Application of ^{13}C NMR Spectroscopy to Acyclic Conformational Analysis

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Abstract: Analyses of acyclic conformational populations by MM-2 force-field calculations were combined with γ-substituent effects derived from cyclic systems to provide reliable predictions of ^{13}C chemical shifts for a series of acyclic alcohols. Predictions for 81 carbons in 18 isomeric hexanols were carried out with an average error of 0.57 δ. Observed shift effects are used to predict conformer populations. The origin of errors and possible applications to other systems are discussed.

We have recently communicated[1] our initial studies on the correlation of stereochemical properties (both conformational and configurational) of acyclic molecules with ^{13}C shifts, where configurational stereochemistry could be predicted based upon ^{13}C effects, and a special situation where the number of energetically viable conformers was limited to two. For this analysis we drew upon the pioneering work of Jurs and Smith[2] and Saunders[3] as well as many others[4] who have independently established a quantitative correlation between conformational populations and the greater upfield effect due to γ substituents that are in a gauche butane-like relationship to a carbon in comparison to that in conformations where the corresponding arrangement is anti. It occurred to us that this approach could represent an extremely valuable tool for acyclic conformational analysis if the correlation could be demonstrated to be general.

Following the lead of Saunders,[3] we have derived the anticipated effects of γ substituents for anti and gauche relationships from cyclic models (in our case the trans-decalins) and thus avoid deriving only self-consistent data and, as well, establish the generality of the technique. Indeed, it does appear that the effect is reasonably constant for both cyclic and acyclic systems. for example, the introduction of a methyl group to form equatorial 2-methyl-trans-decalin results in an upfield shift of 3.8 ppm for the gauche carbon C-10, while the average effect on anti carbons (C-4 and C-6) in this as well as a large number of other compounds is -0.6 ppm. Thus, in butane the effect on C-1 of C-4 as a γ substituent would be predicted to be -0.6 in the anti and -3.8 δ in each of the gauche conformations. Combining these

effects with the solution conformational population of butane (52% anti, 48% gauche)[6] leads to a predicted change between propane and butane due to the additional carbon of -2.1 (0.48* [-3.8] + 0.52* [-0.6]), in good agreement with the observed effect of -2.5. Conversely, the magnitude of the observed shift effect of the added carbon can be used to find the conformational populations by solution of the following, simple set of simultaneous equations, where x is the fraction of gauche and y is the fraction of anti conformers:

$$x + y = 1.0$$

$$(-3.8)^*x + (-0.6)^*y = -2.5$$

$$x = 0.59 \text{ (gauche)}, y = 0.41 \text{ (anti)}$$

In order to establish the reliability of conformationally dependent shift effects on ^{13}C absorptions, we decided to study systematically a set of compounds (all of the acyclic hexanols[5]) for which conformational populations might be reasonably accurately predicted by MM-2 calculations. Analysis of the magnitude of shift effects expected based on the conformational orientation of γ substituents for each conformer and then weight averaging the effects based on populations derived from conformer energies resulted in the shift effect expected due to the presence of the γ substituents. Adding this value to the observed absorption for a model compound lacking γ groups provided a predicted shift. This process is illustrated in Figure 1 for 11.

For example, addition of a hydroxyl and an ethyl group to isobutane leads to an upfield shift of C-1 due to the presence of the new γ substituents (O and CH_2, where 46% of the conformer total population has the oxygen gauche and the new carbon anti to C-1, 40% has the carbon gauche and the oxygen anti, and 14%

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Table I. Predicted and Observed ^{13}C Shifts for Six-Carbon Alcohols (ppm)[a]

