alyzed by LSC. After the appropriate fractions were collected, LSC showed 1.1 μCi (31%) incorporation. The exo and endo pyrophosphates ($[^3H]$-**13**-OPP and $[^3H]$-**14**-OPP) were incubated with kaurene synthetase, using the same procedure. After the column chromatographic separation, only negligible radioactivity (<100 cpm, <1%) was observed in the kaurene fraction in both cases.

Registry No. **2**, 562-28-7; **5a**, 27975-19-5; **5b**, 30217-41-5; **6**, 107540-93-2; **7**, 40140-46-3; **8a**, 107540-94-3; **8b**, 107540-95-4; **9**, 107540-96-5; **10**, 107540-97-6; **11a**, 107540-98-7; **11b**, 107540-99-8; **11b**-*d*, 107541-06-0; **12a**, 107597-53-5; **12b**, 107597-48-8; **12b**-*d*, 107597-51-3; **13**-OH, 107541-00-4; $[^3H]$-**13**-OH, 107541-08-2; **13**-OTs, 107541-01-5; $[^3H]$-**13**-OPP, 107541-09-3; **13**-al, 107541-07-1; **14**-OH, 107597-49-9; **14**-OTs, 107597-50-2; **14**-al, 107597-52-4; **15**, 3564-54-3; **16**, 36627-98-2; **17**, 21561-92-2; **18**, 19882-10-1; **19**, 107541-02-6; **29**, 107541-03-7; pimaric acid, 127-27-5; 2,2-dimethyl-1,3-propanediol, 126-30-7; *ent*-15-diazobeyeran-16-one, 107541-04-8; *ent*-16-[2-(*p*-tolylsulfonyl)-1,1-diazenediyl]beyeran-15-one, 107541-05-9; kaurene synthetase, 9055-64-5.

Theoretical Calculation of Effects of Steric Hindrance on Rates of Esterification and of Acid-Catalyzed Hydrolysis[1]

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We report the calculation of rates of esterification and of acid-catalyzed hydrolysis of esters of a set of acetic acids $R_1R_2R_3CCOOH$ having R_i equal to H, Me, Et, *i*-Pr, and *t*-Bu. The log *k*(rel) are represented as a LFER of relative gas-phase enthalpies of activation calculated by molecular mechanics. The tetrahedral intermediate was used as a model of the transition state on the way to the tetrahedral intermediate. The purpose of the study has been twofold, to gain a better understanding of the role of steric effects in acyl transfer reactions involving highly hindered substrates and to develop further the principles that underlie the use of molecular mechanics as a tool for reliable prediction of rates. The FSE values are transferable and also permit comparisons of steric effects among different esters. The predicted rate constants exhibit curious patterns; the more highly substituted tri-*tert*-butylacetic acid is predicted to react some 10000 times faster than isopropyldi-*tert*-butylacetic acid; both are predicted to react very slowly.

Molecular mechanics has been shown to be a useful tool for the estimation of relative rate constants of certain types of reactions both in the gas phase and in solution. Log *k* is correlated in a LFER expression with the steric energy (SE) of the reactant or with ΔSE between a model of the transition state and the reactant.[1] The correlations of relative rate constants have been quite successful in most cases.[5–37]

The ability to calculate relative rate constants reliably is of great importance, and molecular mechanics is becoming widely used in many laboratories to provide a clearer understanding of the role of steric factors in determining rates of reactions. Our interest has been to examine the underlying theoretical principles so that the calculations may be performed more reliably. We have been concerned with such questions as: Under what circumstances may differences of raw steric energies from a molecular mechanics calculation be taken as proportional to the gas-phase enthalpy of activation? In what respect is the gas-phase enthalpy of activation related to the free energy of activation in solution? How can we compare steric properties of reactants or of transition states?[3]

A practical goal of a molecular mechanics calculation is to estimate the difference of the steric components of the enthalpies of formation of conformer C1 of molecule M1

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(1) Definitions: SE, raw steric energy as calculated by molecular mechanics. FSE, formal steric enthalpy.[2,3] Conformational labels are described in Appendix 1 and are illustrated in ref 4. LFER is linear free energy relationship; see, for example, eq 2 and 7–9.

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and of conformer C2 of molecule M2. If M1 is a reactant and M2 is a model of a transition state and if C1 and C2 are global minima, then the enthalpy difference may be taken as an estimate of the enthalpy of activation in the gas phase, apart from an additive constant. In some cases the difference of steric energies (ΔSE) provides a valid estimate of the enthalpy difference, but it is more general to calculate and to compare formal steric enthalpy values (FSE's). It may be possible to combine the ΔFSE value with appropriate bond enthalpy terms to obtain an estimate of the difference of the enthalpies of formation of two reactants or of two transition states.[3] Formal steric enthalpy values are transferable.

In an earlier study[14] we found a good LFER between log *k*(rel) data and differences of raw steric energies, using the tetrahedral intermediate as a model of the transition state. In the present study we have taken another look at esterification and ester hydrolysis in the light of subsequent theoretical developments. Acyl-transfer reactions such as esterification and ester hydrolysis are of general importance, and they are attractive candidates for the exploration of new approaches since data are available for a broad range of compounds.

The present investigation concerns substituted acetic acids of the class $R_1R_2R_3CCOOH$ in which R_1 is H, Me, Et, *i*-Pr, and *t*-Bu. The advantage of this set is that it involves progressive and systematic deformations as methyl groups are added. In these examples we are concerned with many highly crowded molecules exhibiting severe steric hindrance.

Theoretical Principles. Calculation of Relative Mechanistic Rate Constants. According to transition-state theory relative rate constants may be expressed by eq 1. In earlier studies we and other groups have translated eq 1 into eq 2, using three assumptions. The first is that the double difference of steric energies is a measure of the double difference of enthalpies of formation, eq 3 and 4, t.s. standing for the model of the transition state and r for the reactant or reactants. The second assumption is that the residual of the double difference of entropies is negligible owing to cancellations. The third assumption is that the solvation effects also drop out of the double difference. If the latter two assumptions are valid, then $\Delta H^{\ddagger}$(gas) is an appropriate measure of $\Delta G^{\ddagger}$(solution), eq 1. A linear free energy relationship (LFER), here eq 2, is a generalization of the double difference equation that results from combining eq 1, 3, and 4, with the assumed cancellations of entropies and of solvation effects.

$$\log (k_2/k_1) = (\Delta G^{\ddagger}_1 - \Delta G^{\ddagger}_2)/2.3RT \qquad (1)$$

$$\log k(\mathrm{rel}) = \log (k_2/k_1) = a' + b'SE \qquad (2)$$

$$\Delta\Delta H^{\ddagger} = \Delta H_f(\mathrm{t.s.2}) - \Delta H_f(\mathrm{r2}) - \Delta H_f(\mathrm{t.s.1}) + \Delta H_f(\mathrm{r1}) \quad (3)$$

$$\Delta\Delta H^{\ddagger} = \mathrm{SE(t.s.2)} - \mathrm{SE(r2)} - \mathrm{SE(t.s.1)} + \mathrm{SE(r1)} \quad (4)$$
$$= \Delta\mathrm{SE}_2 - \Delta\mathrm{SE}_1$$

We have examined the above assumptions and find that the first is of limited validity and that the second two are not necessary. With respect to the first assumption, eq 5 is the correct representation of the double difference, eq 3, for esterification and for ester hydrolysis, providing that polar effects and resonance effects are absent or are treated separately.[3] If we compare two acids of the same class, two RCH_2COOH or two $R_2CHCOOH$ for instance, then $\sum c[\text{C-}\alpha]$ is zero; in this case eq 2 is equally correct whether expressed in terms of SE's or of FSE's.

