	1	G[d]	−78	100/0	1	97
11	1	G[e]	−78	100/0	1	98
12	1	G[f]	−78	100/0	1	86
13	2	A	25	**9** only	0.5	93
14	2	A	−78	**9** only	4	81
15	2	E	−78	**9** only	1	49
16	2	G[d]	−78	**9** only	1	55
17	2	G[f]	−78	**9** only	1	98
				15/10		
18	3[g]	A	25	56/44[h]	2	66
19	3[g]	A	−78	56/44[h]	8	50
20	3[g]	B	−78	28/72[h]	0.5	68
21	3[g]	E	−78	46/54[h]	1.5	41
22	3[g]	G[d]	−78	100/0[h]	1	80
23	3[g]	G[f]	−78	100/0[h]	1	70

[a] A, $NaBH_4$; B, $NaBH_4/ZnCl_2$; C, $NaBH_3CN$; D, $LiAlH_4$; E, $(i\text{-}Bu)_2AlH$. [b] From ^1H NMR spectra of the crude reaction. [c] Entries 1–17, isolated yield; entries 18–23, yield determined from ^1H NMR spectra. [d] G, Li(*sec*-Bu)$_3$BH. [e] G, K(*sec*-Bu)$_3$BH. [f] G, Li(Et)$_3$BH. [g] From a 88:12 mixture of 3/2. [h] Absolute ratios from 3.

hexanones supporting sulfur functions on C-2 has never been studied, and so the influence of these functions on the course of these reactions is not well-known. The possibility of achieving the stereospecific synthesis of cyclohexanols with sulfur functions on C-2 is very attractive, because of the great versatility of these functions in organic synthesis, providing a facile entry to different functionalized cyclohexanols, widespread in medical and biologically active compounds.[4]

In this paper, a systematic study of hydride reductions on 2-(methylthio)- and 2-(methylsulfonyl)cyclohexanones is reported. Steric and electronic differences between both functions will give information regarding the influence of these factors on the stereochemical results.

Results and Discussion

2-(Methylthio)cyclohexanone (1) and its trans and cis 4-*tert*-butyl derivatives **2** and **3** (Scheme I) were obtained by sulfenylation of cyclohexanone or 4-*tert*-butylcyclohexanone with dimethyl disulfide, following Trost's procedure.[5] Compounds **2** and **3** were obtained as a mixture (**2**/**3** ratio, 66/34) that could be separated by chromatography yielding **2** as a pure diastereoisomer. Isomerically pure thioether **3** is difficult to obtain. Thus, many of the reactions of this substrate have been carried out on a mixture **2** + **3**, **3** being the main component. Oxidation of thioethers **1**–**3** with MCPBA afforded the corresponding sulfones. The experimental procedure, which involved washing with $NaHCO_3$ solution, caused the epimerization of sulfones that were always obtained as **5** + **6** mixture. Crystallization of this mixture from hexane afforded pure *trans*-4-*tert*-butyl-2-(methylsulfonyl)cyclohexanone (**5**), but isomerically pure cis isomer **6** could not be obtained. Reactions on substrate **6** were carried out with the diastereoisomer mixture (**5**/**6** ratio, 34/66).

The results obtained in the hydride reductions of 2-(methylthio)cyclohexanone (**1**) are indicated in Table I. Small hydrides (entries 1–3 and 5–9) afforded a mixture of *cis*- and *trans*-2-(methylthio)cyclohexanol[6] (**7** and **8**), which is temperature dependent. Bulky hydrides (entries 10–12) yielded exclusively **7**, even at higher temperatures than those indicated in Table I. These reactions are very interesting from a synthetic point of view because they afford a single approach to the preparation of cyclic cis β-hydroxy thioethers, difficult to obtain by other routes.[7]

Two factors may be considered to explain the stereochemical results: conformational composition of **1** and preferred direction of hydride attack. With respect to the first, chemical equilibration of *trans*-4-*tert*-butyl-2-(methylthio)cyclohexanone (**2**) with $NaHCO_3$ in MeOH/H_2O gave a 70/30 ratio of **2** and *cis*-4-*tert*-butyl-2-(methylthio)cyclohexanone (**3**). This suggested the same approximate ratio of conformers **1A** and **1E** in the conformational equilibrium of **1**.[8] A similar ratio of **1A** and **1E** (72/28) was obtained by applying Eliel's method[9] to the chemical shifts of H(2) in compounds **1** (δ 3.25), **2** (δ 3.18) and **3** (δ 3.43). Conformer **1E** should be less stable[10] due to dipolar and repulsive gauche effects.[11]

In order to establish the preferred direction of hydride approach, reduction of rigid models **2** and **3** was carried out. Compound **2** was submitted to reaction with small (entries 13–15 in Table I) and bulky (entries 16 and 17) hydrides, yielding stereospecifically compound **9** in all cases. These results were expected with the small hydrides,

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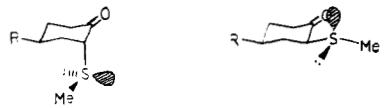

1A (R = H) 1E (R = H)
2 (R = ^{t}Bu) 3 (R = ^{t}Bu)

Figure 1. Spatial picture of axial and equatorial SMe group, showing nonbonding orbital which makes the hydride approach difficult.

where axial attack is favored, but they were a dramatic reversal of the usual equatorial approach observed with bulky hydrides.[12] Studies on 2-alkyl-4-*tert*-butylcyclohexanones[13] showed that the steric effect of the axial substituent modifies the preferred direction of bulky hydride approach; however, a certain amount of the product resulting from equatorial attack is always obtained. Taking into account that bulkier alkyl groups other than the SMe yield mixtures of diastereoisomers, the stereospecificity observed in our substrates may be explained assuming that, in addition to the steric effect of the axial SMe group, a stereoelectronic effect must be exerted by sulfur, whose unshared electron pairs make the equatorial hydride approach more difficult (see Figure 1). In this case, the theory of charge-transfer stabilization of the transition state for nucleophilic addition to a carbonyl group by electron donors, proposed by Cieplak[1d] and supported by other authors,[1f] can also explain that the axial attack was more favored than expected on steric grounds. The greater electron-donating power of the σ_{CS} axial bond in **1A** and **2** (Figure 1) with respect to the σ_{CH} or σ_{CC} axial bonds can justify the observed high preference for axial attack.

