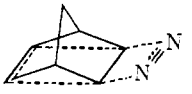
denness" have been based on ring opening of cyclobutenes to butadienes; they fall in the range 10–15 kcal/mol.[12] Even if one ignores the matter of heats of reaction raised above, the price of forbiddenness should not have a unique value; it should be a function of the reactions chosen for its measurement. The smaller the energy difference between the highest occupied and lowest vacant molecular orbitals of a polyene, for example, the smaller one may expect the activation energy difference to be between allowed and forbidden pathways for electrocyclization. In the fragmentation of **6**, a retro-2+2 cycloaddition, the very large energy gaps for C–N σ *vs.* σ^* levels in the reactant and π *vs.* π^* levels in the products are undoubtedly responsible for the great effectiveness of symmetry forbiddenness.

Thermal decomposition of the unsaturated azo compound **3**, which proceeded somewhat faster in the vapor phase than that of **6** (Table I), yielded both norbornadiene and quadricyclane (93.6:6.4 in diglyme at 111°). Higher temperatures increased the proportion of quadricyclane formed in solution, but only slightly. Photodecomposition of **3** gives the tetracyclic hydrocarbon as the major and the diene as the minor product. Presently available evidence permits no firm conclusions regarding the mechanisms for fragmentation of **3** and **6**, but it is noteworthy that concerted decomposition of **3** to quadricyclane (transition state **9**) is orbital symmetry allowed both in the ground[10b] and lowest excited states. Considering the thermal decomposition, one may be surprised that the symmetry-allowed process



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competes poorly, if at all (quadricyclane may be generated in a stepwise manner), with the symmetry-forbidden formation of norbornadiene. That fact is understandable, however, when account is taken of the great additional strain which must be built into the molecular skeleton en route to quadricyclane.[13]

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(12) (a) G. R. Branton, H. M. Frey, D. G. Montague, and I. D. R. Stevens, *Trans. Faraday Soc.*, **62**, 659 (1966); G. R. Branton, H. M. Frey, and R. F. Skinner, *ibid.*, **62**, 1546 (1966); J. I. Brauman and D. M. Golden, *J. Amer. Chem. Soc.*, **90**, 1920 (1968); E. C. Lupton, Jr., *Tetrahedron Lett.*, 4209 (1968); G. A. Doorakian and H. H. Freedman have estimated a lower limit of 7.3 kcal/mol (*J. Amer. Chem. Soc.*, **90**, 5310, 6896 (1968)). (b) NOTE ADDED IN PROOF. A. Dahmen and R. Huisgen have found the difference in ΔG between allowed and forbidden pathways for electrocyclization of *trans,cis,cis, trans*-2,4,6,8-decatetraene to be ~11 kcal/mol (*Tetrahedron Lett.*, 1465 (1969)).

(13) R. B. Turner, P. Goebel, B. J. Mallon, W. von E. Doering, J. F. Coburn, Jr., and M. Pomerantz, *J. Amer. Chem. Soc.*, **90**, 4315 (1968).

(14) Holder of a Fulbright-Hays Travel Grant.

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Acyloxyphosphonium Salts as Acylating Agents. A New Synthesis of Peptides

Sir:

"Onium" salts derived from polar, aprotic solvents are versatile intermediates in organic synthesis.[1] We considered that the resonance-stabilized acyloxyphosphonium salts (**3**) derived from hexamethylphosphoramide (phosphoric trisdimethylamide, HMPA)[2] would be effective acylating agents with properties particularly suited to peptide synthesis. We now describe a new, practical method of peptide synthesis based on the presumed intermediacy of these salts.

$$(Me_2N)_3PO + Ts_2O \longrightarrow \underset{\mathbf{1}}{[(Me_2N)_3\overset{+}{P}\text{—}OTs\ TsO^-]} \xrightarrow{(Me_2N)_3PO} \underset{\mathbf{2}}{(Me_2N)_3\overset{+}{P}\text{—}O\text{—}\overset{+}{P}(NMe_2)_3\ 2TsO^-} \xrightarrow{RCOO^-} \underset{\mathbf{3}}{RCO\text{—}O\text{—}\overset{+}{P}(NMe_2)_3\ TsO^-} \xrightarrow{R'NH_2} RCO\text{—}NHR' + (Me_2N)_3PO$$

