affect the stability of $B\cdot^+$ relative to BH^+. Lone pair interactions are one of the more intriguing origins of such deviations.

(2) A measure of the resonance stabilization afforded radical cations by lone pair interactions may be obtained from a comparison of their BH^+ homolytic bond dissociation energies to those of model compounds in which such interactions are absent.

(3) The stabilization afforded radical cations by lone pair interactions is manifest in the chemical reactivity of these species. It is thus significant that diazabicyclooctane,[16] hydrazine,[16] and azomethane[17] radical cations are unreactive with the parent neutral. This is in direct contrast to the behavior of the majority of nitrogen bases, where the radical cation reacts rapidly to form the protonated parent[20] and is a direct consequence of the reduction of $D(B^+-H)$ to a value below carbon hydrogen bond dissociation energies in the neutral molecule.

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(20) It is interesting to note that in solution diazabicyclooctane undergoes reversible one-electron oxidation at a platinum electrode [S. F. Nelsen and P. J. Hintz, *J. Amer. Chem. Soc.*, **94**, 7114 (1972)] and is long enough lived to give a well-resolved esr spectrum [T. M. McKinney and D. H. Geske, *ibid.*, **87**, 3013 (1965)].

(21) Camille and Henry Dreyfus Teacher–Scholar, 1971–1976.

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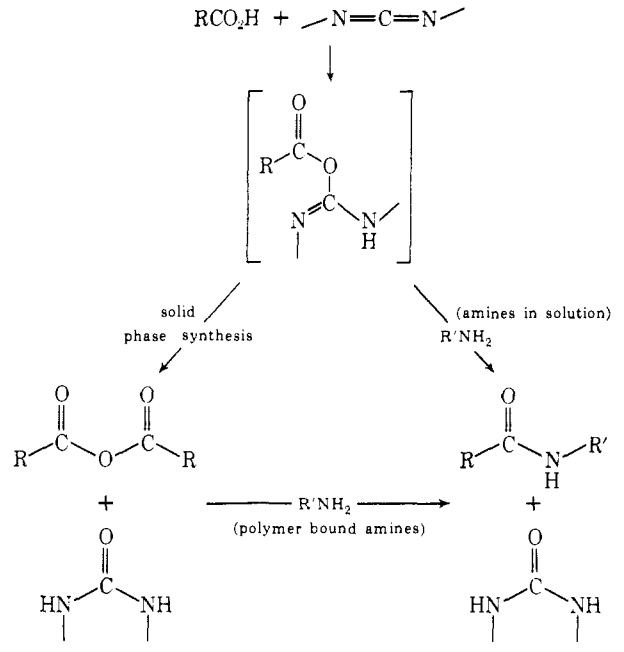
Mechanism of the Carbodiimide Reaction. II. Peptide Synthesis on the Solid Phase

Sir:

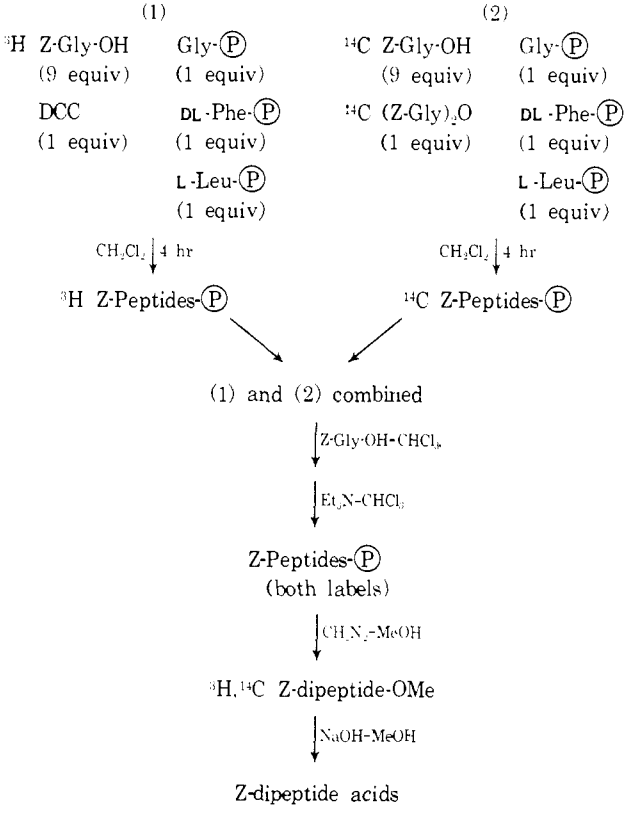
Recently we reported a mechanistic study of the reaction of carboxylic acids with amines mediated by *N,N'*-dicyclohexylcarbodiimide (DCC).[1] Our evidence indicated that the initial acylating agent in the DCC reaction was distinguishable from the carboxylic acid anhydride (Scheme I) under conditions normally encountered during peptide synthesis *in solution*. The *O*-acylisourea, as originally postulated by Khorana,[2] appears to be the actual acylating agent. We now present evidence that under the conditions of *solid phase* peptide synthesis[3] the DCC reaction mechanism follows the alternate path and the actual acylating agent is the symmetrical anhydride.