	model	effect	pred	obsd	error		model	effect	pred	obsd	error
1-hexanol (1)											
C-1	64.2	−1.2	63.0	62.6	0.4	C-4	34.2	−1.2	33.0	32.0	1.0
C-2	35.0	−1.2	33.8	32.8	1.0	C-5	24.8	−1.2	23.6	22.9	0.7
C-3	34.2	−6.3	27.9	25.9	2.0	C-6	16.1	−1.4	14.7	14.1	0.6
2-hexanol (2)											
C-1	25.3	−1.8	23.5	23.4	0.1	C-4	34.2	−5.8	28.4	28.2	0.2
C-2	68.7	−1.1	67.7	67.3	0.3	C-5	24.8	−1.2	23.6	23.2	0.4
C-3	41.6	−1.6	40.1	39.2	0.8	C-6	16.1	−1.6	14.5	14.3	0.2
3-hexanol (3)											
C-1	16.1	−5.9	10.2	10.0	0.2	C-4	41.8	−1.8	40.0	39.4	0.6
C-2	32.2	−1.7	30.5	30.4	0.1	C-5	24.8	−5.7	19.1	19.1	0.0
C-3	74.5	−1.1	73.4	72.9	0.5	C-6	16.1	−1.3	14.8	14.2	0.6
2-methyl-1-pentanol (4)											
C-1	69.4	−1.9	67.5	68.0	−0.5	C-4	25.2	−4.6	20.6	20.3	0.3
C-2	37.6	−1.2	36.4	35.6	0.8	C-5	16.1	−1.2	14.9	14.4	0.5
C-3	42.0	−5.1	36.9	35.6	1.3	C-6	24.5	−0.2	16.3	16.7	−0.4
3-methyl-1-pentanol (5)											
C-1	64.2	−4.4	59.8	60.8	−1.0	C-4	32.0	−2.1	29.9	29.9	0.0
C-2	41.8	−2.2	39.6	39.7	−0.1	C-5	16.1	−5.1	11.0	11.3	−0.3
C-3	36.6	−3.6	33.0	31.5	1.5	C-6	24.5	−5.4	19.1	19.3	−0.2
4-methyl-1-pentanol (6)											
C-1	64.2	−1.2	63.0	62.3	0.7	C-4	30.1	−1.2	28.9	28.0	0.9
C-2	35.0	−4.7	30.3	30.7	−0.4	C-5	24.5	−2.4	22.1	22.6	−0.5
C-3	42.0	−5.0	37.0	35.2	1.8						
2-methyl-2-pentanol (7)											
C-1	31.1	−2.5	28.6	29.3	−0.7	C-4	"26.3"	−8.3	18.0	17.8	0.2
C-2	71.1	−0.6	70.5	70.9	−0.4	C-5	16.1	−0.9	15.3	14.7	0.5
C-3				46.6							
(2R,3S)-3-methyl-2-pentanol (8)[b]											
C-1	25.3	−5.5	19.8	19.2	0.6	C-4	32.0	−5.6	26.4	25.6	0.8
C-2	72.5	−1.5	71.0	70.7	0.3	C-5	16.1	−5.0	11.1	11.9	−0.8
C-3				41.8		C-6	24.5	−9.2	15.3	14.1	1.2
(2S,3S)-3-methyl-2-pentanol (9)[b]											
C-1	25.3	−5.0	20.3	20.2	0.1	C-4	32.0	−4.9	27.1	25.6	1.5
C-2	72.5	−1.7	70.8	70.4	0.4	C-5	16.1	−5.1	11.0	12.0	−1.0
C-3				41.8		C-6	24.5	−9.3	15.2	14.0	1.2
4-methyl-2-pentanol (10)											
C-1	25.3	−1.6	23.7	23.9	−0.2	C-4	30.1	−4.4	25.7	24.9	0.8
C-2	69.3	−3.8	65.5	65.8	−0.3	C-5	24.5	−2.0	22.6	23.2	−0.7
C-3				48.8		C-6	24.5	−2.5	22.0	22.5	−0.5
2-methyl-3-pentanol (11)											
C-1	24.5	−5.5	19.0	19.0	0.0	C-4	32.2	−4.8	27.4	27.1	0.3
C-2	35.2	−1.5	33.7	33.4	0.3	C-5	16.1	−6.0	10.1	10.5	−0.4
C-3				78.1		C-6	24.5	−6.9	17.6	17.4	0.2
3-methyl-3-pentanol (12)											
C-1/5	16.1	−8.8	7.3	8.3	−1.0	C-3	72.9				
C-2/4	36.5	−2.8	33.7	33.8	0.0	C-6	31.3	−5.1	26.2	25.9	0.3
2-ethyl-1-butanol (13)											
C-1	69.4	−4.7	64.7	64.7	0.0	C-3/5	31.6	−7.6	24.0	23.1	0.9
C-2				43.8		C-4/6	16.1	−5.2	10.9	11.2	−0.3
2,2-dimethyl-1-butanol (14)											
C-1	73.2	−2.4	70.8	71.4	−0.6	C-4	16.1	−7.7	8.4	8.2	0.2
C-2				35.1		C-5	31.7	−8.7	23.0	23.4	−0.4
C-3	36.9	−5.3	31.6	31.0	0.6						
2,3-dimethyl-1-butanol (15)											
C-1	69.4	−4.7	64.7	65.7	−1.0	C-4	24.5	−5.6	18.9	18.1	0.8
C-2				34.8		C-5	24.5	−11.9	12.6	12.7	−0.1
C-3	34.2	−4.4	39.8	31.1	−1.3	C-6	24.5	−4.9	19.6	20.7	−1.1
3,3-dimethyl-1-butanol (16)											
C-1	"65.7"	−7.0	58.7	59.0	−0.3	C-3	30.5	−2.0	28.5	29.4	−0.9
C-2				46.2		C-4,5,6	31.7	−2.4	29.3	29.7	−0.4
2,3-dimethyl-2-butanol (17)											
C-1	31.3	−5.3	26.0	26.4	−0.4	C-3				73.0	
C-2				38.9		C-4	24.5	−8.3	16.3	17.7	−1.4
3,3-dimethyl-2-butanol (18)											
C-1	25.3	−7.7	17.6	18.0	−0.4	C-3				34.6	
C-2				74.9		C-4,5,6	31.7	−6.2	25.5	25.5	0.0

[a]Shifts are from "Sadtler Standard Carbon-13 NMR Collection" Sadtler Research Laboratories: Philadelphia, PA. 1985 (CDCl₃) except for those for **2**, **8**, and **9** which are from ref 5 with CS_2 as solvent. [b]The assignment of these diastereomers was made on the basis of best fit with predictions and is opposite to that made by Williamson.[5]

has both γ substituents gauche). Adjusting the shift perturbations for each conformational arrangement (−5.9, −3.85, and −8.85, respectively; vide infra, Figure 2) by the population predicted for each conformation leads to an expected shift perturbation of −5.5, the same as observed. Predictions can be made in a similar fashion