If the acids are from different families, then it is better to use FSE values. Although the $\sum c[\text{C-}\alpha]$ term does not cancel in this case, its value is in principle independent of the force field. That independence does not hold if steric energies are used instead of formal steric enthalpies. The $\sum c[\text{C-}\alpha]$ term in eq 5 and 7 is the double difference

$$\Delta\Delta H_f = \Delta\Delta\mathrm{FSE} + \sum c[\text{C-}\alpha] \qquad (5)$$

$$\log k_{\mathrm{rel}} = a + b\mathrm{FSE} + \text{C-corr} \qquad (6)$$

$$a = a'' + \sum c[\text{C-}\alpha] \qquad (7)$$

of formal bond enthalpies of the groups α to the $C(OH)_2(OCH_3)$ group and the corresponding groups α to a COOH group. The former values are known since they are the alkane values. That is, $c[CH_3]$ has the same value whatever is the attached sp^3 carbon. Unless enthalpy data are available to provide estimates of $c[C_i\text{-}\alpha]$, then it may not be possible to combine data for the monosubstituted, the disubstituted, and the trisubstituted acids except empirically. The calculation of $\sum c[\text{C-}\alpha]$ is illustrated below.

We have previously examined the implications of using gas-phase enthalpies of activation in the calculation of rates in solution.[3] This is justified as a first-order approximation since solvation effects and entropy effects may be expected to parallel steric effects. As a consequence, log *k* should be linearly related to $\Delta\Delta H_f$(g) and hence to ΔFSE, but the slope may depart from the theoretical value of $1/2.3RT$.[3] In other words, the existence of a linear free energy relationship such as eq 2 or 7 does not require that solvation effects and entropy effects cancel; it requires only that they be proportional to the steric effects as represented by ΔFSE. For cyclization reactions the entropy change will not cancel out, nor can it be expected to parallel the steric effect; it must be estimated independently.[16]

If a reactant has several conformers of low energy, or if there are several low energy conformers of the model of the transition state, then it is necessary to consider a correction for the conformer sets. The reactant conformers constitute the usual population of conformers in rapid equilibrium under the reaction conditions; due to the presence of multiple conformers the enthalpy of formation of the reactant is more positive than is the estimate based on the conformer of lowest energy. On the other hand, the several conformers of the model of the transition state are not presumed to be in equilibrium. Instead they constitute separate reaction channels. We have shown elsewhere how this system of multiple conformers should be treated.[38] Equation 6 is the corrected linear free energy equation and C-corr is the conformer correction term. The method of calculating C-corr is shown below.

A central problem in calculating rate constants is to find a suitable model of the transition state. We have again used the tetrahedral intermediate $RC(OH)_2(OCH_3)$ as a model of the transition state on the way to the tetrahedral intermediate.[14] In the actual transition state the three C–O bonds will presumably be of different lengths. The choices in modeling the acyl-transfer reactions are either to work with a reasonable model for which the force field calibration is known or else to select a "better" model and then have to invent some dozen or so new force field parameters presumed to be applicable to the improved model of the transition state. For the reactions under investigation it turns out that there are no clear indications that a different model would perform any better.

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Table I. Molecular Mechanics Runs on Esters and on Tetrahedral Intermediates

ID[a]	R1	R2	R3[b]	conformation[c]			SE[d] EST	FSE[e] EST	GAUCHE[f] EST	SE[d] TET	FSE[e] TET	GAUCHE[f] TET
1	H	H	H	H	H	H	1.76	0.85	0.85	3.02	0.54	0.40
2	Me	H	H	Me	H	H	2.17	0.85	0.85	3.99	0.72	0.70
3A	Et	H	H	T	H	H	2.97	0.87	0.85	4.82	0.77	0.70
3B				R	H	H	3.12	1.02	1.00	5.62	1.57	1.50
4A	*i*-Pr	H	H	TBAR	H	H	4.85	1.21	1.15	8.10	2.51	2.30
4B				RBAR	H	H	4.73	1.09	1.00	7.48	1.89	1.50
5	*t*-Bu	H	H	*t*-Bu	H	H	7.72	1.41	1.15	11.53	3.27	2.30
6	Me	Me	H	Me	Me	H	3.38	0.90	0.85	5.77	0.96	1.00
7A	Et	Me	H	T	Me	H	4.80	1.53	1.55	7.43	1.84	1.70
7B				R	Me	H	4.36	1.09	1.00	7.92	2.33	1.80
7C				L	Me	H	4.96	1.69	1.70	7.85	2.26	2.50
8A	*i*-Pr	Me	H	TBAR	Me	H	7.02	2.21	1.85	10.96	3.83	3.30
8B				RBAR	Me	H	7.23	2.42	2.40	10.49	3.36	3.20
8C				LBAR	Me	H	7.05	2.24	1.70	11.65	4.52	2.50
9	*t*-Bu	Me	H	*t*-Bu	Me	H	10.90	3.42	2.55	16.48	6.68	4.00
10A	Et	Et	H	T	T	H	7.69	3.64	3.50	10.67	4.29	3.65
10B				T	R	H	6.37	2.32	2.40	9.45	3.07	3.20
10C				T	L	H	5.82	1.77	1.70	9.90	3.52	2.50
10D				R	R	H	6.00	1.95	1.85	9.75	3.37	3.30
10E				R	L	H	5.39	1.34	1.15	10.66	4.28	2.60
10F				L	R	H	8.36	4.31	3.80	11.32	4.94	5.25
11A	*i*-Pr	Et	H	TBAR	T	H	8.50	2.91	2.55	13.03	5.11	4.00
11B				TBAR	R	H	10.35	4.76	3.95	14.12	6.20	6.05
11C				TBAR	L	H	8.05	2.46	2.00	13.28	5.36	4.10
11D				RBAR	T	H	10.00	4.41	4.35	13.61	5.69	5.15
11E				RBAR	R	H	10.47	4.88	4.50	14.01	6.09	5.95
11F				RBAR	L	H	8.42	2.83	2.55	12.71	4.79	4.00
11G				LBAR	T	H	10.08	4.49	3.65	15.28	7.36	4.45
11H				LBAR	R	H	8.74	3.15	2.55	13.42	5.50	4.00
11I				LBAR	L	H	8.25	2.66	1.85	14.91	6.99	3.30
12A	Et	*t*-Bu	H	T	*t*-Bu	H	14.30	6.04	4.50	20.26	9.67	5.95
12B				R	*t*-Bu	H	12.13	3.87	2.70	19.71	9.12	4.80
12C				L	*t*-Bu	H	14.61	6.35	4.65	19.93	9.34	6.75
13A	*i*-Pr	*i*-Pr	H	TBAR	TBAR	H	12.73	5.60	4.10	17.72	8.26	6.85
13B				TBAR	RBAR	H	10.79	3.66	2.70	17.85	8.39	4.80
13C				TBAR	LBAR	H	12.98	5.85	4.65	16.91	7.45	6.75
13D				RBAR	RBAR	H	12.74	5.61	4.50	18.80	9.34	5.95
13E				RBAR	LBAR	H	13.88	6.75	6.45	17.96	8.50	7.90
13F				LBAR	RBAR	H	13.55	6.42	3.80			
14A	*i*-Pr	*t*-Bu	H	TBAR	*t*-Bu	H	16.92	7.12	4.80	24.63	12.50	7.55
14B				LBAR	*t*-Bu	H	18.27	8.47	6.60	25.33	13.20	8.70
14C				RBAR	*t*-Bu	H	17.82	8.02	4.65	29.21	17.08	6.75
15	*t*-Bu	*t*-Bu	H	*t*-Bu	*t*-Bu	H	23.80	11.33	6.75	35.18	20.38	9.50
16	Me	Me	Me	Me	Me	Me	6.03	1.10	0.85	8.83	1.35	1.30
17A	Et	Me	Me	T	Me	Me	9.83	4.11	2.25	11.36	3.10	2.70
17B				R	Me	Me	7.80	2.08	1.70			2.80
18A	*i*-Pr	Me	Me	TBAR	Me	Me	11.77	4.51	2.55			4.30
18B				RBAR	Me	Me	11.42	4.16	3.10	16.21	6.41	4.20
19	*t*-Bu	Me	Me	*t*-Bu	Me	Me	16.96	7.03	3.95	23.36	10.89	5.70
20A	Et	Et	Me	T	T	Me	12.33	5.83	4.90	15.79	6.74	5.35
20B				T	R	Me	10.07	3.57	3.10	14.45	5.40	4.20
20C				T	L	Me	10.27	3.77	3.10	14.12	5.07	4.20
20D				R	R	Me	10.16	3.66	2.55	14.45	5.40	4.30
20E				R	L	Me	9.79	3.29	2.55			4.30
20F				L	R	Me	12.16	5.66	3.80	15.41	6.36	5.55
21A	*i*-Pr	Et	Me	TBAR	T	Me	14.10	6.06	3.95	19.05	8.46	5.70
21B				TBAR	R	Me	16.47	8.43	4.65	20.37	9.78	7.05
21C				TBAR	L	Me	14.32	6.28	3.40	20.00	9.41	5.80
21D				RBAR	T	Me	15.27	7.23	5.75	20.41	9.82	6.85
21E				RBAR	R	Me	15.03	6.99	5.20	20.49	9.90	6.95
21F				RBAR	L	Me	13.72	5.68	3.95	19.02	8.43	5.70
21G				LBAR	T	Me	16.14	8.10	5.75	21.75	11.16	6.85
21H				LBAR	R	Me	13.64	5.60	3.95	18.78	8.19	5.70
21I				LBAR	L	Me	13.55	5.51	3.95	21.12	10.53	5.70
22A	Et	*t*-Bu	Me	T	*t*-Bu	Me	21.39	10.68	6.60	28.32	15.06	8.35
22B				R	*t*-Bu	Me	19.67	8.96	4.80	27.88	14.62	7.20
22C				L	*t*-Bu	Me			6.05			8.45
23A	*i*-Pr	*i*-Pr	Me	TBAR	TBAR	Me	21.83	12.25	5.50	26.27	14.14	8.55
23B				TBAR	RBAR	Me	17.80	8.22	4.80	25.22	13.09	7.20
23C				TBAR	LBAR	Me	20.28	10.70	6.05	26.08	13.95	8.45
23D				RBAR	RBAR	Me	19.37	9.79	6.60	26.59	14.46	8.35
23E				RBAR	LBAR	Me			7.85	26.59	14.46	9.60
23F				LBAR	RBAR	Me			6.60			8.35
24A	*i*-Pr	*t*-Bu	Me	TBAR	*t*-Bu	Me	28.48	16.23	6.90			9.95
24B				RBAR	*t*-Bu	Me			8.70	35.18	20.38	11.10
24C				LBAR	*t*-Bu	Me	26.34	14.09	7.45	37.43	22.63	9.85