The reaction of compound **3** with small hydrides (entries 18, 19, and 21) showed very low stereoselectivity (the results are independent of the temperature) in contrast with the results obtained in the reductions of alkyl-substituted cyclohexanones with these hydrides, where the axial approach is always favored.[13] This attack is clearly not preferred when the SMe group adopts the equatorial disposition in spite of the size of the SMe group, which is smaller than other alkyl groups studied.[13] The lack of stereoselectivity observed in reactions of **3** with $NaBH_4$ and $(i\text{-Bu})_2AlH$ can also be a consequence of the electronic repulsion between the occupied nonbonding orbitals on sulfur and the hydride (lower with $(i\text{-Bu})_2AlH$ because this is an electrophilic hydride) that, in this case, makes the axial approach difficult (see Figure 1). In this case, the spatial arrangement of the σ_{CS} equatorial bond with respect to the σ_{CH} orbitals in the transition states resulting from the axial or equatorial hydride approach is not suitable for giving a stabilizing interaction. Thus, Cieplak's theory[1d] cannot be applied to justify the stereochemical results.

The results obtained in the reduction of **3** with bulky hydrides were to be expected (entries 22 and 23 in Table I).

We can now easily explain the behavior of substrate **1**. The exclusive axial approach of the small hydride on the carbonyl group of the major conformer **1A** justified the formation of *cis*-2-(methylthio)cyclohexanol (**7**) as the main product. The trans isomer **8** will be formed from the minor conformer **1E**, whose reduction is not stereoselective. The decrease in temperature, and the less polar solvent shift the conformational equilibrium of **1** to the more stable **1A**, increasing the proportion of compound **7** in the mixture.

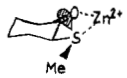

Figure 2. 2-(Methylthio)cyclohexanone favored conformer in presence of $ZnCl_2$.

On the other hand, reductions of **1** with bulky hydrides yielded exclusively the alcohol **7**, derived from axial attack on **1A** and/or equatorial attack on **1E**.

As we have proposed, if the stereoelectronic effect of the SMe group is responsible for the stereochemical results when SMe is equatorial, the presence of a chelating agent such as $ZnCl_2$ should be able to modify the stereochemical results. Reaction of **1** with $NaBH_4/ZnCl_2$ yielded a mixture of **7** and **8** where the trans isomer was the major component (entry 4 in Table I). The decrease of stereoselectivity was expected because $ZnCl_2$ must stabilize conformer **1E**, shifting the conformational equilibrium (Figure 2). Nevertheless, the predominance of **8** was difficult to explain because the equatorial attack of $NaBH_4$ was slightly favored when the SMe group adopted the equatorial disposition (entries 18 and 19) and the cis isomer **7** should have been produced as major component in the mixture.

It was necessary to assume that the preferred direction of hydride attack on the chelated especies **1E** must be the axial one. In order to demonstrate this assumption, we carried out the reduction of **3** with $NaBH_4/ZnCl_2$ (entry 20). As can be seen, the results indicated the major formation of isomer **10**, produced from axial approach of the hydride, with the stereoselectivity similar to that exhibited by $NaBH_4$ in the reductions of alkylcyclohexanones.[13] Differences induced by $ZnCl_2$ on the stereoselectivity of reductions of **3** can be attributed to the decrease of electronic density on sulfur, as a consequence of the chelation, which minimized the mentioned stereoelectronic effect of the SMe group.[14]

The results obtained in the reductions of 2-(methylsulfonyl)cyclohexanone[15] (**4**) with different hydrides are summarized in Table II. The observed stereoselectivity is similar to that observed in the reductions of compound **1**, but the explanation must obviously be different. Treatment of *trans*-4-*tert*-butyl-2-(methylsulfonyl)cyclohexanone (**5**) with $NaHCO_3$ in $MeOH/H_2O$ afforded an equilibrium mixture of **5** and its cis isomer **6** (35:65 ratio). This suggested the predominance of **4E** in the conformational equilibrium of **4**.[8] In this case, the larger size of the SO_2Me group with respect to the SMe one[16] and the different electronic distribution in both functions (sulfur is positively charged in the sulfonyl group) justified the preference of the isomer **6**, with the SO_2Me group in equatorial disposition.

Reaction of **5** with small and bulky hydrides stereospecifically afforded compound **13** (entries 12–15 in Table II). This stereochemical result is similar to that observed in thioethers; nevertheless a small percentage of reduction products of sulfone **6**, resulting from epimerization of **5**, was always detected. The equatorial hydride approach must be very difficult due to the large size of the methylsulfonyl group. The stereoelectronic repulsive effect between the hydride and the unshared electron pairs on sulfonylic oxygen during the equatorial attack and the