for all of the carbons except for C-3 which as no γ substituents. This process was carried out for all predictable carbons (those with γ substituents) for all 18 of the hexanols, with the results summarized in Table I. In general, the fit between predicted and observed perturbations due to γ substituents was quite good,
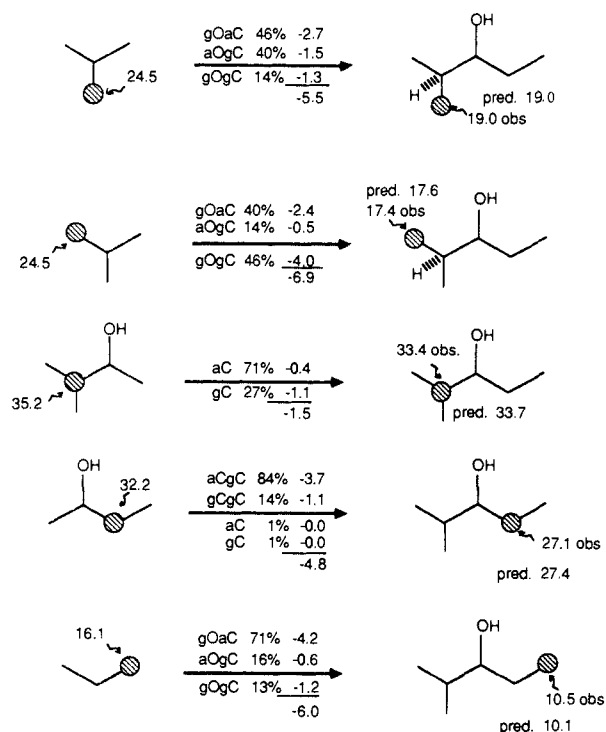
Table II

2-methyl-1-pentanol (4)

1-2	2-3	3-4	MM2	Norm	%
a	a	a	5.64	0.00	14
-	a	a	5.65	0.01	13
a	+	a	5.66	0.02	13
+	+	a	5.70	0.06	12
+	a	a	5.77	0.13	11
-	-	a	6.22	0.58	5
a	-	a	6.24	0.60	5
-	a	-	6.33	0.69	4
a	a	a	6.35	0.71	4
a	+	+	6.36	0.72	4
-	+	a	6.38	0.74	4
+	+	+	6.41	0.77	4
+	a	-	6.56	0 92	3
-	+	+	7.04	1.40	1
+	-	a	7.29	1.65	1
a	a	a	8.02	2.38	0
+	+	-	8.02	2.38	0
-	a	+	8.03	2.39	0
+	a	+	8.14	2.50	0
a	+	-	8.15	2.51	0
a	-	-	8.64	3.00	0
a	-	+	8.64	3.00	0
-	-	+	8.72	3.08	0
-	+	-	8.73	3.09	0
-	-	-	8.81	3.17	0
+	-	-	9.78	4.14	0
+	-	+	10.38	4.74	0

3-methyl-1-pentanol (5)

1-2	2-3	3-4	MM2	Norm	%
a	a	a	6.40	0.00	11
a	a	+	6.41	0.01	11
a	-	a	6.43	0.03	11
+	a	+	6.66	0.26	7
+	a	a	6.68	0.28	7
-	-	a	6.69	0.29	7
a	+	+	6.71	0.31	7
a	-	-	6.72	0.32	7
a	+	a	6.84	0.44	5
a	a	-	6.84	0.44	5
-	-	-	6.98	0.58	4
+	a	-	7.18	0.78	3
-	a	+	7.50	1.10	2
-	a	a	7.56	1.16	2
+	-	a	7.58	1.18	2
+	+	+	7.70	1 30	1
+	-	+	7.72	1.32	1
-	+	+	7.74	1.34	1
+	+	a	7.82	1.42	1
+	+	a	7.82	1.42	1
-	+	a	7.84	1.44	1
a	-	+	7.86	1.46	1
-	a	-	7.88	1.48	1
-	-	+	8.13	1.73	1
+	-	+	8.93	2.53	0
a	+	-	9.18	2.78	0
-	+	-	10.29	3.89	0

4-methyl-1-pentanol (6)

1-2	2-3	3-4	MM2	Norm	%
a	a	-	5.18	0.00	16
a	a	a	5.18	0.00	16
+	a	a	5.45	0.27	10
-	a	-	5.46	0.28	10
+	a	a	5.53	0.35	9
-	a	a	5.54	0.36	9
a	-	-	5.89	0.71	5
a	+	a	5.90	0.72	5
a	a	+	5.92	0.74	5
-	-	-	6.13	0.95	3
+	+	a	6.13	0.95	3
+	a	+	6.25	1.07	3
-	a	+	6.25	1.07	3
-	-	a	6.81	1.63	1
-	+	a	6.83	1.65	1
a	-	a	7.54	2.36	0
a	+	-	7.74	2.56	0
+	+	-	7.86	2.68	0
-	-	a	7.87	2.69	0
a	+	+	8.30	3.12	0
-	+	-	8.32	3.14	0
a	-	+	8.37	3.19	0
+	+	+	8.49	3.31	0
+	-	a	8.73	3.55	0
-	-	+	8.74	3.56	0
-	+	+	9.13	3.95	0
+	-	+	9.77	4.59	0

1-hexanol (1)