Table I (Continued)

ID[a]	R1	R2	R3[b]	conformation[c]			SE[d] EST	FSE[e] EST	GAUCHE[f] EST	SE[d] TET	FSE[e] TET	GAUCHE[f] TET
25	*t*-Bu	*t*-Bu	Me	*t*-Bu	*t*-Bu	Me	37.16	22.24	9.55	47.57	30.10	12.60
26A	Et	Et	Et	T	T	T			8.80			9.25
26B				T	T	R	14.15	6.86	5.75	19.04	9.21	6.85
26C				T	R	R	12.49	5.20	3.95	17.36	7.53	5.70
26D				T	R	L	12.01	4.72	3.95	17.61	7.78	5.70
26E				T	L	R	15.99	8.70	5.20	19.88	10.05	6.95
26F				R	R	R	13.32	6.03	3.40	17.49	7.66	5.80
26G				R	R	L	14.41	7.12	4.65	19.98	10.15	7.05
27A	*i*-Pr	Et	Et	TBAR	T	T			6.60			8.35
27B				TBAR	T	R	16.58	7.75	4.80	23.76	12.39	7.20
27C				TBAR	T	L			6.05			8.45
27D				TBAR	R	R	19.46	10.63	5.50	26.07	14.70	8.55
27E				TBAR	R	L	19.95	11.12	6.75	26.49	15.12	9.80
27F				TBAR	L	R			5.50			8.55
27G				RBAR	T	T			9.65			10.75
27H				RBAR	T	R			6.60			8.35
27I				RBAR	T	L	17.70	8.87	6.60			8.35
27J				RBAR	R	T			7.85			9.60
27K				RBAR	L	T			6.60			8.35
27L				LBAR	R	R	16.94	8.11	4.80			7.20
27M				LBAR	R	L			6.05			8.45
27N				LBAR	L	R	18.36	9.53	6.05	25.18	13.81	8.45
27O				LBAR	L	L	17.44	8.61	6.05			8.45
28A	Et	Et	*t*-Bu	T	T	*t*-Bu			10.50			12.25
28B				T	R	*t*-Bu	24.21	12.71	7.45	32.20	18.16	9.85
28C				T	L	*t*-Bu			8.70	33.56	19.52	11.10
28D				R	R	*t*-Bu	25.61	14.11	6.90	33.45	19.41	9.95
28E				R	L	*t*-Bu			8.15	35.54	21.50	11.20
28F				L	R	*t*-Bu	25.23	13.73	6.90	33.21	19.17	9.95
29A	*i*-Pr	*i*-Pr	Et	TBAR	TBAR	T			6.90	32.91	20.00	9.95
29B				TBAR	TBAR	R			7.60			11.30
29C				TBAR	RBAR	T			7.45			9.85
29D				TBAR	RBAR	R	22.88	12.51	6.90	30.92	18.01	9.95
29E				TBAR	RBAR	L	23.67	13.30	6.90	30.37	17.46	9.95
29F				TBAR	LBAR	T			8.70	30.71	17.80	11.10
29G				TBAR	LBAR	R	23.82	13.45	6.90	29.99	17.08	9.95
29H				TBAR	LBAR	L			8.15			11.20
29I				RBAR	RBAR	T			10.50			12.25
29J				RBAR	RBAR	R	26.07	15.70	8.70	31.72	18.81	11.10
29K				RBAR	RBAR	L			7.45	31.59	18.68	9.85
29L				RBAR	LBAR	T			11.75			13.50
29M				RBAR	LBAR	R	23.32	12.95	10.50	31.05	18.14	12.25
29N				LBAR	RBAR	T			8.70			11.10
29O				LBAR	RBAR	L			8.70			11.10
30A	*i*-Pr	Et	*t*-Bu	TBAR	T	*t*-Bu			9.55			12.60
30B				TBAR	R	*t*-Bu	35.68	22.64	9.00	44.75	29.17	12.70
30C				TBAR	L	*t*-Bu	37.24	24.20	9.00	43.43	27.85	12.70
30D				RBAR	T	*t*-Bu			11.35			13.75
30E				RBAR	R	*t*-Bu	31.72	18.68	9.55	46.29	30.71	12.60
30F				RBAR	L	*t*-Bu			9.55			12.60
30G				LBAR	T	*t*-Bu			12.60			15.00
30H				LBAR	R	*t*-Bu			9.55			12.60
30I				LBAR	L	*t*-Bu			10.80			13.85
31A	Et	*t*-Bu	*t*-Bu	T	*t*-Bu	*t*-Bu	45.23	29.52	13.45	59.57	41.32	16.50
31B				R	*t*-Bu	*t*-Bu	44.00	28.29	10.40	58.47	40.22	14.10
32A	*i*-Pr	*i*-Pr	*i*-Pr	TBAR	TBAR	TBAR			9.70			14.05
32B				TBAR	TBAR	RBAR	31.65	19.74	9.00			12.70
32C				TBAR	RBAR	RBAR	30.83	18.92	9.55	39.64	25.19	12.60
32D				TBAR	RBAR	LBAR	28.80	16.89	9.55	40.06	25.61	12.60
32E				TBAR	LBAR	RBAR			10.80	38.86	24.41	13.85
32F				RBAR	RBAR	RBAR			11.35			13.75
32G				RBAR	RBAR	LBAR			12.60			15.00
33A	*i*-Pr	*i*-Pr	*t*-Bu	TBAR	TBAR	*t*-Bu	47.70	33.12	11.10	54.23	37.11	15.45
33B				TBAR	RBAR	*t*-Bu			11.65	52.10	34.98	15.35
33C				TBAR	LBAR	*t*-Bu	42.06	27.48	10.40			14.10
33D				RBAR	RBAR	*t*-Bu			13.45			16.50
33E				RBAR	LBAR	*t*-Bu			13.45			16.50
33F				LBAR	RBAR	*t*-Bu			14.70			17.75
34A	*i*-Pr	*t*-Bu	*t*-Bu	TBAR	*t*-Bu	*t*-Bu	60.83	43.58	13.75	74.55	54.76	18.10
34B				RBAR	*t*-Bu	*t*-Bu	54.38	37.13	15.55	69.96	50.17	19.25
35	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	75.90	55.98	17.65	86.08	63.62	22.00