In the preferred procedure, tosic anhydride[3] is allowed to react with excess dry HMPA (5–10 equiv) at room temperature forming the ditosylate **2**.[4] After 15 min, the solution is cooled to 0° and the acylamino acid or peptide triethylammonium salt dissolved in HMPA is added. After 5–10 min, the amino acid or peptide ester is added as the free base together with a further equivalent of triethylamine, and the reaction mixture allowed to warm to room temperature overnight. Alternatively, the solution of the phosphonium salt may be added slowly to a pH-controlled aqueous solution of the amino acid sodium salt.

Tosyl chloride or thionyl chloride could replace tosic anhydride with equal efficiency in the initial activation step, and the former is a more easily purified and convenient reagent applicable where there is no possibility of racemization (see below). The dibromo adduct[5] of tris(dimethylamino)phosphine (phosphorus trisdimethylamide)[6] was less satisfactory, but good yields were obtained in an oxidative reaction using the freshly distilled phosphine and an inorganic oxidant (*e.g.*, mercuric chloride) in HMPA solution.[7] Peptide derivatives prepared by these procedures are listed in Table I.

Little, if any, racemization of optically active carboxyl components was detected in the examples given in the

(1) *E.g.*, (a) W. W. Epstein and F. W. Sweat, *Chem. Rev.*, **67**, 247 (1967), and references therein; (b) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **89**, 2416 (1967); (c) K. Torssell, *Acta Chem. Scand.*, **21**, 1 (1967); (d) J. R. Parikh and W. von E. Doering, *J. Amer. Chem. Soc.*, **89**, 5505 (1967); (e) D. Bethell, G. W. Kenner, and P. J. Powers, *Chem. Commun.*, 227 (1968).

(2) H. Normant, *Angew. Chem. Intern. Ed. Engl.*, **6**, 1046 (1967).

(3) L. Field, *J. Amer. Chem. Soc.*, **74**, 394 (1952); the product was recrystallized several times from benzene.

(4) Evidence for the formation of 2 was provided by the nmr spectrum of the ether-precipitated product. This showed the equivalent numbers of tris(dimethylamino) and tosylate protons expected for **2** but not for the initial adduct 1. Similar evidence was obtained for the formation of **3**, R = $ZNHCH_2$.

(5) H. Nöth and H. J. Vetter, *Chem. Ber.*, **98**, 1981 (1965).

(6) V. Mark, *Org. Syn.*, **46**, 42 (1966).

(7) It is probable that some recently described reactions[8,9] of triphenylphosphine and of triethyl phosphite involve acyloxyphosphonium salt intermediates.

(8) T. Mukaiyama, M. Ueki, H. Maruyama, and R. Matsueda, *J. Amer. Chem. Soc.*, **90**, 4490 (1968).

(9) Y. V. Mitin and G. P. Vlasov, *Dokl. Akad. Nauk SSSR*, **179**, 353 (1968).

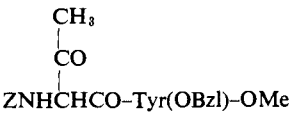
Table I[a]