Merrifield resins[4] were separately loaded with *tert*-butoxycarbonylglycine (0.52 mequiv/g), *tert*-butoxycarbonyl-DL-phenylalanine (0.34 mequiv/g), and *tert*-butoxycarbonyl-L-leucine (0.39 mequiv/g) then combined, N deblocked, and assayed according to standard procedures.[5] Samples of the mixed resin were equilibrated with saturated (0.03 *M*) solutions of either (1) ^3H or (2) ^{14}C-labeled benzyloxycarbonylglycine (Z-Gly-OH) in CH_2Cl_2, according to the stoichiometry indicated in Scheme II. The suspensions were then treated with limited amounts of DCC and anhydride, respectively, followed by shaking for 4 hr. The two resin batches were then combined, washed with $CHCl_3$ saturated with unlabeled Z-Gly-OH and 10% Et_3N–$CHCl_3$, and subjected to diazomethane catalyzed transesterification[6] to liberate the peptides from the resin as their

Scheme I



Scheme II



(1) J. Rebek and D. Feitler, *J. Amer. Chem. Soc.*, **95**, 4052 (1973).
(2) H. G. Khorana, *Chem. Ind. (London)*, 1087 (1955).
(3) R. B. Merrifield, *Advan. Enzymol.*, **32**, 221 (1969).
(4) Available from Calbiochem, San Diego, Calif.
(5) J. Stewart and J. Young, "Solid Phase Peptide Synthesis," W. H. Freeman, San Francisco, Calif., 1969.

(6) H. Bredereck, R. Siekeo, and L. Kamphenkel, *Chem. Ber.*, **89**, 1169 (1956). This somewhat obscure catalytic reaction is ideal for removing peptides from the polymer under essentially neutral conditions. Typically, the resin-bound peptide is over-layered with meth-

methyl esters. The esters were saponified and aliquots of the mixture were diluted with the highly crystalline dipeptide acids which were recovered and recrystallized to constant activity.

We feel that the constancy of the $^3H/^{14}C$ ratios (Table I) of the products provides compelling evidence

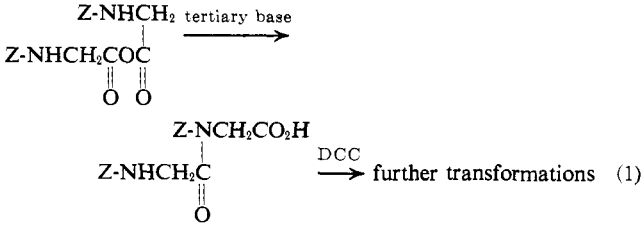
Table I

Peptide	$^3H/^{14}C$	Product distributions[a] DCC	Anhydride
Z-Gly-Gly-OH	3.71	1.01	1.04
Z-Gly-DL-Phe-OH	3.78	1.26	1.28
Z-Gly-L-Leu-OH	3.84	1.00	1.00
	Overall yields[b]	90%	95%

[a] Normalized to Z-Gly-L-Leu. [b] For coupling, transesterification, and saponification (based on acylating agent).

for a common product-determining step, *i.e.*, that the same acylating agents are involved in both reactions. The product distributions of the three polymer bound amines probably reflect resin loadings as well as their intrinsic nucleophilic properties and deserve little comment; however, the competition between the amine (on the solid phase) and the carboxylic acid (in solution) for the *O*-acylisourea (in solution) has a different outcome from that in solution. The *O*-acylisourea can be intercepted by amines and some phenols[7] in solution but not by polymer-bound amines during solid-phase peptide synthesis.