[a] Identification symbol used in the text, in the tables, in the figure, and in ref 4. [b] For $R_1R_2R_3CCOOCH_3$ = EST and $R_1R_2R_3CC(OH)_2(OCH_3)$ = TET. [c] See Appendix 1; see also ref 4. [d] The steric energy given by the DETSB force field, ref 2, 4, 67. [e] See eq 13. [f] See text.

Theoretical Principles. Mechanistic and Phenomenological Rate Constants. In order to compare calculated rate constants with observation it is necessary to determine how the "observed" phenomenological rate constants are related to the mechanistic constants. A phenomenological constant is either an observed rate constant or else a rate constant derived by stoichiometry from the observed rate constant. For example, it might be a pseudo-second-order rate constant for esterification derived by dividing the pseudo-first-order constant by the concentration of catalytic acid. The problem in esterification or hydrolysis is to determine the relationship between the reported pseudo-second-order rate constants and the mechanistic constants.[39]

In esterification and in ester hydrolysis the formation of the tetrahedral intermediate is reversible, and the phenomenological rate constant is therefore the product of the required mechanistic constant and a distribution factor. The behavior of this distribution factor must be considered. Unless there is specific steric interaction between the R group of the acid component and the R′ group of the alkoxyl component, it seems safe to assume that the distribution factor is either constant or perhaps proportional to the overall steric factor. We chose to make calculations on the methyl esters rather than on the acids in order to monitor the possible onset of any specific interaction. There is none even for tri-*tert*-butylacetic acid.

Rate Data. Prior to 1950 many groups were active in studying esterification and ester hydrolysis.[40–60] An especially extensive and careful study of rates of esterification of alkyl-substituted acetic acids in methanol is that of Hilton Smith in the 1930s. Earlier measurements from many laboratories provide additional data. These several studies include acids exhibiting only a limited range of steric effects.

The range was greatly extended by Newman in the 1950s.[61] More recently Sniegoski carried out an interesting competitive study using modern gas chromatographic techniques to measure product ratios.[62] This technique provides a way to study highly hindered acids in the face of gradual loss of catalytic acid; relative rates should be independent of loss of catalyst. The competitive method has an obvious disadvantage in that errors in the standards are passed on down the line. Sniegoski's paper reports individual rate ratios and gives details of the derivation of the reported rate constants. The Dubois group used a similar competitive method for an interesting series of dialkyl- and trialkylacetic acids.[63]

Relative rate constants for acetic acid and for many RCH_2COOH reported by different laboratories are concordant to within 1% or 2%. Comparisons of the few independently reported rate constants for modestly crowded acids indicate discrepancies of perhaps 20% [0.08 in log *k*(rel)]. Values for hydroxide-mediated hydrolysis show greater variability. (Data are summarized in Table IIIS.[64])

Data for highly hindered acids are less well-established. For two important reference acids the reported rate constants for esterification are widely divergent. These are triethylacetic acid for which reported log *k*(rel) values are −3.79 (Newman),[61] −4.65 (Sniegoski),[62] and −5.29 (Dubois),[63] and *tert*-butyldimethylacetic acid for which reported log *k*(rel) values are −3.91 (Newman) and −5.40 (Dubois). For both reference acids this amounts to a thirtyfold discrepancy, 1.5 in log *k*(rel).

A possible complication with trialkylacetic acids that seems not to have been considered is decarbonylation as a side reaction. Although the carbonylation–decarbonylation process is usually carried out in more concentrated acid, it might become a factor when esterification is very slow, as it is here.[65]

For diisopropylacetic acid two sets of reported log *k*(rel) values appear to be concordant: −5.01 (ref 63) and −4.96 and −4.95 (ref 62). However, these values are tied by competitive measurements to discordant rate constants for triethylacetic acid. In view of the confusion, values for i-Pr_2CH-$COOH$, t-Bu-i-PrCHCOOH and t-$Bu_2CHCOOH$, together with the other values in ref 63 must be considered unknown.

An examination of the available data shows that relative rate constants based on acetic acid as the reference are nearly independent of temperature (over the ranges reported), of solvent, and of reaction, whether for esterification in methanol or in primary alcohols or for acid-catalyzed hydrolysis of the corresponding esters. We have therefore combined all available data to give an overall average.

We had hoped to include hydroxide-mediated hydrolysis as well, but the data are less consistent than are those for the acid-catalyzed reactions. For R = ethyl (propionic acid) the average log *k*(rel) values are −0.33 for RCOOMe, −0.55 for RCOOEt, and −0.30 for RCOOPR-*n*; for R = *t*-Bu (trimethylacetic acid) the values are −1.41 for RCOOMe, −2.13 for RCOOEt, and −1.99 for RCOOPr-*n*. Nor is there a consistent trend with substitution in the acyl group. We have therefore not used the data for hydroxide hydrolysis in the correlations. (Data for hydroxide hydrolysis are summarized in Table IIS.[64])

Results and Discussion. There are 35 acids in the set of $R_1R_2R_3CCOOH$ having R_1 equal to H, Me, Et, *i*-Pr, and *t*-Bu. There is one CH_3COOH, there are four $R'CH_2COOH$, ten $R'_2CHCOOH$, and 20 R'_3CCOOH. The 43 staggered conformations of the 15 acids $R_1R_2CHCOOH$ included in this study are shown in Figure 1 of ref 4. In that study and in the present work we have adopted a simplified notation for the conformations of the R groups. For $R = R_1R_2R_3C$ there are three possible key torsions, one about the C_α–C_β bond of R_1 and similar torsions for R_2 and

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R_3. Of the groups investigated only two, Et and *i*-Pr, have more than one staggered conformation. The conventions are presented briefly in Appendix 1 for convenient reference.