Example	Product	Method	Yield,[b] %	Yield,[c] %	Mp,[c] °C
1	Z-Asn-Phe-OMe	C	92	85	192–194
2	Z-Gln-Gly-OMe	C	86	81	158–161
3	Z-Gly-Leu-OMe	A	93	88	62–65
4	Z-Ile-Gly-OMe	B	90	87	131–132
5	Z-Phe-Gly-OMe	A	91	89	119–120
6	Z-Phe-His-OMe	B	91	89	115–117
7	Z-Trp-Gly-OMe	C	95	87	158–159
8	Z-Tyr-Gly-OMe	C	82	79	140–142
9	Z-Tyr-Thr-OMe	C	77	73	134–136
10	Z-Val-Gly-OMe	B	96	92	160–162
		C	95	87	160–162
		D	94	86	158–160
		E	88	77	155–157
11	Z-Gly|Ala-Pro-NH_2	B	91	83	154–156
12	Z-Gly-Gly|Phe-OMe	A	93	80	98–101
13	Z-Ile-Gly|Val-OMe	B	93	90	147–148
14	Z-Trp-Leu|Ala-Phe-NH_2	B	84[d]	81	258–260
15	Z-Val-Gly|Ala-Pro-NH_2	B	91	85	179–180
16	Z-Gly-Leu|Ala-Phe-Ala-Gly-OMe	B	91	79	210–212
17	Z-Ile-Gly|Val-Gly-Ala-Pro-NH_2	B	89	84[e]	242–244
	Z-Ile-Gly-Val|Gly-Ala-Pro-NH_2	B	84[f]	80	239–242
18	Z-Gly-Leu-Leu-Gly-Gly|Phe-Ala-Gly-OMe	B	86	81	221–224
19	Z-Thr(OBu-*t*)-Ala|Ile-Gly-Val-Gly-Ala-Pro-NH_2	B	81	75	212–214
20	Z-Ile-Gly-OH	F	87[g]	69	124–125
21	Z-Phe-His-OH	F	84[g]	65	195–197
22	Z-Val-Gly-OH	F	95[g]	82	133–134

[a] All optically active amino acids were of L configuration. In examples 11–19 the vertical line indicates the point of coupling. Conditions: A, 1 equiv (relative to amine) of tosic anhydride and 1 equiv of the carboxylate salt used; B, 1.1 equiv each of tosic anhydride and the carboxylate salt; C, 1.1 equiv each of tosyl chloride and the carboxylate salt; D, 1 equiv each of thionyl chloride and the carboxylate salt; E, 1 equiv of tris(dimethylamino)phosphine added to 1 equiv of carboxylate salt and 2 equiv of mercuric chloride; F, the activated carboxyl component prepared by method A was added slowly to an aqueous solution containing 3 equiv of the amino acid maintained at pH 8.5 by addition of 1 *N* sodium hydroxide. [b] Yield of chromatographically homogeneous neutral fraction. [c] Yield and melting point after one crystallization. Melting points are in good agreement with literature values; satisfactory elemental analyses were obtained for new compounds. [d] $[\alpha]^{22}D$ −34.1°; material prepared by Mr. D. Waters by stepwise active ester synthesis had $[\alpha]^{22}D$ −33.9°. [e] $[\alpha]^{21}D$ −13.2°. [f] $[\alpha]^{21}D$ −13.0°. [g] Total acidic fraction.

table (see especially examples 14 and 17). The stringent Young racemization test[10] gave *uncrystallized* benzoyl-L-leucylglycine ethyl ester (95%) [mp 153–155°; $[\alpha]^{21}D$ −33.7°. *Anal.* Calcd for $C_{17}H_{24}O_4N_2$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.66; H, 7.59; N, 9.00] corresponding to better than 99% L isomer.[11] We ascribe this remarkable freedom from racemization even in the polar solvent hexamethylphosphoramide to the low intrinsic reactivity of the resonance-stabilized acyloxytris(dimethylamino)phosphonium system **3**. It is possible that the aminolysis reaction (but not oxazolone formation) is catalyzed by anchimeric assistance from the dimethylamino groups,[12] or by initial attack at the phosphorus atom. In the presence of chloride ion appreciable racemization is observed (*e.g.*, use of glycine ester hydrochloride and 1 equiv of triethylamine gave 95% L isomer), and this "chloride ion effect"[13] is marked in the tosyl chloride and thionyl chloride variants of the method even when free glycine ester is used as the amino component.