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Table II. Reductions of 2-(Methylsulfonyl)cyclohexanone (4) and *trans*- and *cis*-4-*tert*-Butyl-2-(methylsulfonyl)cyclohexanone (5 and 6)

entry	start materl	hydride[a]	T, °C	diastereoisomers ratio[b]	reacn time, h	yield, %[c]
				11/12		
1	4	A	25	90/10	0.10	95
2	4	A	−15	92/8	0.16	97
3	4	A	−78	95/5	0.25	97
4	4	B	25	74/26	1	74
5	4	C	25	85/15	0.5	82
6	4	C	−15	89/11	2	81
7	4	D	−78	80/20	1	99
8	4	E	−78	54/46	1	85
9	4	F	−78	74/26	1.5	67
10	4	G[d]	−78	100/0	1	79
11	4	G[e]	−78	100/0	1	70
12	5	A	25	13 only	*h*	81
13	5	D	−78	13 only	1	97
14	5	E	−78	13 only	1	93
15	5	G[e]	−78	13 only	1	45
				16/14		
16	6[f]	A	25	66/34[g]	0.16	58
17	6[f]	A	−78	65/35[g]	0.25	85
18	6[f]	B	25	43/57[g]	1	88
19	6[f]	B	−78	43/57[g]	3	53
20	6[f]	D	−78	41/59[g]	2	70
21	6[f]	E	−78	25/75[g]	2	53
22	6[f]	F	−78	45/55[g]	2.5	53
23	6[f]	G[e]	−78	100/0[g]	2	60

[a] A, $NaBH_4$; B, $NaBH_4/ZnCl_2$; C, $NaBH_3CN$; D, $LiAlH_4$; E, $(i\text{-Bu})_2AlH$; F, $(i\text{-Bu})_2AlH/ZnCl_2$. [b] From ^1H NMR spectra of the crude reaction. [c] Entries 1–15, isolated yield; entries 16–23, yield determined from ^1H NMR spectra. [d] G, Li(*sec*-Bu)$_3$BH. [e] G, Li(Et)$_3$BH. [f] From a 66:34 mixture of 6/5. [g] Absolute ratios from 6. [h] Instantaneous.

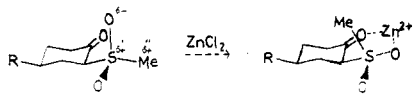

Figure 3. Change in favored rotamers around C–S bond in compounds **4E** (R = H) and **6** (R = *t*-Bu) induced by $ZnCl_2$.

stabilization of the transition state, for the axial hydride approach by the σ_{CS} axial bond,[1d] could also be invoked to explain the observed results.

Reduction of *cis*-4-*tert*-butyl-2-methylsulfonylcyclohexanone (**6**), yielded different ratios of cyclohexanols **16** and **14**, depending on the hydride (see Table II). With $NaBH_4$, the equatorial approach of the reagent is clearly favored (entry 16), yielding **16** as the main product in the mixture. The anomalous preference for the equatorial attack of this small hydride can be explained considering the favored rotamer around the C–S bond of **6** represented in Figure 3, for which repulsive interactions between carbonylic and sulfonylic oxygens are minimized. The steric hindrance of the sulfonyl group, which always exhibits one sulfur substituent making difficult the axial approach of the hydride, and the stereoelectronic repulsive effect exerted by the sulfonylic oxygen may be responsible for this behavior.

The results obtained with $(i\text{-Bu})_2AlH$ are different (entry 19), indicating the formation of **14** (resulting from the axial attack) as the main product. This change in the stereoselection must be related to the electrophilic character of the hydride, which can be associated with the sulfonylic oxygen (slightly nucleophilic) facilitating the axial approach from the favored rotamer in Figure 3.

The presence of $ZnCl_2$ modifies the stereochemical results which become identical with both small hydrides (entries 18 and 22). The preference for the equatorial attack, shown by $NaBH_4$, and for the axial attack, exhibited by $(i\text{-Bu})_2AlH$, practically disappear in the presence of $ZnCl_2$. Taking into account that complexation with Zn^{2+} must involve both the carbonylic and one of the sulfonylic oxygens, the favored spatial arrangement must be that indicated in Figure 3 (dipolar repulsion is minimized) and now the stereoisomer proportion will not only depend on the size of the hydride.

The results obtained with $LiAlH_4$ (entry 20) are difficult to explain. The diastereoisomer ratio is similar to that obtained with $NaBH_4$ and $(i\text{-Bu})_2AlH$ in the presence of $ZnCl_2$ (entries 18 and 22), suggesting the possibility that the Li^+ was able to chelate the oxygens[3c] in a similar way as the $ZnCl_2$ in Figure 3.

Finally, the bulky hydride Li(Et)$_3$BH afforded exclusively the expected compound **16** (entry 23) resulting from the equatorial attack on substrate **6**.

On these basis, the stereoselectivity observed in reduction of compound **4** (entries 1–11 in Table II) can be satisfactorily explained. With $NaBH_4$ the exclusive axial attack on **4A** and the preferred equatorial attack on **4E** will give the diastereoisomer **12**, obtained as major product (entries 1–3). In addition, we could demonstrate, from the reduction of an equimolecular mixture of **5** and **6** with $NaBH_4$, that the axial diastereoisomer **5** evolved approximately twice as fast as the equatorial **6**. Thus, the high stereoselectivity observed in the reduction of **4** and its variation with the temperature (entries 1–3) must partially be a consequence of the higher reactivity of **4A**, determining the conformational equilibrium shift toward this conformer. As expected, the moderately bulkier hydride $NaBH_3CN$ showed a slightly lower preference for axial attack in the reductions of **1** and **4** (entries 5 and 6 in Tables I and II) than that observed with $NaBH_4$. The stereoselectivity decrease observed when $LiAlH_4$ or $(i\text{-Bu})_2AlH$ are used as reagents (entries 7 and 8) is in accordance with the expected decrease in the preference for the equatorial attack on **4E**. The addition of $ZnCl_2$ (entries 4 and 9) modifies the stereochemical results, which become identical in reactions with $NaBH_4$ and $(i\text{-Bu})_2AlH$. This could be expected, taking into account the normal behavior of these hydrides (both considered as small hydrides) and the starting species are identical in both cases. The exclusive formation of **11** in the reaction of **4** with bulky hydrides (entries 10 and 11 in Table II) is in accordance with the axial attack on **4A** and equatorial attack on **4E**,

both yielding the cyclohexanol 11.