There are 147 staggered conformers in the set of 35 acids and a similar number for the tetrahedral intermediates. There are additional minima for several of the crowded conformers and numerous minor minima that concern the orientation of the alkoxyl group. Specific examples have been discussed for esters 1 to 15.[4] We have made calculations for all 43 staggered conformers of the methyl esters and for all but one of the conformers of the tetrahedral intermediates of the first 15 acids, and we have examined additional minima such as the pairs of plus and minus helical conformers that occur when g^+g^- interactions are present. We have calculated FSE values for many of the conformers of the trisubstituted acids.

Table I summarizes SE and FSE values of the methyl esters and of the tetrahedral intermediates. The FSE values, as defined in terms of the standards described below, are independent of force field and are transferable. The values in Table I, however, are estimates whose validity depends on the validity of the DETSB force field (and on the calculations). They will agree with FSE values calculated by some other force field insofar the two force fields correctly reproduce enthalpies of formation.

The difference in the steric components of the enthalpies of formation of any two esters is represented by the difference of the FSE values. As an example, in terms of the standards defined below our estimate is that $Et_3CCOOCH_3$ (FSE = 5.03 kcal/mol) is more crowded than is $Me_3CCOOCH_3$ (FSE = 1.50) by some 3.53 kcal/mol.

Detailed data are reported in Tables IS[64] for conformers of the tetrahedral intermediates of compounds 1 to 15. This is the counterpart of the data reported previously for the corresponding methyl esters.[4]

Table II summarizes the calculations of rate constants for R_1CH_2COOH and $R_1R_2CHCOOH$ while Table III summarizes the calculations for $R_1R_2R_3COOH$. Entries are as follows: The ID is uniform throughout this paper and the earlier paper.[4] The R_1 and R_2 groups of $R_1R_2CHCOOH$ are shown in Table II and all three R_i groups are shown in Table III. Compound **1**, for example, is acetic acid, compound **2** is propionic acid, compound **16** is 2,2-dimethylpropanoic acid (pivalic acid). The notation for the conformations is defined in Appendix 1 and in ref 4. The next entries are the formal steric enthalpy of the global minimum for the ester RCOOMe and the FSE of the global minimum for the tetrahedral intermediate $RC(OH)_2(OCH_3)$ followed by the difference of these two FSE's. It is possible that for some compounds in Table III the lowest FSE value is not the globsal minimum, but it is unlikely that any is as much as 1 kcal/mol greater than the global minimum. The compounds in question are flagged; the molecular mechanics calculations for these did not include all members of the gauche subsets as described below.

The conformational correction C-corr, explained below, corrects for the presence of reactant conformers and for multiple reaction channels. The log *k*(rel) average is based on all esterifications with methanol and with primary alcohols plus all data for acid-catalyzed hydrolysis of methyl esters, ethyl esters, and *n*-propyl esters. The calculated value, log *k*(rel) calculated, is derived from eq 8 for the entries in Table II and from eq 9 for entries in Table III. These equations are specific instances of eq 6. The last column gives the difference between log *k*(rel) observed and log *k*(rel) calculated. The correlation is shown for several instances of compounds 1 to 15 in Figure 1.

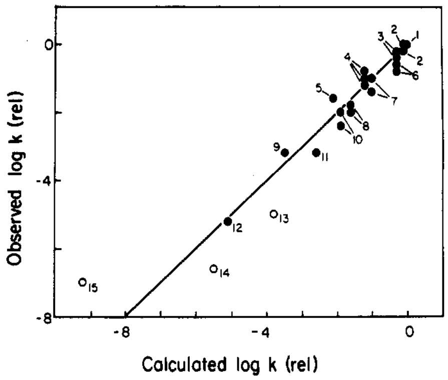

Figure 1. Observed log *k*(rel) vs. calculated log *k*(rel). The data shown are for acid-catalyzed reactions. The compounds are identified in Table II. The open circles represent compounds for which the experimental values are uncertain. See text. The line has unit slope.

$$\log k(\text{rel}) = -0.3032-0.9904(\text{DEL FSE}) + \text{C-corr} \tag{8}$$

$$\log k(\text{rel}) = -1.2632 - 0.9904(\text{DEL FSE}) + \text{C-corr} \tag{9}$$

The complete set of literature rate constants we have used is summarized in Table IIIS.[64] As discussed above, experimental data for many of the highly substituted acids are uncertain owing to inconsistencies. The spread of the data is illustrated in part by the multiple entries in Table III for *tert*-butyldimethylacetic acid (**19**) and for triethylacetic acid (**26**). Values regarded as uncertain are shown in parentheses.

The theoretical slope for a correlation at 40 °C should be about 0.7 if the (DEL FSE) represents the free energy of activation in solution. As indicated above and elsewhere, entropy effects and solvation effects are expected to contribute to the value of the slope.[3] Another contributor could be a distribution constant that depends on the steric effect. The distribution constant is the partitioning of the tetrahedral intermediate between formation of product and reversion to reactant.[39] Other contributers to the slope can be a force field that does not properly represent the steric component of the enthalpy of formation and a model of the transition state that does not properly mirror steric effects. Incidentally, a slope that is too large implies that the model of the transition state is too "loose". It would appear that the tetrahedral intermediate should be too "tight".

Equations 6 and 7 provide the rationale for eq 8 and 9; the log *k*(rel) values should be correlated by sets of LFER's having the same slopes but different intercepts owing to the $\sum c[\text{C-}\alpha]$ term of eq 6 and 7. Empirically the data were treated as follows: The data for acids 1 to 12 were used to derive *a* and *b* of eq 8. Acids 13 to 15 were omitted from the derivation of *a* and *b* since the experimental values are considered unreliable for reasons discussed above. The data do not support assigning different intercepts for the primary acids (**2–5**) and the secondary acids (**5–12**).

The intercept needed for the trisubstituted acids was determined from the limited data available, viz. for acids **16**, **17**, **20**, and the Newman value for **26**. The intercept correlation of −0.96 was obtained from these, thus resulting in eq 9.

As shown elsewhere,[3] all bond enthalpy increments cancel in the double difference except for the four represented as $\sum c[\text{C-}\alpha]$ in eq 6 and 7. This means that the $\sum c[\text{C-}\alpha]$ correction is zero as long as a comparison is made with a given set of acids. The RCH_2COOH acids form one set, the $R_2CHCOOH$ form a second set, and the R_3CCOOH form a third set.