No difficulties were observed when the side chains of asparagine, glutamine, methionine, tryptophan, or tyrosine were present in the activated carboxyl component, but the aliphatic hydroxyamino acids and histidine deserve special comment. The reaction between benzyloxycarbonylthreonine and O-benzyltyrosine methyl ester yielded only 15% of the crystalline ketone **4**; clearly, the HMPA–tosic anhydride combination can under certain circumstances function as an oxidizing agent for aliphatic alcohols (*cf.* ref 1b).



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The dipeptide derivative, Z-Phe-His-OH, could not be coupled satisfactorily with the methyl esters of glycine or threonine; this difficulty may be due to the intervention of acylated imidazole derivatives (*cf.* ref 14), and protection of the imidazole ring will presumably be necessary.

With the exceptions noted above, the procedure appears to be quite general and to offer advantages over many existing methods. It involves only readily accessible reagents and operates in a polar solvent in which even large peptides are often soluble. The intermediates are relatively stable in anhydrous solution; no diminution in yield was observed when the solution of **2** was kept for 2 hr before addition of the carboxyl component, nor when a solution of the phosphonium salt **3**, R = $ZNHCH_2$, was kept for 30 min before addition of the amino acid ester. Isolation of neutral products is simple, often requiring only dilution of the reaction mixture with water. All the coproducts of the reaction are water soluble, and neutral peptide deriva-

(10) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 881 (1963).
(11) Lit.[10] mp 153–155°, $[\alpha]D$ −34.0°.
(12) *Cf.* J. H. Jones and G T. Young, *Chem. Commun.*, 35 (1957).
(13) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 3701 (1964).
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tives are generally obtained directly in a chromatographically pure state before recrystallization. The risk of racemization under normal conditions appears to be very small, and the method promises to be particularly useful for the synthesis of large peptides in cases where racemization would otherwise be a serious risk.

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Relative Stabilities of Alkylbenzene Negative Ions

Sir:

Electron affinities of polynuclear aromatic hydrocarbons have been determined in the gas phase by electron capture techniques[1] and in solution by potentiometric[2] and polarographic[3] determination of the electrochemical potential required for one-electron reduction. Relative electron affinities have also been measured by ultraviolet spectroscopic determination of the concentrations of radical anions in partially reduced mixtures of hydrocarbons.[4] All of the methods of absolute determination, however, require that the one-electron reduction products be relatively easily formed in the gas or liquid phases, while the use of spectroscopy requires that extinction coefficients be accurately known. None of these methods seems to be applicable to the study of the reduction potentials of benzene or alkylbenzenes for which the electron affinities have been estimated to be negative.[5] Such measurements are of interest, however, both on theoretical grounds and for their possible application to the understanding of the chemistry of this important class of hydrocarbons.

We report here an estimate of the relative electron affinities of benzene and some alkylbenzenes based on the free energy change for equilibrium 1 as determined

$$C_6H_6 + R_1R_2C_6H_4\cdot^- \underset{}{\overset{K_1}{\rightleftharpoons}} C_6H_6\cdot^- + R_1R_2C_6H_4 \qquad (1)$$

by electron spin resonance of the radical anions in partially reduced binary solutions of the hydrocarbons. Mixtures of carefully measured known concentrations of benzene and alkylbenzenes were reduced *in vacuo* by sodium–potassium alloy in tetrahydrofuran–dimethoxyethane solution.[6a] Esr spectra were recorded at $-100°$.[6b] Equilibrium constants were calculated from the relative concentrations of the free radicals, as determined by double integration of the esr spectra, in solutions where reduction had proceeded to less than 1%.[7] Separate quantitative determination of the concentrations of both radical species is possible under these conditions because the rate of chemical exchange is slow in these systems[8] and makes it possible for a high concentration of the unreduced species to be present without producing collapse of the multiplet structure or even appreciable broadening of the lines of the esr spectrum.