1-2	2-3	3-4	4-5	MM2	Norm	%
a	a	a	a	4.36	0.00	19
+	a	a	a	4.66	0.30	11
-	a	a	a	4.66	0.30	11
a	+	a	a	5.23	0.87	4
a	-	a	a	5.23	0.87	4
-	-	a	a	5.24	0.88	4
a	a	a	+	5.24	0.88	4
a	a	a	-	5.24	0.88	4
a	a	+	a	5.28	0.92	4
a	a	-	a	5.28	0.92	4
-	-	a	a	5.49	1.13	3
-	-	a	a	5.49	1.13	3
+	a	a	+	5.54	1.18	3
-	a	a	+	5.54	1.18	3
+	a	a	a	5.55	1.19	3
+	a	a	a	5.55	1.19	3
-	a	+	+	5.57	1.21	2
-	a	-	a	5.57	1.21	2
+	a	+	a	5.64	1.28	2
-	a	+	a	5.64	1.28	2
a	a	+	+	5.97	1.61	1
a	a	-	-	5.97	1.61	1
a	-	a	+	6.04	1.68	1
a	-	a	-	6.04	1.68	1
+	-	a	a	6.20	1.84	1
-	+	a	a	6.20	1.84	1
+	-	a	-	6 24	1.88	1
a	+	a	-	6.24	1.88	1

2-hexanol (2)

2-3	3-4	4-5	MM2	Norm	%
-	a	a	4.92	0.00	33
a	a	a	5.46	0.54	13
+	a	a	5.76	0.84	8
-	a	-	5.77	0.85	8
-	-	a	5.79	0.87	8
-	a	+	5.85	0.93	7
a	+	a	6.18	1.26	4
a	a	+	6.27	1.35	3
-	-	-	6.43	1.51	3
a	a	a	6.46	1.54	3
+	a	-	6.60	1.68	2
-	+	a	6.63	1.71	2
+	-	a	6.75	1.83	2
a	+	+	6.85	1.93	1
+	-	a	7.09	2.17	1
-	+	+	7.21	2.29	1
+	-	-	7.74	2.82	0
-	-	+	8.04	3.12	0
+	+	a	8.08	3.16	0
a	-	a	8.32	3.40	0
a	-	-	8.60	3.68	0
-	+	-	8.62	3.70	0
a	+	+	8.77	3.85	0
+	+	+	9.14	4.22	0
+	-	+	9.77	4.85	0
+	+	-	large	large	0
a	-	+	large	large	0

3-hexanol (3)

1-2	2-3	3-4	MM2	Norm	%
-	+	a	5.38	0.00	29
a	+	a	5.90	0.52	12
-	a	a	6.02	0 64	10
+	+	a	6.12	0.74	8
-	-	a	6.16	0.78	8
-	+	+	6.20	0.82	7
a	-	a	6.44	1 06	5
+	a	a	6.50	1.12	4
a	+	+	6.64	1.26	4
-	a	-	6.68	1.30	3
-	+	-	7.08	1.70	2
+	+	+	7.10	1.72	2
+	a	-	7.19	1.81	1
-	-	+	7.40	2 02	1
+	+	-	7.58	2 20	1
a	-	+	7.70	2 32	1
a	+	-	7.81	2 43	1
a	a	a	7.89	2.51	0
-	a	+	8.31	2.93	0
-	-	-	8.48	3.10	0
a	a	+	8.61	3.23	0
+	-	a	8.68	3.30	0
a	-	-	8.87	3.49	0
+	a	+	8.89	3.51	0
+	-	+	9.99	4.61	0
a	a	-	10.29	4.91	0
+	-	-	11.04	5.66	0

4-methyl-2-pentanol (10)

2-3	3-4	MM2	Norm	%
-	a	5.71	0.00	52
a	a	6.12	0.41	26
-	+	6.60	0.89	12
-	-	7.28	1.57	4
+	a	7.29	1.58	4
a	a	7.98	2.27	1
+	+	8.58	2.87	0
a	-	8.58	2.87	0
+	-	9.96	4.25	0

2-methyl-3-pentanol (11)

2-3	3-4	MM2	Norm	%
-	+	7.10	0.00	31
a	+	7.22	0.12	26
-	a	7.58	0.48	14
+	+	7.60	0.50	14
a	-	7.63	0.53	13
a	a	9.14	2.04	1
+	a	9.50	2.40	1
-	-	9.80	2.70	0
+	-	10.50	3.40	0

3-methyl-3-pentanol (12)

2-3	3-4	MM2	Norm	%
a	+	7.32	0.00	22
-	a	7.32	0.00	22
+	+	7.51	0.19	16
-	-	7.51	0.19	16
+	-	7.90	0.58	8
a	-	7.97	0.65	7
+	a	7.97	0.65	7
-	+	9.05	1.73	1
a	a	10.12	2.80	0

2-methyl-2-pentanol (7)

2-3	3-4	MM2	Norm	%
-	a	6.13	0.00	37
+	a	6.13	0.00	37
a	a	6.61	0.48	17
+	-	7.57	1.44	3
-	+	7.59	1.46	3
+	+	8.51	2.38	1
-	-	8.87	2.74	0
a	+	9.12	2.99	0
a	-	9.12	2.99	0

2R,3S-3-methyl-2-pentanol (8)

2-3	3-4	MM2	Norm	%
+	+	7.19	0.00	19
+	a	7.23	0.04	18
a	+	7.23	0.04	18
a	a	7.39	0.20	14
-	a	7.48	0.29	12
a	-	7.48	0.29	12
-	+	7.93	0.74	6
+	-	8.36	1.17	3
-	-	9.78	2.59	0

2S,3S-3-methyl-2-pentanol (9)

2-3	3-4	MM2	Norm	%
+	a	7.25	0.00	24
-	a	7.40	0.15	18
a	+	7.43	0.18	18
a	a	7.48	0.23	16
-	-	7.58	0.33	14
+	-	8.28	1.03	4
-	+	8.32	1.07	4
+	+	8.73	1.48	2
a	-	8.66	2.41	0