Table II. Formal Steric Enthalpy and Rates of Esterification and of Acid-Catalyzed Hydrolysis of Mono- and Disubstituted Acetic Acids[a]

ID[a]	R_1	R_2[b]	FSE EST[c]	FSE TET	DEL FSE[d]	C-corr[e]	–log *k*(rel) av[f]	–log *k*(rel) calc[g]	diff
1	H	H	0.85	0.54	–0.31	0.00	0.00	0.00	–0.01
2	Me	H	0.85	0.72	–0.13	0.00	0.07	0.17	0.11
3	Et	H	0.87	0.77	–0.10	–0.23	0.34	0.43	0.09
4	*i*-Pr	H	1.09	1.89	0.80	–0.08	0.95	1.17	0.23
5	*t*-Bu	H	1.41	3.27	1.86	0.00	1.70	2.15	0.45
6	Me	Me	0.90	0.96	0.06	0.00	0.52	0.36	–0.16
7	Et	Me	1.09	1.84	0.75	0.02	1.06	1.03	–0.03
8	*i*-Pr	Me	2.21	3.36	1.15	–0.22	1.89	1.66	–0.23
9	*t*-Bu	Me	3.42	6.68	3.26	0.00	3.30	3.53	0.23
10	Et	Et	1.34	3.07	1.73	0.16	1.92	1.86	–0.06
11	*i*-Pr	Et	2.46	4.79	2.33	–0.06	3.32	2.67	–0.65
12	Et	*t*-Bu	3.87	9.08	5.21	0.29	5.14	5.18	0.03
13	*i*-Pr	*i*-Pr	3.66	7.45	3.79	0.13	(4.98)[h]	3.93	(–1.06)
14	*i*-Pr	*t*-Bu	7.12	12.43	5.31	–0.02	(6.53)[h]	5.58	(–0.95)
15	*t*-Bu	*t*-Bu	11.33	20.38	9.05	0.00	(6.97)[h]	9.27	(2.30)

[a] Standard identification number. [b] $R_1R_2CHCOOH$. [c] See text for FSE (formal steric enthalpy) calculations. Values listed are for conformers of minimum energy. [d] DEL FSE used in the LFER equation. Value for tetrahedral conformer of minimum energy – value for ester conformer of minimum energy. [e] Correction for conformer population and for multiple reaction channels. See text. [f] Average, relative to acetic acid or acetate esters. [g] log *k*(rel) = –0.3032 – 0.9904(DEL FSE) + C-corr. [h] Reported value, but large discrepancies in reported values of reference standards make correct value uncertain. See text. If, for example, the *i*-Pr value is referenced to the probably more correct Newman value for triethylacetic acid used as the reference, it would become 4.10. See text.

Table III. Formal Steric Enthalpy and Rates of Esterification of Trisubstituted Acetic Acids

ID[a]	R_1	R_2	R_3[b]	FSE EST[c]	FSE TET	DEL FSE[d]	C-corr[e]	–log *k*(rel) av[f]	–log *k*(rel) calc[g]	diff
16	Me	Me	Me	1.10	1.35	0.25	0.00	1.46	1.51	0.05
17	Et	Me	Me	2.08	3.10[i]	1.02	–0.01	2.23	2.29	0.06
18	*i*-Pr	Me	Me	4.16	6.39[i]	2.23	–0.19	3.54	3.66	0.12
19	*t*-Bu	Me	Me	7.03	10.81	3.78	0.00	4.66	5.01	0.35
19	*t*-Bu	Me	Me					3.91[j]		1.10
19	*t*-Bu	Me	Me					5.40[k]		–0.39
20	Et	Et	Me	3.29	5.07[i]	1.78	–0.06	3.50	3.08	–0.42
21	*i*-Pr	Et	Me	5.51	8.19	2.68	–0.11		4.03	
22	Et	*t*-Bu	Me	8.96	14.62	5.66	0.15		6.72	
23	*i*-Pr	*i*-Pr	Me	8.22	13.09[i]	4.87	0.17	(7.38)	5.92	(–1.46)
24	*i*-Pr	*t*-Bu	Me	14.09	20.38	6.29	–0.01	(7.56)	7.50	(–0.06)
25	*t*-Bu	*t*-Bu	Me	22.24	30.10	7.86	0.00		9.05	
26	Et	Et	Et	4.72	7.53	2.81	0.20	4.60	3.85	–0.76
26	Et	Et	Et					3.81[j]		0.04
26	Et	Et	Et					5.29[k]		–1.44
26	Et	Et	Et					4.65[l]		–0.80
27	*i*-Pr	Et	Et	7.75	12.39[i]	4.64	–0.25	(6.20)	6.11	(–0.09)
28	Et	Et	*t*-Bu	12.71	18.16	5.45	0.04	(7.21)	6.62	(–0.59)
29	*i*-Pr	*i*-Pr	Et	12.51[i]	17.08[i]	4.57	0.08	(7.38)	5.71	(–1.67)
30	*i*-Pr	Et	*t*-Bu	18.68[i]	27.85[i]	9.17	0.05	(6.62)	10.30	(3.68)
31	Et	*t*-Bu	*t*-Bu	28.29	40.22	11.93	0.01		13.07	
32	*i*-Pr	*i*-Pr	*i*-Pr	16.89[i]	24.41[i]	7.52	0.20	(6.73)	8.51	(1.78)
33	*i*-Pr	*i*-Pr	*t*-Bu	27.48	34.98[i]	7.50	0.01		8.68	
34	*i*-Pr	*t*-Bu	*t*-Bu	37.13	49.29	12.16	0.00		13.31	
35	*t*-Bu	*t*-Bu	*t*-Bu	55.98	63.62	7.64	0.00		8.83	

[a] Footnotes same as for Table II except as noted. Experimental values in parentheses considered unreliable. See text. [g] log *k*(rel) = –0.3032 – 0.96 – 0.9904(DEL FSE) + C-corr. [i] This value may not be the global minimum, but it should be close; the subset for which FSE values were calculated did not include all conformers for which the gauche enthalpy is the minimum plus 1 kcal/mol. See Table I and text. [j] Reference 61. [k] Reference 63. [l] Reference 62.

In principle the value of the $\sum c[\text{C-}\alpha]$ term can be calculated if enthalpies of formation are available for enough acids or esters. Unfortunately the available enthalpies of formation are inconsistent; key enthalpies of formation that should differ by no more than 0.5 kcal/mol or less actually differ by more than 5 kcal/mol.

We show the calculation of $\sum c[\text{C-}\alpha]$ for the three sets of acids in order to illustrate how the principle can be applied. In eq 10–12 we use a precise notation for the groups whose increments are required.[66]

$$\text{for } RCH_2COOH \ \sum c[\text{C-}\alpha] = 0.34 \pm 0.3 = c[\underset{-5.14}{\text{C C C H H}}] - c[\underset{-5.14}{\text{C C CDH H}}] - c[\underset{-10.06}{\text{C C H H H}}] + c[\underset{-10.40}{\text{C CDH H H}}] \qquad (10)$$

$$\text{for } R_2CHCOOH \ \sum c[\text{C-}\alpha] = 3.2 \pm 1.5 = c[\underset{-2.190}{\text{C C C C H}}] - c[\underset{-5.02}{\text{C C C CDH}}] - c[\underset{-10.06}{\text{C C H H H}}] + c[\underset{-10.40}{\text{C CDH H H}}] \qquad (11)$$

$$\text{for } R_3CCOOH \ \sum c[\text{C-}\alpha] = 3.1 \pm 2.5 = c[\underset{-0.22}{\text{C C C C C}}] - c[\underset{-3.0}{\text{C C C C CD}}] - c[\underset{-10.06}{\text{C C HH}}] + c[\underset{-10.40}{\text{C CDH H H}}] \qquad (12)$$

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(66) DeTar, D. F. *Comp. Chem.* **1987**, in press. Programs QCMP026 and QCMP027 are available from Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University, Bloomington, IN.