Experimental Section

Melting points were obtained on a Büchi 594392 type S apparatus in open capillary tubes and are uncorrected. Microanalyses were performed by the Instituto de Química Orgánica of the C.S.I.C. in Madrid with a Perkin-Elmer Model 240 analyzer. Infrared spectra were recorded under the conditions specified for each compound on a Pye-Unicam SP-1100 or a Nicolet FT-5DX spectrometers and are given in cm^{-1}. Mass spectra were recorded in a Hewlett-Packard 5985 spectrometer at 70 eV. ^1H NMR (200 MHz) and ^{13}C NMR (50.32 MHz) spectra were recorded in the FT mode on a Bruker WM-200-SY instrument (Aspect 2000, 80K computer) transforming 16K data points. Chemical shifts are reported in ppm downfield from internal Me_4Si and are accurate within 0.1 Hz. Diastereoisomer ratios were established by integration of the signals corresponding to the methylsulfenyl or methylsulfonyl groups and/or the proton at C-1 of the alcohols in the mixture resulting from hydrolysis. The solvent was $CDCl_3$, unless otherwise indicated. Thin-layer chromatography was made of E. Merck AG Darmstad silica gel PR-254. Eluting solvents are indicated in the text. Flash column chromatography was performed with silica gel Merck-60 (230–400 mesh). Dry solvents such as ether and tetrahydrofuran were distilled from sodium/benzophenone, and methanol was refluxed over calcium oxide. Apparatus for all experiments was dried by flaming in a steam of dry argon. During workup of reactions, routine drying was performed over anhydrous sodium sulfate unless otherwise indicated. Reductions were monitored by TLC (eluent $CHCl_3$). Temperatures, reaction times, yields, and diastereoisomer ratios obtained are listed in Tables I and II.

2-(Methylthio)cyclohexanone (1) was synthesized from cyclohexanone and dimethyl disulfide following Trost's procedure[5] and characterized by comparison with the spectroscopic data: bp 54 °C (1 mm); ^{13}C NMR (CS_2) δ 203.6, 53.53, 36.88, 32.58, 27.07, 21.85, 14.93.

***trans*- and *cis*-4-*tert*-Butyl-2-(methylthio)cyclohexanone (2 and 3).** A solution of lithium diisopropylamide (60.9 mmol) was prepared by addition in dry N_2 atmosphere of 40.6 mL (60.9 mmol) of a 1.5 M solution of *n*-butyllithium by syringe to a solution of 6.56 g (65 mmol) of diisopropylamine in 50 mL of THF at −78 °C. After the mixture was stirred for 30 min at this temperature, 4.4 g (28.6 mmol) of 4-*tert*-butylcyclohexanone, solved in a mixture of 10 mL of THF and 30 mL of HMPA (distilled from calcium hydride) were added dropwise by syringe. The resulting solution was stirred at −78 ° for 1 h, and the dry ice–methanol bath was replaced by an ice bath. After being stirred 1 h at 0 °C and 35 min at room temperature, the mixture was cooled at 0 °C and 6.1 g (65.3 mmol) of dimethyl disulfide was added. The reaction mixture was then stirred for 10 min at 0 °C and 35 min at room temperature. The solution was poured into a separatory funnel containing ethyl acetate and 15% aqueous hydrochloric acid. The aqueous layer was separated, and the organic phase was washed once with water and saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude material obtained 4.8 g, 84%) was a (66/34) mixture of **2** and **3**. Flash column chromatography (ethyl ether–hexane 1/10) afforded pure *trans*-4-*tert*-butyl-2-(methylthio)cyclohexanone (2) and cis diastereoisomer **3** contaminated by a 12% of **2**: MS *m/e* (relative intensity) [**2**] 206 (6), 200 (100), 185 (4), 154 (32), 153 (10), 139 (45), 125 (3), 111 (14), 95 (32), 81 (10), 67 (40), 57 (60), [**3**] 202 (6), 200 (92), 185 (3), 154 (75), 139 (91), 125 (4), 111 (14), 95 (43), 81 (16), 67 (63), 57 (84), 41 (100); ^1H NMR δ [**2**] 3.18 (m, 1 H) superimposed upon 3.20–3.02 (m, 1 H), 2.05 (s, 3 H) superimposed upon 2.25–1.20 (m, 6 H), 0.90 (s, 9 H), [**3**] 3.43 (ddd, 0.88 H, J = 12.2, 6.0, and 1.1 Hz), 3.20–3.02 (m, 0.24 H), 2.12 and 2.02 (2 s, for total 3 H, 7.3/1 ratio) superimposed upon 2.62–1.20 (m, 6.88 H), 0.93 and 0.90 (2 s, for total 9 H, 7.3/1 ratio); ^{13}C NMR δ [**2**] 207.71, 52.93, 41.55, 37.79, 33.17, 32.01, 27.49, 27.35, 15.20, [**3** (values in parentheses corresponding to compound **2**)] (207.71), 206.97, 54.78, (52.93), 47.33, (41.55), 40.50, (37.79), 35.18, (33.17), 32.62, (32.01), 27.71, 27.52, (27.49), (27.35), (15.20), 14.20; IR [**2**] (Nujol) 1709, 1328, 1231, 1219, 944, [**3**] (film) 2961, 2872, 1714, 1366, 1219, 1162, 959, 944.

Oxidation of Thioethers. Preparation of Sulfones. A solution of *m*-chloroperbenzoic acid (10 mmol) in 20 mL of chloroform was added over the solution of 5 mmol of sulfide in 20 mL of chloroform at 0 °C. ^1H NMR analyses showed complete disappearance of the starting material after 20 min. The resulting solution was washed with several portions of saturated aqueous sodium bicarbonate solution until the washing aqueous phase remained alkaline. The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo to yield the sulfones, which were purified by recrystallization.