Values of K_1 are given in Table I. As might be anticipated on chemical grounds, introduction of an alkyl substituent into the benzene ring renders the molecule more resistant to one-electron reduction. A plot of ln K_1 *vs.* σ^* inductive constants[9] for the monosubstituted compounds is linear. The ρ^* value of 5 determined in this way is typical of carbanionic processes.[10] Similar, though smaller, effects of alkyl substitution have been observed in electron addition reactions of the higher polyacenes. For example, the polarographic half-wave potential of naphthalene becomes more negative with increased alkyl group substitution.[11] Similarly, the rate of the metal–ammonia reduction of benzene, which is presumed to proceed *via* the intermediacy of the radical anion, is retarded by alkyl substituents.[12]

Table I. Equilibrium Constants and Free Energy Changes for Benzene Radical Anion Relative to Alkylbenzene Radical Anions[a]

$$R_1R_2C_6H_4\cdot^- + C_6H_6 \underset{}{\overset{K_1}{\rightleftharpoons}} C_6H_6\cdot^- + R_1R_2C_6H_4$$

R_1	R_2	K_1[b]	$-\Delta G_{173}°$, eV
CH_3	H	4.4 ± 1.0	0.02_2
CH_2CH_3	H	22 ± 3	0.04_6
$CH(CH_3)_2$	H	40 ± 9	0.05_5
$C(CH_3)_3$	H	110 ± 19	0.07_0
CH_3	*o*-CH_3	890 ± 180[c]	0.10_0
CH_3	*m*-CH_3	51 ± 13[c]	0.05_9
CH_3	*p*-CH_3	9.1 ± 1	0.03_3
CH_2CH_3	*p*-CH_2CH_3	120 ± 20	0.07_1
$CH(CH_3)_2$	*p*-$CH(CH_3)_2$	629 ± 110	0.09_1
$C(CH_3)_3$	*p*-$C(CH_3)_3$	>4300[d]	$>0.12_4$

[a] Solvent THF–DME (1:1, v/v), reducing agent Na–K (1:2), temperature $-100 \pm 2°$, total hydrocarbon concentration 0.15–0.30 *M*. [b] Errors are one standard deviation for the average of eight to ten measurements. [c] Calculated from the equilibrium constants relative to *p*-xylene. [d] 1,4-Di-*t*-butylbenzene does not produce a detectable amount of radical anion under these conditions.

We believe that the equilibrium constants reported in this preliminary communication are a good approximation to the corresponding quantities in the gas phase primarily because the effects of solvation and ion pairing should be approximately constant for ions and molecules, such as those involved here, which are of similar

(1) (a) W. E. Wentworth, E. Chen, and J. E. Lovelock, *J. Phys. Chem.*, 70, 445 (1966); (b) R. S. Becker and E. Chen, *J. Chem. Phys.*, **45**, 2403 (1966).

(2) G. J. Hoijtink, E. deBoer, P. H. van der Meij, and W. P. Weijland, *Rec. Trav. Chim.*, **75**, 487 (1956).

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(5) G. Briegleb, *Angew. Chem. Intern. Ed. Engl.*, **3**, 617 (1964).

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(7) Under these conditions a small amount of decomposition of the radical ions will not change the concentration of neutral species appreciably and will therefore have negligible effect on K_1 provided that equilibrium between neutral and ionic species and reducing agent is attained at a rate which is rapid compared to that of the side reactions. Failure of these conditions was demonstrated occasionally by the observation of nonreproducible ratios of radical ion concentrations on successive scans of the esr spectrum of a sample. Samples exhibiting this behavior were rejected.

(8) (a) G. L. Malinowski and W. H. Bruning, *J. Amer. Chem. Soc.*, **89**, 5063 (1967); (b) E. deBoer and C. MacLean, *J. Chem. Phys.*, **44**, 1334 (1966).

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(10) A. Streitwieser, Jr., and H. F. Koch, *J. Amer. Chem. Soc.*, **86**, 404 (1964).

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(12) (a) A. P. Krapcho and A. A. Bothner-By, *J. Amer. Chem. Soc.*, **81**, 3658 (1959); (b) A. P. Krapcho and M. E. Nadel, *ibid.*, **86**, 1096 (1964); (c) H. Smith, "Organic Reactions in Liquid Ammonia," Vol. 1, Part 2, John Wiley & Sons, Inc., New York, N. Y., 1963.