The several c[X] terms are group increments for formal bond enthalpy. For example, c[C C H H H] is the value for a CH_3 group attached to an sp^3 carbon atom as in CH_3R of an alkane or $CH_3C(OH)_2(OCH_3)$ of the tetrahedral intermediate derived from acetic acid. Its value has been found to be −10.064 kcal/mol.[2,3] Similarly c[C C C H H] is for a CH_2 group attached to two sp^3 carbon atoms; its value is −5.141 kcal/mol, c[C C C C H] is −2.190, and c[C C C C C] is −0.220. The CH_2 group of RCH_2COOH is attached to one sp^3 carbon and one sp^3 carbon. It may be represented as [C C CDH H] and has a defined value equal to that for c[C C C H H] or −5.141; C is an sp^3 carbon and CD is an sp^2 carbon. Rough estimates of increments for the groups α to the carboxyl have been derived elsewhere;[2,3] the data available are fragmentary and not very consistent; the estimate for c[C C C C CD] is −3.0 ± 2.

We find the results tantalizing. There is excellent agreement between observed and calculated rate constants for many compounds, but there are discrepancies that ought to be tracked down. It appears that we can expect to achieve an accuracy of better than a factor of two in predicted rate constants for mono- and disubstituted acetic acids. On this basis the calculated value for compound **5** (*tert*-butylmethylacetic acid) is somewhat divergent, and the value for compound **11** (isopropylethylacetic acid) is off by more than a factor of 4. Either the experimental data or the calculations (or both) are incorrect. As indicated in the footnotes of Table II, a corrected value for diisopropylacetic acid (**13**) based on the Newman value for triethylacetic acid[61] and the Sniegoski ratio[62] is close to the calculated value.

Experimental data for the trisubstituted acids are sparse. The only data that appear trustworthy are for the acids used in deriving eq 9, viz. **16**, **17**, **20**, and the Newman value for **26**. There are some interesting predictions. Although the FSE values increase with increasing substitution (Table I), the predicted rate constants show inversions. Thus triisopropylacetic acid (**32**), *tert*-butyldiisopropylacetic acid (**33**), and tri-*tert*-butylacetic acid (**35**) are predicted to react at about the same rate and some 10 000 times faster than di-*tert*-butylethylacetic acid (**31**) or di-*tert*-butylisopropylacetic acid (**34**).

Some of the acids are so highly hindered that synthesis will pose a considerable challenge, but synthesis is perhaps not out of the question. Almost certainly the rate data will have to be based on alkaline hydrolysis of active esters.

Calculations. We used the set of programs MOLMEC and the DETSB force field as described elsewhere.[2,67] Steric energies were converged to better than ±0.02 kcal/mol. The steric energy and the geometry of a given conformer was always highly reproducible even when approached from different initial geometries. On the basis of the results for crowded alkanes obtained with the DETSB force field, and calculations on alcohols and ethers, the relative accuracy of differences of FSE's may be 0.3 kcal/mol or better.

We visually checked the progression of the geometries with increasing methyl substitution. As a specific example, t-$Bu_2CHCOOMe$ was superposed on its tetrahedral partner t-$Bu_2CHC(OH)_2OCH_3$ as well as on conformers of related molecules such as i-Pr-t-BuCHCOOMe and its tetrahedral partner. Such comparisons invariably showed reasonable progressions in the conformational details. For the few conformers whose FSE values deviate from a smooth progression we carried out extensive searches for additional minima. We believe that in most cases we have located the conformer that is the global minimum. The few possible exceptions are for trisubstituted acid derivatives for which FSE values have been calculated for selected conformations.

Gauche Enthalpies. Our search for the global minima was guided by calculations of gauche enthalpies for all conformers. These are obtained by adding up individual gauche interactions according to the following assignments of gauche enthalpies:

C3–C3–C3–C3	0.70 kcal/mol
C3–C3–C3–C3–C3 g^+g^-	1.25 additional, each occurrence
C3–C3–C3–O3	0.15
C3–C3–C3–C=O	0.15
C3–O3–C3–O3	0.20
C3–C3–C3–C(OH)2(OCH3)	0.80
C3–O3–C2–O2	0.85 (for torsion of 0°)

There is a trend for low gauche enthalpies to correlate with low FSE values. A subset of conformers that includes the one having the lowest gauche enthalpy plus the other conformers having a gauche enthalpy less than the minimum value plus 1 kcal/mol, includes the global minimum in all the cases for which we have relatively complete data.

Standards for Definition of FSE. The formal steric enthalpy for a given class of compounds is defined in terms of a chosen set of standard molecules.[2-4,67] For each standard an arbitrary but reasonable formal steric enthalpy is assigned to the conformer of minimum energy. To derive FSE values from steric energies it is sufficient to select just enough standard molecules to provide correction terms. To derive FSE values and bond increments from enthalpies of formation, it is advisable to use a larger set of standards.[2,4,67] In the present calculations we are concerned only with FSE values derived from SE values, eq 13.

$$\mathrm{FSE} = \mathrm{SE} - \sum n_i d_i \qquad (13)$$

In Table IV are listed the standards we have used in this study, the FSE values we have assumed, the calculated SE values, the SM term, and the enthalpy of formation that would be used to calculate the c_i values of eq 14. These are the c values used in eq 10–12.

$$\Delta H_f - \mathrm{SM} = \sum n_i c_i + \mathrm{FSE} \qquad (14)$$

Certain d values and c values are undefined and must be assigned some arbitrary value. A hydrogen atom or any unsubstituted atom such as the =O atom of a carbonyl group is arbitrarily assigned a value of 0. We use the protocol of assigning the c[C C C H H] value to all c[C C H H X] groups and the d[C C C H H] value to all d[C C H H X] groups.

The simple calculations can be illustrated by deriving the value for d[O C C] from the SE value of 1.68 and the assigned FSE value of 0 for the extended conformer of diethyl ether. The applicable form of eq 13 is shown in eq 15. The result is that d[O C C] = −0.13. Further examples may be found in Table IVS.[64,66]

$$0.00 = 1.68 - 2(0.120) - 2(0.785) - d[\mathrm{O\ C\ C\ }] \qquad (15)$$

Conformational Corrections. The calculation of the C-corr terms may be illustrated for compound **8**, iso-

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Table IV. Standard Compounds for Definition of FSE's

compound	FSE[a]	SE[b]	SM[c]	HF[d]
$CH_3CH_2CH_2CH_3$	0.00	1.81	0.27	−30.23
$CH_3(CH_2)_6CH_3$	0.00	4.95	1.19	−49.83
$(CH_3)_2CHCH_2CH_3$	0.70	4.05	0.09	−36.76
$(CH_3)_3CCH_2CH_3$	1.40	7.42	0.00	−44.35
$CH_3CH_2OCH_2CH_3$	0.00	1.68	0.50	−60.16
$CH_3CH_2OCH_3$	0.00	1.50	0.27	−51.72
$CH_3CH_2CH_2OH$	0.00	1.37	0.09	−60.90
$CH_3CH_2CH(OH)CH_3$	0.15	2.56	0.25	−70.46
$CH_3CH_2C(CH_3)_2OH$	0.85	5.27	0.09	−79.06
$CH_3CH_2COOCH_3$	0.85	2.17	0.00	
CH_3COOCH_3	0.85	1.76	0.00	−98.00
$CH_3CH_2CH(CH_3)COOCH_3$	1.09	4.36	0.23	−117.69
$CH_3CH_2C(CH_3)_2COOCH_3$	2.08	7.80	0.00	
$CH_3CH_2C(OH)_2(OCH_3)$	0.72	3.99	0.00	

[a] Defined value of FSE for the conformer of lowest energy, ref 3. [b] For the DETSB force field. [c] Statistical mechanical correction. See eq 14 and ref 2–4 and 67. [d] Value selected in ref 3 from ref 68 and 69.