2-(Methylsulfonyl)cyclohexanone (4). Oxidation of 2-(methylthio)cyclohexanone (1) following the procedure described above afforded compound **4** as a white solid, which was purified by recrystallization from hexane and characterized by comparison with the spectroscopic data of an authentic sample:[15] yield, 95%; mp 55–56 °C (lit.[15] mp 57–58 °C); MS *m/e* (relative intensity) 176 (11), 148 (13), 107 (30), 97 (33), 81 (61), 68 (100), 55 (71), 41 (90); ^{13}C NMR δ 203.3, 70.49, 41.44, 40.65, 25.84 ($2CH_2$), 22.32.

***trans*- and *cis*-4-*tert*-Butyl-2-(methylsulfonyl)cyclohexanone (5 and 6).** Oxidation of a 66/34 mixture of *trans*- and *cis*-4-*tert*-butyl-2-(methylthio)cyclohexanone (**2** and **3**) afforded a white solid, which was identified as a 38/62 mixture of sulfones **5** and **6**; yield 95%. The same diastereoisomer ratio was obtained when **2** was the starting material. Pure diastereoisomer **5** was obtained by fractional crystallization of the mixture from hexane as a white solid; mp 118–120 °C. From the mother liquors compound **6** was obtained by crystallization from pentane, contaminated by 25% of **5**. This was the better ratio obtained, but the diastereoisomer mixture used for reductions was 66/34 **6**/**5**: MS, *m/e* (relative intensity) [**5**] 232 (1), 217 (5), 176 (11), 161 (5), 153 (24), 97 (100), 81 (25), 79 (16), 57 (69), 41 (28), [**6**] 232 (1), 217 (5), 176 (9), 153 (22), 97 (100), 81 (22), 79 (15), 57 (73), 41 (30); ^1H NMR δ [**5**] 3.74 (m, 1 H, J = 6.8 and 2.0 Hz), 2.96 (s, 3 H), 2.94–2.78 (m, 2 H), 2.65–2.51 (m, 1 H), 2.21–2.05 (m, 1 H), 2.02–1.68 (m, 2 H), 1.58–1.35 (m, 1 H), 0.95 (s, 9 H), [**6** (mixture of diastereoisomers)] 3.85 (dd, 0.75 H, J = 12.4 and 5.4 Hz), 3.74 (m, 0.25 H, J = 6.8 and 2.0 Hz), 3.11 and 2.96 (2 s, for total 3 H, 3/1 ratio), 2.94–2.78 (m, 1.25 H), 2.76–2.51 (m, 1 H), 2.48–2.30 (m, 0.75 H), 2.21–2.05 (m, 1 H), 2.12–1.35 (m, 3 H), 0.97 and 0.95 (2 s, for total 9 H, 3/1 ratio); ^{13}C NMR δ [**5**] 202.9, 70.80, 41.66, 41.03, 40.45, 32.45, 27.21, 26.45, 26.35, [**6** (values in parentheses corresponding to compound **5**)] 203.6, (202.9), (70.80), 69.55, 45.19, (41.66), (41.03), 40.95, 40.61, (40.45), (32.45), 32.38, (27.21), 27.06, (26.45), (26.35), 25.72 ($2CH_2$); IR [**5**] (Nujol) 1706, 1300, 1290, 1122, 953, [**6**] (KBr) 2945, 2882, 1707, 1363, 1321, 1293, 1124, 955. Anal. Calcd for $C_{11}H_{20}O_3S$: C, 56.90; H, 8.62; S, 13.79. Found (**5**): C, 56.73; H, 8.91; S, 13.31.

Chemical Equilibration of *trans*-4-*tert*-Butyl-2-(methylthio)cyclohexanone (2) or *trans*-4-*tert*-Butyl-2-(methylsulfonyl)cyclohexanone (5). A mixture of 0.25 mmol of **2** or **5** in 5 mL of methanol and 5 mL of saturated aqueous sodium bicarbonate solution was stirred at room temperature for 24 h. The organic material was extracted with CH_2Cl_2 and the resulting solution dried and evaporated in vacuo to yield a 70/30 mixture of compounds **2** and **3** (86% from **2**) or a 34/66 mixture of compounds **5** and **6** (80% from **5**).

General Procedures for Hydride Reductions. Method A. $NaBH_4$. To a solution of the β-keto thioether or β-keto sulfone (0.35 mmol) in 5 mL of methanol was added a mixture of 5 mg (0.13 mmol) of $NaBH_4$ and 5 mL of methanol at the indicated temperature in Tables I and II. When the reaction was complete, 20 mL of water was added. The organic material was extracted with methylene chloride and the resulting solution dried and concentrated to dryness at reduced pressure to afford the hydroxy thioethers or hydroxy sulfones as diastereoisomer mixtures.

Method B. $NaBH_4/ZnCl_2$. A mixture of the β-keto thioether or β-keto sulfone (0.35 mmol) and anhydrous zinc chloride (0.70 mmol) in 5 mL of methanol was stirred at room temperature for 2 h and cooled when necessary. $NaBH_4$ (1.4 mmol) was then added and the resulting mixture stirred. After completion of the reaction, hydrolysis was performed as indicated in method A.

Method C. $NaBH_3CN$. To a solution of 2-(methylthio)-cyclohexanone (1) or 2-(methylsulfonyl)cyclohexanone (4) (0.35 mmol) in 5 mL of methanol at the indicated temperature were added 23 mg (0.37 mmol) of $NaBH_3CN$ and 1 mg of methyl orange. A solution of 5 N HCl in methanol was added dropwise

to maintain the pH below 4, and the reaction mixture was stirred. After the disappearance of the starting material, hydrolysis was carried out following procedure described in method A.

Method D. $LiAlH_4$. A solution of β-keto thioether or β-keto sulfone (0.31 mmol) in 5 mL of tetrahydrofuran was added over a suspension of 12 mg (0.31 mmol) of $LiAlH_4$ in 3 mL of tetrahydrofuran under N_2 atmosphere. The mixture was stirred at −78 °C. When the reaction was complete, 1.5 mL of saturated ammonium chloride solution was added and the organic material extracted with ethyl ether. Drying and evaporation of the organic solvent in vacuo afforded a diastereoisomer mixture of hydroxy thioethers or hydroxy sulfones.