2-ethyl-1-butanol (13)

1-2	2-3	2-5	MM2	Norm	%
+	+	-	6.88	0.00	10
+	+	a	6.91	0.03	9
+	a	-	6.91	0.03	9
a	+	a	7.06	0.18	7
-	a	-	7.06	0.18	7
a	-	a	7.15	0 27	6
-	a	+	7.15	0.27	6
-	-	a	7 18	0.30	6
a	a	+	7.18	0.30	6
a	+	+	7.27	0.39	5
-	-	-	7.27	0.39	5
+	-	a	7.75	0.87	2
a	a	-	7.75	0.87	2
-	+	-	7.84	0.96	2
a	+	-	7.84	0.96	2
-	+	+	7.93	1.05	2
a	-	-	7.93	1.05	2
+	+	+	8.01	1.13	2
+	-	-	8.01	1.13	2
+	-	a	8.08	1.20	1
+	a	+	8.08	1.20	1
+	a	a	8.08	1.20	1
-	a	a	8.37	1.49	1
a	a	a	8.37	1.49	1
-	-	+	9.50	2.62	0
a	-	+	9.50	2.62	0
+	-	-	10.98	4.10	0

2,2-dimethyl-1-butanol (14)

1-2	2-3	MM2	Norm	%
+	+	6.53	0.00	17
-	-	6.53	0.00	17
a	+	6.70	0.17	13
-	a	6.70	0.17	13
a	-	6.70	0.17	13
+	a	6.70	0.17	13
a	a	6.83	0.30	10
-	+	7.58	1.05	3
+	-	7.58	1.05	3

2,3-dimethyl-1-butanol (15)

1-2	2-3	MM2	Norm	%
+	a	7.84	0.00	22
a	-	7.94	0.10	18
a	+	7.95	0.11	18
-	-	8.03	0.19	16
a	a	8.16	0.32	13
-	a	8.71	0.87	5
-	+	8.91	1.07	4
+	+	9.16	1.32	2
+	-	9.31	1.47	2

3,3-dimethyl-1-butanol (16)

1-2	MM2	Norm	%
a	5.85	0.00	78
+	7.01	1.16	11
-	7.01	1.16	11

2,3-dimethyl-2-butanol (17)

2-3	MM2	Norm	%
+	7.95	0.00	38
a	8.09	0.14	31
-	8.09	0.14	31

3,3-dimethyl-2-butanol (18)

Single conformation, 100%

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[a] Conformations are defined as anti (a) or gauche (+/-) from a perspective along the bond from the lower to higher numbered carbon using oxygen if present or the lowest numbered carbon on both the front and back carbons for reference (clockwise = +).

with an overall average error of 0.57 δ.

Methods

MM-2 Calculations were effected using Model to determine relative energies for all of the possible conformers by systematic, "hand"-driven conformer searches for **2** through **18** where the number of conformers varies between 1 and 27. For 1-hexanol (**1**), the presence of four conformationally important bonds affords

a total of 81 conformers. Since many of these would be relatively high energy and thus make only minor contributions to the conformational equilibrium, the search was limited in this case to only those conformers with two or fewer gauche-oriented bonds. Table II summarizes the calculated MM-2 energies of all the conformers.

In general, it may be anticipated that MM-2 should provide reasonably reliable estimates for solution populations for relatively

Figure 1.

gOaC 46% -2.7 / aOgC 40% -1.5 / gOgC 14% -1.3 / -5.5 → pred. 19.0 / 19.0 obs

gOaC 40% -2.4 / aOgC 14% -0.5 / gOgC 46% -4.0 / -6.9 → pred. 17.6 / 17.4 obs

aC 71% -0.4 / gC 27% -1.1 / -1.5 → 33.4 obs. / pred. 33.7

aCgC 84% -3.7 / gCgC 14% -1.1 / aC 1% -0.0 / gC 1% -0.0 / -4.8 → 27.1 obs / pred. 27.4

gOaC 71% -4.2 / aOgC 16% -0.6 / gOgC 13% -1.2 / -6.0 → 10.5 obs / pred. 10.1

$gC = -3.8$
$aC = ((-0.5) + (-0.7))/2 = -0.6$
$gO = ((-6.9) + (-8.1))/2 = -7.5$
$aO = ((-2.8) + (-2.5))/2 = -2.65$
$gOgC = ((-9.0) + (-8.7))/2 = -8.85$
$aOgC = ((-3.5) + (-4.2))/2 = -3.85$
$gOaC = ((-5.4) + (-6.4))/2 = -5.9$

			$\Delta\delta$	
Eq	Ax	C-4	C-6	C-10
CH$_3$	H	-0.5	-0.7	-3.8
OH	H	-2.8	-2.5	-5.2
H	OH	-6.9	-8.1	-4.7
CH$_3$	OH	-5.4	-6.4	-9.0
OH	CH$_3$	-3.5	-4.2	-8.7

Figure 2. Derivation of shift-of-shift effects for carbon and hydroxyl substituents.