Table V. *d* Values Calculated from Table IV and Equation 13

d[C C H H H][a]	0.120	from butane and octane
d[C C C H H]	0.785	from butane and octane
d[C C C C H]	2.205	from 2-methylbutane
d[C C C C C]	4.755	from 2,2-dimethylbutane
d[C C H H O]	0.785	defined
d[O C C]	−0.130	from diethyl ether
d[C H H H O]	0.725	from ethyl methyl ether
d[O C H]	−0.295	from 1-propanol
d[C C C H O]	1.680	from 2-butanol
d[C C C C O]	3.570	from 2-methyl-2-butanol
d[C C CDH H]	0.785	defined
d[ODCD]	0.0	defined
d[CDC O OD]	−0.310	from methyl propanoate
d[C CDH H H]	0.495	from methyl acetate
d[C C C CDH]	1.830	from methyl 2-methylbutanoate
d[C C C C CD]	4.160	from methyl 2,2-dimethylbutanoate
d[C C O O O]	2.230	from $CH_3CH_2C(OH)_2(OCH_3)$
d[C(OH)2(OCH3)]	2.365	composite

[a] For notation see ref 66. The first symbol is the central atom, the following symbols are the nearest neighbor atoms; C is sp^3 C, CD is sp^2 C, etc. The first unit, for example, is the CH_3 of an alkane or CH_3 attached to any sp^3 carbon atom.

propylmethylacetic acid.[38] Examination of Table I shows that there are three important conformers of the methyl ester, having FSE values of 2.21, 2.42, and 2.24. There are three corresponding conformers of the tetrahedral intermediate having FSE values of 3.83, 3.36, and 4.52.

The calculation of C-corr is shown in eq 16–20; for the FSE values for compound 8 C-corr = −0.22. In eq 16 log

$$\log k(\text{min-min}) = \log \text{const} - (\text{DEL FSE min-min})/2.303RT \quad (16)$$

$$\log k(\text{corr}) = \log \text{const} - (1/D)\sum[\text{FSE(t.s)}_i - \text{FSE(r-min)}]/2.3RT \quad (17)$$

$$\text{C-corr} = \log k(\text{corr}) - \log k(\text{min-min}) \quad (18)$$

$$D = 1 + \exp[-[\text{FSE}(r_2) - \text{FSE}(r_1)]/RT] + \ldots \quad (20)$$

k(min-min) is based on DEL FSE for the tetrahedral intermediate of lowest (minimum) energy and the reactant of lowest energy (i.e. the DEL FSE values as given in Tables II and III). Equation 17 represents the corrected rate constant for the total reaction going through the three major channels as a summation of the individual rate constants for each channel. The rate constant for a given channel is computed from the difference of the FSE of the given transition state and the FSE of the reactant conformer of *lowest* energy. *D* in eq 17 is the Boltzmann denominator, eq 20, r_1 being the reactant conformer of lowest energy.

In calculating the C-corr values it is necessary to use a consistent assignment of conformers. We have chosen to limit the set to one each of the staggered conformers, and we have used the same set for both the ester and the tetrahedral intermediate. It is in principle necessary to double conformer "B" for compounds **3** and **4**, and conformers "B", "C", and "D" for compounds **10** and **13**. We have done so, although doubling the conformers makes little actual difference in the correlations.

The estimates of C-corr for compounds **16** to **35** are approximate because of gaps in the molecular mechanics calculations and the conformer corrections are at present of minor significance for these compounds.

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Appendix 1

The sequence $C_\gamma C_\beta C_\alpha C'$ is used to denote the conformation of the Et group. The conformer having a torsion closest to 180° is T, closest to 60° is R, and closest to 300° is L. The torsion H_β-$C_\beta C_\alpha C'$ is used similarly for *i*-Pr, with the designations TBAR, RBAR, and LBAR to emphasize the important difference in definitions for Et and for *i*-Pr.

We use the priority order *i*-Pr, Et, *t*-Bu, Me, H. Since we are dealing with enthalpies, we consider only one enantiomer. It should be noted that the "standard" designation L(Et Me H) is the mirror image of the nonstandard designation R(Et H Me) while L(Et H Me) denotes a different conformation.[4]

The effect of changing the "attitude" of the COOMe group by 180° has been investigated for several conformers. The energy difference ranges from 0 to about 0.15 kcal/mol.[4]

Registry No. **1**, 64-19-7; **1** (methyl ester), 79-20-9; **2**, 79-09-4; **2** (methyl ester), 554-12-1; **3**, 107-92-6; **3** (methyl ester), 623-42-7; **4**, 503-74-2; **4** (methyl ester), 556-24-1; **5**, 1070-83-3; **5** (methyl ester), 10250-48-3; **6**, 79-31-2; **6** (methyl ester), 547-63-7; **7**, 116-53-0; **7** (methyl ester), 868-57-5; **8**, 14287-61-7; **8** (methyl ester), 30540-29-5; **9**, 19910-29-3; **9** (methyl ester), 19910-30-6; **10**, 88-09-5; **10** (methyl ester), 816-11-5; **11**, 32444-32-9; **11** (methyl ester), 32444-33-0; **12**, 6967-84-6; **12** (methyl ester), 88246-54-2; **13**, 32118-53-9; **13** (methyl ester), 94991-59-0; **14**, 3302-11-2; **14** (methyl ester), 54461-01-7; **15**, 41785-81-3; **15** (methyl ester), 10250-50-7; **16**, 75-98-9; **16** (methyl ester), 598-98-1; **17**, 595-37-9; **17** (methyl ester), 813-67-2; **18**, 49714-52-5; **18** (methyl ester), 1727-57-7; **19**, 30407-41-1; **19** (methyl ester), 50902-76-6; **20**, 19889-37-3; **20** (methyl ester), 5296-70-8; **21**, 75612-70-3; **21** (methyl ester), 102439-52-1; **22**, 38541-67-2; **22** (methyl ester), 67732-11-0; **23**, 23119-04-2; **23** (methyl ester), 55519-33-0; **24**, 67029-92-9; **24** (methyl ester), 73981-19-8; **25**, 16021-12-8; **25** (methyl ester), 51211-84-8; **26**, 813-58-1; **26** (methyl ester), 10250-49-4; **27**, 61415-95-0; **27** (methyl ester), 107475-03-6; **28**, 67029-93-0; **28** (methyl ester), 67732-16-5; **29**, 7498-50-2; **29** (methyl ester), 78616-96-3; **30**, 67029-94-1; **30** (methyl ester), 107475-04-7; **31**, 107475-00-3; **31** (methyl ester), 107475-05-8; **32**, 69447-94-5; **32** (methyl ester), 1185-12-2; **33**, 107475-01-4; **33** (methyl ester), 107475-06-9; **34**, 107475-02-5; **34** (methyl ester), 107475-07-0; **35**, 41785-81-3; **35** (methyl ester), 107475-08-1.

Supplementary Material Available: Tables of formal steric enthalpies of conformers of $R_1R_2CHC(OH)_2OMe$, rate constants for esterification and hydrolysis, literature data for hydrolysis, and group increments for alcohols, ethers, and esters (16 pages). Ordering information is given on any current masthead page.