Method E. $(i\text{-Bu})_2AlH$. To a mixture of 0.34 mL (0.34 mmol) of 1 M hexane solution of Dibal and 3 mL of tetrahydrofuran was added, at −78 °C under N_2, a solution of 0.31 mmol of β-keto thioether or β-keto sulfone in 3 mL of dry THF. Stirring was maintained until completion of the reaction, and then 3 mL of methanol was added. The solvents were evaporated in vacuo, and the resulting mixture was diluted with 10 mL of water and extracted with methylene chloride. The organic phase was dried and concentrated to dryness in vacuo to yield the diastereoisomer mixture of hydroxy thioethers or hydroxy sulfones.

Method F. $(i\text{-Bu})_2AlH/ZnCl_2$. A solution of β-keto sulfone (0.76 mmol) and anhydrous zinc chloride (1.7 mmol) in 2 mL of dry THF was stirred for 2 h at room temperature under N_2. Over the cooled mixture (−78 °C) was added 1.7 mL (1.7 mmol) of 1 M hexane solution of Dibal and the resulting solution stirred until completion of the reaction. The mixture was then hydrolyzed with 15 mL of water and extracted with methylene chloride. The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo to yield the diastereoisomer mixture of hydroxy thioethers or hydroxy sulfones.

Method G. L-Selectride, K-Selectride, or Super Hydride. To a solution of 0.35 mmol of β-keto thioether or β-keto sulfone in 2 mL of dry THF at −78 °C was added under N_2 a solution of the hydride in hexane (0.40 mmol). The mixture was stirred and when the reaction was complete, poured into a separatory funnel containing 20 mL of ethyl acetate and 10 mL of 5% HCl. The organic phase was washed with a solution of 15% NaOH, dried, and concentrated to dryness in vacuo to yield the hydroxy thioether or hydroxy sulfone as pure diastereoisomers.

Reduction of 2-(Methylthio)cyclohexanone (1). *cis*- and *trans*-2-(Methylthio)cyclohexanol (7 and 8). Reduction of compound 1 following methods A–F afforded a yellow oil, which was characterized as a mixture of diastereoisomers 7 and 8 (Table I). Method G afforded pure diastereoisomer 7 as a yellow oil, which was purified by distillation at reduced pressure, bp 54–56 °C (1 mm). *trans*-2-(Methylthio)cyclohexanol (8) was characterized in the mixture by comparison with the spectroscopic data described by Zefirov: MS, *m/e* (relative intensity) [7] 148 (3), 146 (69), 128 (7), 118 (6), 103 (25), 98 (24), 81 (81), 80 (100), 70 (97); ^1H NMR δ [7] 3.88 (m, 1 H), 2.81 (m, 1 H), 2.53 (br s, 1 H), 2.10 (s, 3 H), 1.90–1.17 (m, 8 H); ^{13}C NMR (CD_3COCD_3) δ [7] 66.53, 52.41, 31.58, 27.71, 24.82, 20.44, 14.07, [8] 72.83, 53.24, 35.09, 31.88, 26.34, 24.77, 13.01; IR [7] (neat) 3480, 2950, 2890, 1450, 1115, 1075, 980, 755.

Reduction of *trans*- and *cis*-4-*tert*-Butyl-2-(methylthio)cyclohexanone (2 and 3). *t*-4-*tert*-Butyl-*c*-2-(methylthio)-*r*-1-cyclohexanol (9). Reduction of compound 2 following methods A, E, and G afforded a colorless oil, which was purified by flash column chromatography (eluent chloroform). The white solid obtained was characterized as *t*-4-*tert*-butyl-*c*-2-(methylthio)-*r*-1-cyclohexanol (9) (Table I): mp 68–70 °C; R_f 0.24; MS, *m/e* (relative intensity) 202 (19), 137 (9), 97 (15), 80 (58), 57 (100), 41 (70); ^1H NMR δ 3.66 (dt, 1 H, J = 11.5 and 4.2 Hz), 3.10 (m, 1 H), 2.52 (br s, 1 H), 2.17 (s, 3 H), 2.19–1.6 (m, 3 H), 1.5–0.87 (m, 4 H), 0.86 (s, 9 H); ^{13}C NMR δ 71.59, 55.14, 41.28, 32.01, 31.74, 31.57, 27.41, 25.21, 16.77. IR (KBr) 3241, 2966, 2868, 1361, 1350, 1098, 1068.

***c*-4-*tert*-Butyl-*c*-2-(methylthio)-*r*-1-cyclohexanol (15) and *t*-4-*tert*-Butyl-*t*-2-(methylthio)-*r*-1-cyclohexanol (10).** Reduction of *cis*-4-*tert*-butyl-2-(methylthio)cyclohexanone (3) containing a 12% of the trans isomer 2 by methods A, B, E, and F afforded a colorless oil, which was characterized as a mixture of diastereoisomers 15, 10, and a small quantity of 9. (Table I). Flash column chromatography allowed the isolation of compound 15 as a white solid, mp 89–91 °C; R_f 0.38. Compound 10 (R_f 0.18) was obtained as a colorless oil contaminated by 16% of *t*-4-*tert*-butyl-*c*-2-(methylthio)-*r*-1-cyclohexanol (9) resulting from isomer 2 present in the starting material: MS, *m/e* (relative intensity) [15] 204 (3), 202 (42), 187 (6), 184 (5), 169 (5), 145 (20), 137 (18), 127 (6), 98 (22), 80 (31), 57 (100), 41 (97), [10] 202 (0.7), 155 (100), 137 (9), 81 (7), 80 (1.4), 57 (22), 41 (18); ^1H NMR δ [15] 3.89 (m, 1 H), 2.72 (ddd, 1 H, J = 12.4, 2.4, and 2.4 Hz), 2.55 (br s, 1 H), 2.09 (s, 3 H) superimposed upon 2.21–0.88 (m, 7 H), and 0.87 (s, 9 H), [10 (mixture of diastereoisomers)] 3.66 (m) and 3.31 (td, J = 4.3 and 10.1 Hz, for total 1 H, 1/5.2 ratio), 3.10 (m, 0.16 H), 2.55 (br s, 1 H), 2.17 and 2.08 (s, for total 3 H) superimposed upon 2.42–0.87 (m, 7.84 H), 0.86 (s, for total 9 H); ^{13}C NMR δ [15] 64.09, 52.14, 48.69, 32.62, 31.68, 27.60, 27.45, 19.97, 13.29, [10 (values in parentheses corresponding to compound 9)] (71.59), 71.52, (55.14), 53.81, 48.30, (41.28), 33.77, 32.89, 32.43, (32.01), (31.74), (31.57), 27.55, (27.41), 25.41, (25.21), (16.77), 11.56; IR [15] (KBr) 3391, 1364, 1283, 1269, 1061, 956, [10] (Nujol) 3507, 1311, 1284, 1241, 1096, 1065, 984, 959 and 931.