Figure 3.

simple molecules such as the hexanols. However, a systematic error in favor of anti conformers should be expected for those molecules where solution populations are affected by relatively large changes in molar volumes. For example, with butane the solution population of the gauche forms is significantly greater than that predicted from gas-phase ΔH values from microwave studies and ΔS considerations. Since the difference in ^{13}C shift effects for anti versus gauche substitution of oxygen is greater than for carbon, the overemphasis of the anti form by MM-2 will result in larger errors for carbons γ to oxygen than those γ to carbon. Thus, the error will be greater for those carbons in relatively linear arrays with a γ oxygen substituent. Indeed, there is significant error in the prediction for C-3 (γ to oxygen) in the following:

		pred	obsd	error
1-hexanol (1)	C-3	27.9	25.9	2.0
2-methyl-1-pentanol (4)	C-3	36.9	35.6	1.3
3-methyl-1-pentanol (5)	C-3	33.0	31.5	1.5
4-methyl-1-pentanol (6)	C-3	37.0	35.2	1.8

The error for **1** is especially large because C-3 here has both a γ oxygen and a γ carbon substituent (C-6), although it can be seen that the increment in error due to the γ carbon is less than for the γ oxygen. It is important to note that these errors most likely result from inaccurate conformational populations based on MM-2 energies, not from a lack of correlation of substituent effects in the ^{13}C spectral data. Excluding the shift predictions for these four carbons from the total results in an average error over 77 predictions of only 0.52 δ, with the largest only 1.6 δ.

γ-**Substituent shift effects** were modeled from appropriately substituted, conformationally locked *trans*-decalins, as depicted in Figure 2.[7,8] Certain errors are quite likely in this analysis, but unavoidable. For example, the effect of multiple substituents is clearly not additive; the sum of the effects of an anti carbon and a gauche oxygen (-0.6 and -7.5) is clearly larger than the effect
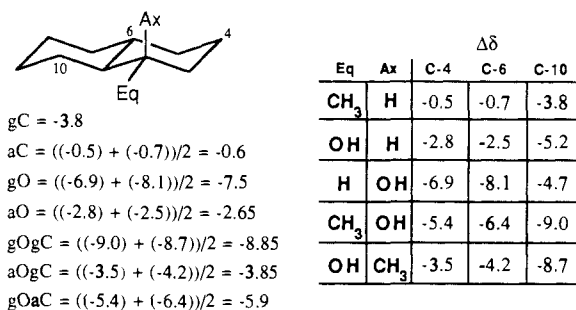
(7) The effect for a γ gauche hydroxyl was estimated from the average of the effects on C-4 and C-6 (rather than that on C-10 as is the case with carbon) because to do otherwise results in substantial errors. The difference in approach can be justified on the basis of a difference in symmetry between the two groups.

(8) A compilation of spectral data for a large number of decalins as well as other bicyclic systems can be found in: Whitesell, J. K., Minton, M. A. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*; Chapman and Hall: London, 1987.
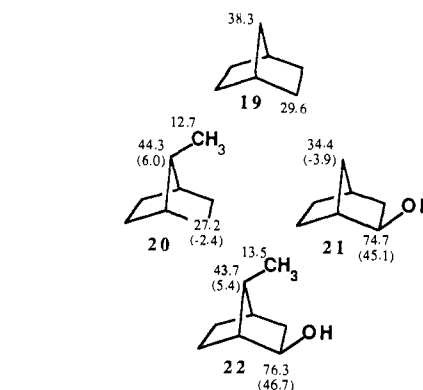
(-5.9) when both groups are present. While the effect of two substituents can be derived for the 2,2-disubstituted decalins, there can be no appropriate conformationally fixed model for the effect of three substituents except when all are identical. The effect of three γ carbon substituents, when treated as the sum of the effects of two gauche and one anti group, would be predicted to be -8.2 (-3.8 × 2 + -0.6 × 1), quite close to (but larger than) the observed effect (-7.7) on C-2 in the progression from methylcyclohexane to *tert*-butylcyclohexane. Thus, for C-4 in **14**, C-1 in **16**, and C-1 in **18**, a value of -7.7 was used for the effect of one anti and two gauche carbons. Unfortunately, there is no conformationally unambiguous model for the effect of one oxygen and two carbon substituents. In this situation the lesser of the effects derived as the sum of the effect of two of the substituents together added to the effect of the remaining substituent was used: for gauche oxygen, gauche carbon, anti carbon, -9.45; for anti oxygen and two gauche carbons, -7.65. The magnitude of these effects is probably too large, as predictions for the affected carbons (C-4 in **7** and **17**, and C-1 in **12**) are all upfield of observed absorptions (-0.2, -1.6, and -1.0).

The effect of δ interactions on ^{13}C shifts is quite unclear simply because there are very few clear-cut examples. In the limited number of rigid bicyclic molecules with clearly defined interactions of this type, predictions of shift effects appear empirically to be better when the δ interaction is ignored. This has a different effect depending on where the carbon under analysis is located. If it is one of the terminal atoms of the δ interaction, then the presence of the δ atom is ignored, leading to a predicted upfield shift result from the remaining γ gauche substituent; if the carbon is internal from the δ interaction, then the presence of the γ substituent causing the δ interaction is ignored, leading to the loss of a γ gauche interaction. For example, the addition of a C-7 methyl group to **19** to form **20** (Figure 3) results in an upfield shift of

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−2.4 for the γ gauche carbon C-2 (and C-3), while the addition of an exo C-2 hydroxyl group results in an upfield shift of −3.9 for C-7. When both groups are combined (22), however, the shifts for C-2 and C-7 (neither of which is directly involved in the δ interaction) are quite close to the values for the appropriate monosubstituted model. Thus, a prediction for C-7 of 22 based on the perturbation of the shift observed for 20 due to the γ gauche oxygen (44.3 − 3.9 = 40.4) is further from the observed shift of 43.7 than if the effect of the γ oxygen is ignored. The same analysis also holds for C-2. There is a small, *downfield* perturbation of the shift of the methyl group upon introduction of the δ interaction with the hydroxyl group (22), but too few models are available to provide reasonable assurance that this effect will be general. Again, the shift of a carbon involved in a δ interaction is predicted as if the δ group were not present.