During solid-phase synthesis a 1:1 acid–DCC ratio is normally used, and, since these reagents are in excess with respect to the polymer-bound amine, the symmetrical anhydride must build up at the end of the reaction. Our result indicates that the anhydride is the acylating agent during the initial third of the reaction as well. Further, the relative insolubility of Z-Gly-OH makes the present experimental conditions unfavorable to anhydride formation; the common use of *t*-BOC amino acids as much more concentrated solutions during solid-phase synthesis should favor the anhydride mechanism, although steric factors may, in some cases, suppress anhydride formation. If the anhydride mechanism obtains in general, it would appear that the common use of excess DCC is superfluous or even deleterious during solid-phase synthesis. De Tar's demonstration of the lability of these anhydrides to tertiary bases, including DCC[8] (eq 1), is relevant here,



(1)

in that new acids are generated which would lead to side products of the sort that linear synthesis cannot tolerate. The report of loss of acylating power of DCC–acid–tertiary amine mixtures with time should be mentioned in this connection.[9]

We suggest that a 2:1 acid–DCC stoichiometry, or the preformed purified anhydride, be used in solid-phase peptide synthesis. We note that improved results have been reported recently with anhydrides.[10]

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anol and treated with roughly an equivalent of ethereal diazomethane solution and stored overnight in the refrigerator. Under these conditions polymer-bound Z-Gly-L-Leu was converted to the corresponding methyl ester with a reaction half-life of 1–2 hr.

(7) J. Kovacs, L. Kisfaludy, M. Ceprini, and R. Johnson, *Tetrahedron*, **25**, 2555 (1969).

(8) D. F. De Tar, R. Silverstein, and F. Rogers, Jr., *J. Amer. Chem. Soc.*, **88**, 1024 (1966).

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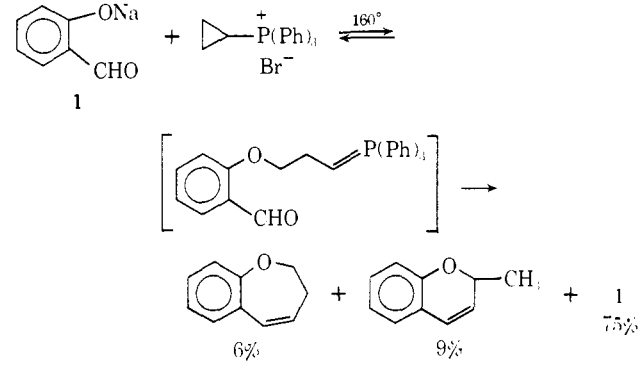
Carboethoxycylopropcyltriphenylphosphonium Fluoroborate. A Reagent for the Facile Cycloalkenylation of Carbonyl Groups

Sir:

Schweizer's exploratory studies on the reaction of cyclopropylphosphonium bromide with the sodium salt of salicylaldehyde have demonstrated that this reagent is of only limited utility as an annulation reagent.[1,2] This limitation is presumably a consequence of the difficulty of the ring opening step.[2]



Since it is well documented that nucleophilic cleavage of cyclopropane rings is most facile when the cyclopropane ring bears two geminal electron-withdrawing groups,[3] it was therefore anticipated that cyclopropylphosphonium salt, **2**, which has a geminal carboethoxy group, should exhibit facile ring opening reactions.

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(2) E. E. Schweizer, T. Minami, and D. M. Crouse, *J. Org. Chem.*, **36**, 4028 (1971).

(3) (a) J. M. Stewart and H. H. Westberg, *J. Org. Chem.*, **30**, 1951 (1965); (b) J. E. Dolfini, K. Menich, P. Corliss, R. Cavanaugh, S. Danishefsky, and S. Chakrabartty, *Tetrahedron Lett.*, 4421 (1966); (c) S. Danishefsky, J. Dynak, and M. Yamoto, *J. Chem. Soc., Chem. Commun.*, 81 (1973); (d) E. J. Corey, P. L. Fuchs, *J. Amer. Chem. Soc.*, **94**, 4014 (1972); (e) G. Daviaud and Ph. Miginiac, *Tetrahedron Lett.*, 997 (1972); (f) D. J. Cram, *et al.*, *J. Amer. Chem. Soc.*, **95**, 4220, 4230, 4237 (1973).