Reduction of 2-(Methylsulfonyl)cyclohexanone (4). *cis*- and *trans*-2-(Methylsulfonyl)cyclohexanol (11 and 12). Reduction of compound 4 following methods A–F afforded a white solid, which was characterized as a mixture of diastereoisomers 11 and 12 (Table II). The minor component of the mixture in all cases was identified as compound 12 by comparison of the spectroscopic data of the mixture with those of an authentic sample obtained by oxidation of thioether 8 (52%) following the general procedure described above, mp 95–96 °C (recrystallized from light petroleum). *cis*-2-(Methylsulfonyl)cyclohexanol (11) was obtained as a pure diastereoisomer from compound 4 following reduction method G (Table II) as a white solid; mp 82–83 °C (recrystallized from hexane); MS, *m/e* (relative intensity) [11] 180 (0.3), 178 (5), 163 (0.5), 150 (2), 135 (4), 122 (5), 107 (24), 99 (28), 81 (100), [12] 178 (3), 107 (22), 99 (27), 81 (100); ^1H NMR δ [11] 4.57 (m, 1 H), 2.95 (s, 3 H), 2.94–2.79 (m, 3 H), 2.13–1.15 (m, 7 H), [12] 4.05–3.89 (m, 1 H), 3.33 (d, 1 H, J = 2.5 Hz), 3.02 (s, 3 H), 2.94–2.81 (m, 1 H), 2.33–2.07 (m, 2 H), 1.94–1.73 (m, 2 H), 1.62–1.22 (m, 4 H); ^{13}C NMR δ [11] 66.09, 64.12, 39.35, 32.89, 25.00, 20.22, 18.51; 12: 69.07, 67.71, 41.55, 34.77, 24.45, 23.97, 23.74; IR [11] (Nujol) 3510, 1290, 1130, 1110, 1010, 960, [12] (Nujol) 3500, 1290, 1275, 1130, 1065, 940, 760.

Reduction of *trans*- and *cis*-4-*tert*-Butyl-2-(methylsulfonyl)cyclohexanone (5 and 6). *t*-4-*tert*-Butyl-*c*-2-(methylsulfonyl)-*r*-1-cyclohexanol (13). Reduction of compound 5 following methods A, D, E, and G allowed the isolation of *t*-4-*tert*-butyl-*c*-2-(methylsulfonyl)-*r*-1-cyclohexanol (13) as a white solid (Table II). A small percentage (6–20% depending on the hydride) of reduction products of *cis*-4-*tert*-2-(methylsulfonyl)-cyclohexanone (6) resulting from epimerization of 5 was always observed. Recrystallization from hexane afforded pure 13: mp 129–131 °C MS, *m/e* (relative intensity) 234 (0.2), 219 (0.4), 201 (0.2), 178 (5), 155 (16), 137 (30), 97 (15), 81 (100), 67 (21), 57 (70), 41 (27); ^1H NMR δ 4.02 (dt, 1 H, J = 11.8 and 5.0 Hz), 3.46 (m, 1 H), 3.06 (s, 3 H), 2.58 (dq, 1 H, J = 14.0 and 2.9 Hz), 2.38 (br s, 1 H), 2.35–2.12 (m, 1 H), 2.00–1.82 (m, 2 H), 1.66–0.95 (m, 3 H), 0.88 (s, 9 H); ^{13}C NMR δ 70.77, 63.72, 45.19, 41.47, 32.26, 30.90, 27.22, 25.70, 25.15; IR (KBr) 3465, 2966, 2868, 1368, 1283, 1120, 1060, 971.

***c*-4-*tert*-Butyl-*c*-2-(methylsulfonyl)-*r*-1-cyclohexanol (16) and *t*-4-*tert*-Butyl-*t*-2-(methylsulfonyl)-*r*-1-cyclohexanol (14).** Reduction of compound 6 containing a 34% of the trans isomer 5 following methods A, B, and D–G afforded a white solid, which was characterized as a mixture of diastereoisomers 16, 14 (see Table II), and a percentage of compound 13 resulting from reduction of *trans*-4-*tert*-butyl-2-(methylsulfonyl)cyclohexanone (5) (34–40% depending on reaction conditions). Separation of diastereoisomers was not possible neither by fractionated crystallization nor by flash column chromatography (ethyl acetate–hexane, 1/3). Crystallization of the mixture obtained by method A at −78 °C from hexane afforded a white solid that was characterized as compounds 16, 14, and 13 in a 43/23/34 ratio: MS, *m/e* (relative intensity) 234 (0.2), 219 (0.3), 178 (12), 154 (22), 137 (54), 97 (13), 81 (100), 67 (15), 57 (51), 41 (20); ^1H NMR δ (mixture of diastereoisomers) 4.53 (m, 0.43 H), 4.02 (dt, 0.34 H, J = 11.8 and 5 Hz) superimposed upon 3.93 (td, 0.23 H, J = 10.8 and 5.1 Hz), 3.46 (m, 0.34 H), 3.38 (br s, 0.23 H), 3.06 (s), 3.03