In all cases δ effects were taken into account, but lead to only relatively minor perturbations in most systems since conformers with γ interactions are generally high in energy and thus minor contributors. An exception of note is 3,3-dimethyl-1-butanol (16) where a total of 22% of the conformer population has a δ interaction between the hydroxyl and the methyl groups. In this system, the methyl groups are predicted by ignoring the δ oxygen, in which case each is gauche to C-1 67% and anti 33%. On the other hand, C-3 is blocked from direct interaction with its γ oxygen by the methyl groups, and the presence of this substituent is ignored in the gauche (22%) conformers, the total effected then predicted on the basis of the 78% anti conformer (−2.5 × 0.78 = −2.0). Similarly, C-1 is perturbed directly by only one of the two gauche methyl groups in the gauche conformers.

Anti H–H Interactions. For 16 there is also a significant error for C-1 when the ¹³C shift prediction is based upon 1-propanol as a model because there is a significant difference between the conformational populations about the analogous bond in 16 and 1-propanol.[6] In a four-atom system in a gauche butane arrangement, the middle carbons (in addition to the terminal carbons) are shifted upfield relative to the anti conformer. We have attributed this shift difference to a change between the gauche and anti arrangements in the spatial orientations of vicinal hydrogens (as anti pair contributing approximately 2.7 ppm downfield shift).[9] Thus, even though C-1 in 1-propanol has no γ substituents, its ¹³C shift is affected by the conformational population about the C-1 to C-2 bond and thus is an inappropriate model for 3,3-dimethyl-1-butanol (16). We have calculated the population of gauche versus anti conformers for 1-propanol as 66:34 based upon the observed upfield shift effect due to a γ oxygen in the change from propane to 1-propanol using the same technique illustrated above for butane.[10] Thus, C-1 of 1-propanol is expected to have a downfield shift due to anti H–H interactions of 3.6 (0.66 × 2.7 + 0.34 × 5.4) while the analogous effect on C-1 of 16 is calculated to be 4.8 (0.22 × 2.7 + 0.78 × 5.4). The "model" value provided for C-1 presents the shift of 1-propanol plus 1.2, the downfield shift expected due to increased anti hydrogen–hydrogen interactions in the substrate. Fortunately, such dramatic conformational differences between model compounds and those under study are the exception and are expected to be significant only when quaternary carbons with substituents involved in steric δ interactions are present. A similar correction in the model shift has also been made for C-4 in 2-methyl-2-pentanol (7).

Errors. It is important to note that a correlation between MM-2 populations and ¹³C chemical shifts for one or two examples might well represent a chance fit of two quite distinct methods that are both inaccurate. On the other hand the excellent correlation (average error 0.52 δ) for the entire set of hexanols would be highly unlikely unless both methods were qualitatively correct. A graph of the predicted shift effect versus the resulting error is provided (Figure 4) from which it can be seen that there is little correlation
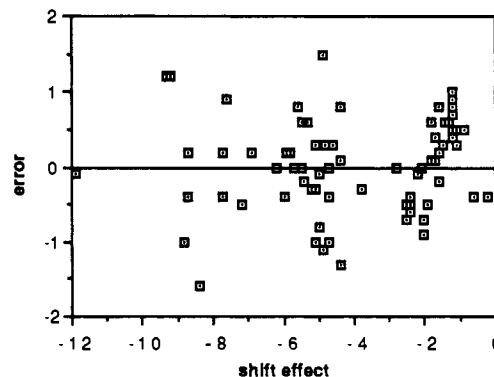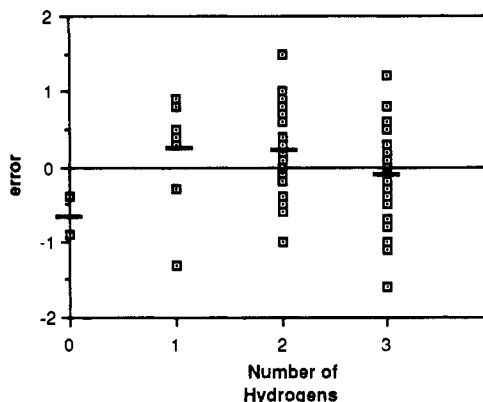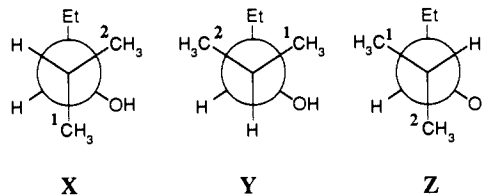

Figure 4.

Figure 5.

Figure 6.

between the magnitudes of the shift effects and the errors (the values for C-3 for 1, 4, 5, and 6 are excluded since these errors can be attributed to differences between gas-phase (MM-2) and solution populations). Thus, the shift-effect parameters used are probably close to the optimum values. Nontheless, it is clear that the magnitude of the γ effect varies with the degree of substitution of both termini (note the difference in effects on C-4 and C-6 in the variously substituted decalins in Figure 2). However, a plot of error versus the number of hydrogens on the predicted carbon (Figure 5) illustrates that there is little correlation of the magnitude or sign of the error with the degree of substitution. It is also likely that the magnitude of the effect varies with precise spatial relationships involved, and increased steric interactions will lead to larger deviations from the idealized torsional angle of 60°.