(s) and 2.96 (s) (for total 3 H, 1.47/1/1.87 ratio), 2.94–2.77 (m, 1.43 H), 2.58 (dq, 0.34 H, J = 14.0 and 2.9 Hz), 2.34–1.03 (m, 6.66 H), 0.92 (s), 0.89 (s), and 0.88 (s) (for total 9 H, 1.87/1/1.47); ^{13}C NMR (carbon assignment of diastereoisomers was made in the mixture, on the basis of DEPT and two-dimensional ^{13}C–^{1}H correlation experiments) δ (**16**] (68.02),[a] 63.70, (47.45),[b], 39.40, (33.17),[c] (32.62),[d] 27.33, 20.94, 19.60, [**14**] 69.28, (66.96),[a] (46.68),[b] 41.93, (34.94),[c] (32.40),[d] 27.11, 25.01, 24.63, [**13**] 70.77, 63.72, 45.19, 41.47, 32.26, 30.90, 27.22, 25.70, 25.15 [the chemical shifts of signals in parentheses labeled a–d can be exchanged for compounds **16** and **14**. Signals corresponding to compound **13** were unequivocally assigned before]; IR (KBr) 3480, 2966, 2868, 1352, 1292, 1108, 1084, 987.

Registry No. **1**, 52190-35-9; **2**, 62151-61-5; **3**, 108920-15-6; **4**, 16096-71-2; **5**, 84613-31-0; **6**, 108920-16-7; **7**, 108920-17-8; **8**, 41578-04-5; **9**, 108920-18-9; **10**, 108920-19-0; **11**, 108920-20-3; **12**, 108920-21-4; **13**, 108920-22-5; **14**, 108920-23-6; **15**, 108945-94-4; **16**, 108920-24-7; cyclohexanone, 108-94-1; dimethyl disulfide, 624-92-0; 4-*tert*-butylcyclohexanone, 98-53-3.

Linear Free Energy Relationship Studies of 5-Substituted 2,4-Dioxopyrimidine Nucleosides

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The development of a direct and efficient palladium(0)-catalyzed biaryl coupling reaction permitted the synthesis of a series of N1-substituted 5-aryl-2,4-dioxopyrimidines. The physical and spectral properties of these compounds were determined and correlated by various linear free energy relationships. The relationships between the physical and spectral data with Hammett σ constants proved useful in analyzing the electron distribution of the heterocycle. Although a significant degree of orbital overlap and interaction between the substituents and the pyrimidine ring was observed, it is doubtful that the interactions are comparable to those of a benzene ring system.

The biochemical significance of 2,4-dioxopyrimidines and their N1-substituted derivatives and their polymeric products (RNA, DNA) is evident in the role played in metabolism, control, and regulation. For this reason, the electronic structure of these molecules has been the subject of extensive investigation.

In an earlier study of 5-substituted 2,4-dioxopyrimidines Tarpley and Goldstein[1] found that the ^{13}C chemical shifts of these compounds correlated reasonably well with the total electron charge densities calculated with extended Hückel theory (EHT). In addition, good correlation between the ^{13}C chemical shifts of 5-halo-2,4-dioxopyrimidines and substituent electronegativity (E_X) was observed. Ellis and co-workers[2] using a more complete list of 5-substituted derivatives found that the linear relationship between ^{13}C chemical shifts and E_X no longer holds. Instead, they rationalized the data by considering 5-substituted 2,4-dioxopyrimidines as trisubstituted ethylenes. On the other hand, Chandrasekaran and coworkers,[3] in studying the ^{17}O NMR of the 5-substituted heterocycle, found good correlation between chemical shifts of the 2- and 4-oxygen atoms and Hammett σ values of the substituents. These results indicate that there is considerable interaction between the 5-substituents and both the 2- and 4-oxygen atoms. The ground electronic state of 2,4-dioxopyrimidine has been characterized by O'Donnell and co-workers,[4] using the ab initio molecular fragment floating spherical Gaussian orbital (MF-FSGO) method. The resonance structure that is usually drawn places double bonds along the C2=O2, C4=O4, and C5=C6, resulting in $\sim 3\pi$ bonds. Yet they found a net bond order of $\sim 4.4\pi$ bonds indicating a higher degree of orbital overlap.[4]

While these studies have concentrated on 2,4-dioxopyrimidines, the application of the results to the properties of their biological derivatives is tenuous since the natural derivatives are substituted at N1 with either ribose, 2′-deoxyribose, or their 5′-phosphates. This critical structural change, N1-substitution, effectively limits the resonance contribution of the 5-substituents and seriously hampers the direct application of these results to the heterocyclic structure as it is found in nature.

In an effort to model N1-substitution found in the natural molecules, we have analyzed the physical and spectral properties of 13 2,4-dioxopyrimidine nucleosides substituted at C5 of the pyrimidine ring. The models chosen may be written in the form XGY, where X represents a substituent, Y represents the site at which the observed phenomenon takes place, and G is a skeletal group to which X and Y are attached (Table I). In the classical ionization constant study of substituted benzoic acids by Hammett, X is a set of substituents, G is a phenyl ring, and Y, the reactive site, is the carboxyl moiety. In an analogous manner, the entire 2,4-dioxopyrimidine ring can be considered as the reactive site Y, a phenyl ring as the skeletal group G, and a series of substituents X, attached on the phenyl ring.

The advantages in the proposed model system are as follows:

(1) The planarity of the two rings allows for the transmission of the electronic properties of the substituents to the pyrimidine ring.

(2) The insertion of the phenyl ring between the substituent and the heterocycle should simplify the NMR

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