Determination of Solution Conformational Populations. These results have clear implications for the estimation of conformational populations for acyclic as well as cyclic systems. As with the calculation of butane conformer populations given above, it should be possible in many cases to reverse the approach that we have described here to arrive at a detailed picture of the conformational energy surface based on the observed effects of a number of carbons. In essence, the contribution of effects on the shift of each carbon so affected taken over all reasonable conformations represents the equivalent of a set of simultaneous equations that may have only a finite set of solutions, or even only one unique solution. A limited analysis of 11 should serve to demonstrate this point where only the shifts of the two, diastereotopic methyl groups are considered and the conformational analysis is restricted to the three rotational isomers about the bond from the isopropyl group to the

(9) Whitesell, J. K.; Minton, M. A. *J. Am. Chem. Soc.* 1987, *109*, 225.

(10) A similar preference for the gauche form of 1-propanol has been estimated from ¹H coupling constants. See: Spoormaker, T.; Zwikker, J. W.; de Bie, J. A. *Recl. Trav. Chim. Pays-Bas* 1979, *98*, 253. Abdurahmanov, A. A.; Rahimova, R. A.; Imanov, L. M. *Phys. Lett. A.* 1970, *32*, 123.

carbinol carbon (Figure 6), where each also has the most stable arrangement about the remaining carbon–carbon bond. Fortunately, the major contribution to differences between conformers appears to be restricted to γ substituents and thus each bond can be considered an isolated system.

With the populations of X, Y, and Z as x, y, and z, there are two equations that must simultaneously fit the observed spectral shift-of-shifts in addition to that implicit in the assumption that these three conformations represent the total of those under observation (the shift-to-shift effects used are from Figure 2):

$$x + y + z = 1.0$$

$$(-5.9)x + (-8.85)y + (-3.8)z = -5.5 = 24.5 - 19.0 \quad \text{(C-1)}$$

$$(-8.85)x + (-3.8)y + (-5.9)z = -7.1 = 24.5 - 17.4 \quad \text{(C-6)}$$

Simultaneous solution of these equations leads to a predicted ratio of conformers (x, y, and z, below) quite close to that predicted by MM-2 calculations.

	x		y		z
MM-2 ratio	42	:	13	:	44
NMR ratio	50	:	12	:	38

To arrive at a unique solution to the appropriate simultaneous equations, the number of observed shifts of carbons that vary with conformation must be equal to or greater than the number of distinct conformations minus one (the additional equation being provided by the identity that the sum of all conformer populations must equal 1), but in practice quite useful information can be obtained by a "local" analysis similar to that carried out above. It should be pointed out that this type of analysis can result in substantial errors in population percentages as our average shift prediction error (0.5) represents a significant fraction of the shift difference between anti and gauche relationships for both oxygen (Δ 5.2) and carbon (Δ 3.2) substituents. While this relatively soft fit excludes the possibility of obtaining precise, relative energies for various conformers, the qualitative results from such a direct solution determination rival those obtained from extrapolation of gas-phase observations that are carried out by molecular mechanics calculations. Certainly, these results confirm the quantitative relationship between shift effect and spatial orientation of γ substituents and provide ample justification for the application of the shift effect values used here for the experimental determination of conformational populations in appropriately substituted systems.

Relaxation or Fluctuation of the Ionic Atmosphere in Charge-Transfer Reactions. An ab Initio Study of the Charge Transfer in the $(H_3O_2)^-$ and $(FCH_3F)^-$ Systems

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Abstract: To discuss the intervention of the ionic atmosphere on charge-transfer reactions, ab initio calculations have been carried out on the proton-transfer reaction in the $(H_3O_2)^-$ system, and on the fluoride-exchange reaction in the $(FCH_3F)^-$ system. In a simplified model, no solvent molecules have been considered, and a very limited number of neighboring ions have been taken. Li^+ and H^+ cations and the positive charge have been chosen as counterions. It has been found that counterion parameters belong to the reaction coordinate, so that fluctuations of counterions may induce the chemical process. An insight to these energetic results is made from the changes in charge density produced by neighboring ions. The main conclusion is that external perturbations to the chemical system have the same effect as variations in the internal coordinates of the system, thus showing that the concept of reaction coordinate is wider than usually thought.

At present, most theoretical studies on chemical reactivity deal with isolated systems. Although a few new methods like flowing-afterglow[1] and techniques like ion cyclotronic resonance[2] allow the study of reactions at very low pressures, nearly all experimental studies are carried out in a condensed medium. Actually, experimental work is usually done in solution, where environmental effects are quite important. These effects are due simultaneously to the solvent and the ionic atmosphere. The influence of solvent on chemical reactions already has been studied in a large number of cases. However, the effect due to the presence of neighboring ions has been investigated far less. The study of this last effect is the ultimate goal of the present paper.

Let us summarize first the various models of the solvent, since there is an analogy with the different ways of representing the ionic atmosphere. The solvent effect on chemical reactions has been extensively studied within the framework of transition-state theory.[3,4] The first studies of Debye[5] and Onsager,[6] which used a continuum model for the solvent, have been recently improved by Jørgensen[7-10] by means of a Monte Carlo study. In these static approaches, the solvent is supposed to be in equilibrium with the chemical system by a relaxation that follows the chemical process. Studies of the dynamical effect of the solvent were introduced by Kramers[11] in 1940, and have been widely developed by Hynes[12,13] using a generalized Langevin equation. In this stochastic

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